THE APPLICATION OF NEW TECHNOLOGY TO COLORECTAL SURGERY

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by

Andrew James Luck, M.B., B.S. (Adel), F.R.A.C.S.

The work described was performed within
the Department of Surgery of the
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The Queen Elizabeth Hospital

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SUMMARY

The impact of several technological advances and their appropriate clinical application to the field of colorectal surgery was investigated in this thesis.

Intra-operative ultrasound was shown to be valuable in the assessment of the liver for hepatic metastases at the time of resection of colorectal cancer. This technology is best applied in the assessment of abnormalities that have been found on pre-operative computed tomography, rather than as the definitive screening tool itself. Laparoscopic ultrasound was found to be a difficult technique to master. Further investigation will be required in order to assess the role of laparoscopic ultrasound of the liver during laparoscopic colectomy for cancer.

Intra-operative ultrasound of the colon is a technique that was developed in the two years of this thesis. Excellent images of colon and colonic neoplastic lesions were produced during a benchtop study, particularly when the colonic lumen was filled with fluid. In vivo investigation is continuing in order to assess the value of this technique in the localisation and assessment of impalpable colonic lesions for resection.

Laparoscopic reversal of Hartmann's procedure and laparoscopic-assisted colonoscopic polypectomy were shown, in small series, to be feasible and safe procedures that appear to provide many of the short-term post-operative patient advantages that have been reported with other laparoscopic procedures.

A case-controlled study of the core temperature changes during surgery showed that there is no difference in the incidence of hypothermia between laparoscopic and open colorectal surgery. The use of a forced-air warming device was shown to decrease the incidence of hypothermia in laparoscopic colorectal surgery, a finding not previously reported. A subsequent analysis suggested that this device might only be of value in female patients. The unanswered questions posed by this study led to the designing of a randomised follow up trial that has recently commenced.

The ability of the new technique of immunobead reverse transcriptase-polymerase chain reaction to detect small numbers of free intraperitoneal malignant cells at colorectal cancer resection was tested. Although long-term follow up will be required to assess its true prognostic value, early anecdotal evidence suggests that this technique may be able to identify some patients who have early stage, but poor prognosis colorectal cancer.

The results of the first three years of a project designed to enable the performance of ligation excision haemorrhoidectomy as day surgery was reported. This project achieved a high same day discharge rate, with low rates of readmission and complications and a high level of patient satisfaction. This project also provided a prospective database for the assessment of post-haemorrhoidectomy pain. Wide ranges of pain scores were recorded, but in general pain was well controlled by a multimodal peri-operative analgesic regime. Pain was worst at the time of the first bowel action after surgery, but all patients except one were able to manage at home.

Pain scores were particularly low in the first four hours after surgery. It was hypothesised that this was due to the effect of a pre-emptive, local anaesthetic, ischio-rectal fossa block. This hypothesis was tested in 1998 in a prospective, randomised, double blind trial. Patients who received the block had significantly lower pain scores and lower analgesic requirements in the first 24 hours after surgery than a control group who had infiltration of the haemorrhoidal complexes only.

The relative merits of pharmacological treatment using glyceryl trinitrate paste and surgical treatment with lateral sphincterotomy were assessed in a prospective randomised trial. The healing rate for lateral sphincterotomy was significantly higher and considerably quicker. Many patients would still, however, prefer first-line treatment to be medical. A preliminary assessment of pain scores suggested that it might be possible to predict the chances of a fissure healing with glyceryl trinitrate early in the treatment period, but that larger patient numbers are required. A protocol combining the best aspects of both treatments is presented.

The final section shifted the emphasis to an investigation of whether new technology can have a direct impact on a patient's preparation for surgery. This was assessed in the form of a randomised trial analysing the effect of an information video on the anxiety and knowledge levels of patients prior to colonoscopy. Patients randomised to watch the video had significantly lower anxiety levels prior to colonoscopy than those who did not watch the video. The difference was greatest in the group of patients who had severe initial anxiety, but was still significant in low anxiety patients. The patients who watched the video also had significantly

better knowledge about the purpose, procedural details and potential complications of colonoscopy than those who did not watch the video.

The assessment of new technology and its application to surgery must be ongoing. The studies reported in this thesis have answered many questions regarding the appropriate clinical role of some aspects of new technology to colorectal surgery. In addition, they have led to several changes in clinical practice and considerable further research, which will attempt to answer those questions that have been left unanswered.

DECLARATION

I declare that this thesis contains no material that has been accepted for the award of any other degree or diploma in any University and that to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. I further consent to the thesis being made available for photocopying and loan if applicable if accepted for the award of the degree.

ANDREW LUCK

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The work that is presented in this thesis was made possible by the financial support of the Division of Surgery at The Queen Elizabeth Hospital. Personal financial assistance was in the form of a post-graduate industry award from the University of Adelaide, in conjunction with Kendall Industries.

This thesis consists of a number of clinical studies that touch on many aspects of colorectal surgery and that have required the assistance of a number of departments within The Queen Elizabeth Hospital. The consultant general surgeons and surgical registrars referred patients for all studies on a regular basis, and without exception were patient and understanding during those studies that required operating time to be extended. Theatre nursing staff in both the General Theatres and the Day Surgery Unit were similarly patient and in many cases assisted with data collection.

Specific acknowledgements are best mentioned in the order that the studies appear in the thesis. The ultrasound studies required considerable assistance from the Department of Medical Imaging. The original protocols were designed in conjunction with Professor Phillip Costello and much of the early liver ultrasound work, whilst the technique was being mastered, was performed by Senior Radiographers Ann Murphy and Michelle Rose. Ann and Michelle also provided invaluable technical advice throughout the two years. The final liver ultrasound videotapes were reported by Dr Jane Copley, who also reviewed all liver computed tomography scans.

The core temperature study was supported by the Department of Anaesthesia and Intensive Care, and in particular Professor Don Moyes. Anaesthetic medical staff placed the oesophageal temperature probes and, in many cases, also recorded the temperature data.

The immunobead reverse transcriptase-polymerase chain reaction (RT-PCR) project was a component of a large project being performed by research workers from the Department of Haematology/Oncology and the Division of Surgery. This work has been supported by an Anti-Cancer Foundation scholarship. The immunobead RT-PCR work presented in this thesis was performed by Mrs Jenny Hardingham during the final year of her Ph.D. Her supervisor, Dr Alex Dobrovic was responsible for the original concept of testing peritoneal washing specimens by this technique. Mr Grant King, Senior Hospital Scientist, performed the cytology for this project and the immunocytochemistry was prepared by Ms Suzy Dosljak in the Department of Pathology and reported by Dr Wendy Lew.

The day case haemorrhoidectomy project was designed by Dr Lesley Hunt, a surgical registrar from Leicester in the United Kingdom, to where she returned in August 1996, at which time the project became a component of this thesis. The nursing staff in the recovery areas of the Day Surgery Unit, the Convalescent Unit and with the Hospital at Home Service performed considerable data collection for this project. Analysis of the pain scores was performed in conjunction with Dr Robin Limb and Dr Glenda Rudkin from the Department of Anaesthesia and Intensive Care.

Ms Sue Pearson, B.A.(Psychol), a Ph.D student with the Division of Surgery, provided important advice for the video information study and collected the data from approximately 25% of the patients.

Statistical data analysis was performed by Mr Phillip Leppard from the University of Adelaide's Department of Statistics. Assistance with clerical matters and advice regarding the typing of this thesis was often sought from staff in the Division of Surgery and was always supplied in a patient and constructive manner. Tribute must be paid in particular to Mrs Sandra Ireland, Ms Lyn Martin and Ms Alison Paget.

This thesis was supervised by Mr Peter Hewett, Head of the Colorectal Surgical Unit and Professor Guy Maddern, the R.P.Jepson Professor of Surgery at The Queen Elizabeth Hospital, both of whom were essential to its success. Mr Hewett was closely involved in many of the studies reported in the thesis and provided constructive and practical advice at all times. Professor Maddern, as well as providing the necessary financial support, supervised the research throughout with regular formal review of progress and considerable informal advice.

Final tribute for the success of this thesis must go to my wife Jodie, who as well as providing enormous moral support throughout the research period, proof-read the manuscript numerous times before it was considered satisfactory for submission.

PREFACE

Some of the work described in this thesis has been published or accepted for publication by peer-reviewed journals. A further five papers have been written and submitted and are, at the time of submission of this thesis, under consideration for publication. These publications are listed below in the order in which they were submitted.

Luck A.J., Hensman I.C., Hewett P.J. (1998) Laparoscopic colectomy for cancer: A review. *Aust N Z J Surg* 68(5):323-332

Luck A.J., Thomas M.L., Roediger W.E.W., Hewett P.J. (1999) Localisation of impalpable colonic polyps with intra-operative ultrasound. *Surg Endosc* (In press)

Luck A.J., Maddern G.J. (1999) Intra-operative abdominal ultrasonography. *Br J Surg* (In press)

Hensman I.C., Luck A.J., Hewett P.J. (1999) Laparoscopic-assisted colonoscopic polypectomy. *Surg Endosc* (In press)

Hunt L., Luck A.J., Rudkin G., Hewett P.J. (1999) Day case haemorrhoidectomy. *Br J Surg* (In press)

Luck A.J., Moyes D., Maddern G.J., Hewett P.J. (1999) Core temperature changes in open and laparoscopic colorectal surgery. *Surg Endosc* (In press)

Luck A.J., Copley J., Hewett P.J. (1999) Ultrasound of colonic neoplasia: An intra-operative tool? *Surg Endosc* (Submitted for publication)

Luck A.J., Hensman I.C., Karatassas A., Hewett P.J. (1999) Laparoscopic reversal of Hartmann's procedure: Technique and preliminary results. *Surg Endosc* (Submitted for publication)

Luck A.J., Hewett P.J. (1999) A pre-emptive, local anaesthetic, ischio-rectal fossa block decreases pain after haemorrhoidectomy: A prospective, randomized, double blind clinical trial. *Dis Colon Rectum* (Submitted for publication)

Luck A.J., Pearson S., Maddern G.J., Hewett P.J. (1999) Video information: Its effects on pre-colonoscopy knowledge and anxiety levels. *The Lancet* (Submitted for publication)

Limb R., Rudkin G., Luck A.J., Hunt L., Hewett P.J. (1999) The pain of haemorrhoidectomy: A prospective study. *Anaes Intens Care* (Submitted for publication)

SECTION I

AIMS

The aim of this thesis is to examine the impact that new technology has had on colorectal surgery, to investigate the application of new technology to the field of colorectal surgery and finally to recommend where appropriate, from the results of the studies reported in the thesis, appropriate protocols for the clinical use or further investigation of the technologies that have been studied. In order to achieve these aims, this thesis must pose and attempt to answer a number of questions.

1.1 Intra-operative ultrasound

How accurate is open intra-operative ultrasound of the liver in the detection of colorectal metastases at the time of primary colorectal resection?

Is laparoscopic intra-operative ultrasound as accurate as the open technique in the detection of colorectal metastases?

How does the accuracy of intra-operative ultrasound compare with that of pre-operative computed tomography and intra-operative inspection and palpation in the detection of hepatic colorectal metastases?

What is the optimal peri-operative protocol for assessment of the liver at the time of primary colorectal resection?

Can accurate images of the colon and colorectal neoplasia be produced by ultrasound?

Under what conditions does ultrasound of the colon produce the best images?

Can ultrasound of the colon be used as an intra-operative tool in the localisation and assessment of colonic neoplastic lesion?

If ultrasound of the colon can localise impalpable lesions, how does it compare with other localisation techniques?

1.2 Laparoscopic colorectal surgery

Is laparoscopic reversal of Hartmann's procedure a feasible and safe procedure?

Does laparoscopic reversal of Hartmann's procedure provide any of the short-term post-operative patient benefits that have been reported with other minimal access procedures?

Can polyps deemed unsuitable for conventional colonoscopic polypectomy be excised by laparoscopic-assisted colonoscopic polypectomy?

Is laparoscopic-assisted colonoscopic polypectomy a safe procedure?

What is the incidence of hypothermia during laparoscopic colorectal surgery?

How does this incidence compare with the incidence of hypothermia during open colorectal surgery?

Does the use of the Bair Hugger™ forced-air warming device decrease the incidence of hypothermia during prolonged laparoscopic surgery?

Are there any patient demographic criteria that impact on the incidence of hypothermia during surgery?

1.3 Advanced prognostic techniques in colorectal cancer

What is the sensitivity of conventional cytology in the detection of small numbers of free intra-peritoneal malignant cells at the time of colorectal cancer resection?

Is immunocytochemistry, using the best known markers, Ber-EP4 and AUA 1, more sensitive than conventional cytology for this purpose?

Can immunobead reverse transcriptase-polymerase chain reaction (RT-PCR) of peritoneal washings taken during colorectal cancer resection detect cells that are undetectable by other techniques?

Could the results of immunobead RT-PCR of peritoneal washings be a separate prognostic indicator in adenocarcinoma of the colon and rectum?

Can immunobead RT-PCR of peritoneal washings identify a subset of colorectal cancer patients who have a poor prognosis, despite having early stage disease?

1.4 Ambulatory anal surgery

Can ligation excision haemorrhoidectomy be performed as day surgery?

What are the readmission and short-term complication rates of day case haemorrhoidectomy?

What is the level of patient satisfaction with a day case haemorrhoidectomy project?

Can a multi-modal post-operative analgesic regime control pain after haemorrhoidectomy?

At what times in the post-operative period do haemorrhoidectomy patients have the most pain and require the most analgesia?

Are there any patient characteristics that influence the level of pain reported after haemorrhoidectomy?

What is the effect of a pre-emptive, local anaesthetic, ischio-rectal fossa block on the pain levels and analgesia requirements of post-operative haemorrhoidectomy patients?

Is pain at the time of the first bowel action after haemorrhoidectomy reduced by the bowel action occurring early in the post-operative period?

What is the healing rate of chronic anal fissures treated with topical glyceryl trinitrate paste?

What is the recurrence rate after such treatment?

How does the healing rate for glyceryl trinitrate compare with that produced by lateral sphincterotomy?

Can healing of a fissure with glyceryl trinitrate be predicted by the amount of pain experienced by the patient early in the treatment regime?

What is the ideal management protocol for patients with chronic anal fissures?

1.5 Patient information by video

What demographic criteria are associated with an increase in anxiety prior to colonoscopy?

What is the impact of an information video on the anxiety levels of patients scheduled to undergo colonoscopy?

Does the value of an information video depend on the initial level of anxiety experienced by the patient?

Can an information video increase the short-term recall of patients regarding the purpose, procedural details and potential complications of colonoscopy?

SECTION II

INTRODUCTION

2.1 Intra-operative ultrasound

2.2 Laparoscopic colorectal surgery

2.3 Advanced prognostic techniques in colorectal cancer

2.4 Ambulatory anorectal surgery

2.5 Patient information by video

Technological advances have impacted on all aspects of surgical practice. For example, advances in surgical instrumentation occasionally lead to changes in technique. These changes may be subtle, such as the introduction of a better needle holder or a more advanced self-retaining retractor, or they may be profound, such as the advent of diathermy to control bleeding, or the introduction of laparoscopy into general surgical practice. In colorectal surgery, the introduction of surgical staplers, and in particular the circular end-to-end stapler for low rectal anastomoses, has had an enormous impact on the surgical technique for low and ultra-low anterior resection.

The impact of technology on surgery is also felt away from the operating table. Modern anaesthesia and intensive care technology allow surgeons to perform complex procedures with minimal mortality and morbidity in comparison to that which has been possible in the past. Advanced drug technology, in particular the advent of antibiotics, anti-ulcer medication and deep venous thrombosis prophylaxis, has caused revolutionary changes to surgical practice in the past, and continues to do so.

In the diagnosis of surgical disease, improvements in organ imaging technology has brought about the introduction of ultrasound, computed tomography and magnetic resonance imaging, all of which can now produce three dimensional images, and all of which have had a profound influence on surgical practice.

In this thesis, various aspects of more recent technological advances are assessed in terms of their applicability and potential impact on the practice of colorectal surgery. The thesis is divided

into five sections each covering an area of colorectal surgical practice.

In the first section, the role of intra-operative ultrasound in colorectal surgery is evaluated. This evaluation involves two studies. The first study assesses the accuracy of intra-operative ultrasound of the liver in the detection of secondary deposits from colorectal cancer at the time of resection of the primary lesion. The second study is a preliminary assessment of the new technique of intra-operative ultrasound of the colon.

The second section is dedicated to laparoscopic colorectal surgery. The results of two procedures, laparoscopic reversal of Hartmann's procedure and laparoscopic-assisted colonoscopic polypectomy, are presented and discussed. The impact of laparoscopic surgery on the incidence of hypothermia during colorectal surgery is also investigated.

An advanced technique for the assessment of prognosis in patients with colorectal cancer, developed at The Queen Elizabeth Hospital, is evaluated in the third section. This technique is designed to detect small numbers of malignant cells in the peritoneal cavity before and after colorectal resection for malignancy.

The impact of ambulatory surgery on colorectal surgery, and in particular anal surgery, is addressed in the fourth section. This involves reporting the evolution and results of a day case project for ligation excision haemorrhoidectomy. In addition, this thesis reports the interim results of the randomised comparison of a

pharmacological treatment for anal fissure, glyceryl trinitrate paste, with the standard surgical procedure, lateral sphincterotomy.

The fifth section discusses the potential that new technology may have in the imparting of essential information to our patients. This is done by a randomised assessment of the value of an information video in increasing knowledge and decreasing anxiety in patients scheduled to undergo colonoscopy.

2.1 Intra-operative Ultrasound

Ultrasound consists of mechanical sound waves oscillating at a frequency higher than that audible by the human ear (Kremkau 1993). Medical ultrasound waves oscillate at frequencies between 1 and 30 Megahertz (MHz- millions of cycles per second). Different tissues cause variations in the echo produced by the ultrasound waves and allow images of internal organs to be created.

Percutaneous ultrasound of the intra-abdominal organs is limited in its ability to produce high quality images. Firstly the sound waves must traverse the body wall in order to image the appropriate organ. Ultrasound image resolution improves with increased frequency of the sound wave, whereas penetration decreases with frequency. Percutaneous ultrasound transducers must use a relatively low frequency (usually 3.5 MHz) to achieve adequate tissue penetration, with a subsequent decrease in image resolution and quality. Secondly, ultrasound cannot traverse gas. Ultrasound of organs that require the sound waves to pass through bowel often produces images that are suboptimal.

The use of ultrasound during abdominal surgery has the potential to overcome these difficulties. By placing the transducer directly onto the surface of the organ to be imaged, high frequencies can be used with much improved image quality. Intervening bowel loops can also be avoided.

The use of intra-operative abdominal ultrasound was first reported by Schlegel et al in 1961 to localise renal calculi and by Knight and Newell in 1963 to diagnose choledocholithiasis at

cholecystectomy. These groups and other early workers in the field used A-mode ultrasound. A-mode ultrasound presents a one-dimensional image on a monitor screen by displaying the amplitude of the returning echo along the vertical axis and the distance from the transducer along the horizontal axis (Steigmann and McIntyre 1993). Intra-operative A-mode ultrasound is only able to detect interfaces with large differences in their echo pattern and is not easily performed or interpreted. It did not achieve widespread application in the intra-operative setting.

The advent of high resolution, high frequency B-mode transducers in the late 1970's led to renewed interest in the possible applications of intra-operative abdominal ultrasound. B-mode ultrasound displays the images on a screen using a grey-scale where the brightness of the image varies with the amplitude of the corresponding echo (Machi and Sigel 1996). By providing images at approximately 25 per second, the display effectively appears as a real-time representation of the organ being scanned. High quality images of real time anatomy and pathology are possible with 5, 7.5 and 10 MHz intra-operative B-mode ultrasound probes.

Ultrasound of solid organs during abdominal surgery is widely reported to be of value. In liver resection for malignancy, ultrasound has been shown to detect lesions not found by pre-operative investigation or liver palpation in 9.5-28% of patients and to modify surgical strategy in up to 50% of cases (Gozzetti et al 1986, Castaing et al 1986, Parker et al 1989). In pancreatic surgery, ultrasound is reported to be the most sensitive technique for the localisation of islet cell tumours (Angelini et al 1987, Norton et al 1990, Docherty et al 1991). It is also more accurate than pre-

operative techniques in determining the resectability of pancreatic adenocarcinoma (Plainfosse et al 1987, Machi et al 1993). Ultrasound is of value during surgery for the complications of chronic pancreatitis, particularly in the localisation of the pancreatic duct and the detection of small lesions, such as pseudocysts, that were not detected with pre-operative investigations (Sigel et al 1987, Printz et al 1992). The addition of laparoscopic ultrasound to staging laparoscopy has significantly increased the accuracy of the latter technique in the assessment of unresectable malignancy, particularly of the liver (John et al 1994, Barbot et al 1994) and pancreas (John et al 1995, Pietrabissa et al 1996).

In this thesis, the application of intra-operative ultrasound to colorectal surgery is evaluated. The first study investigates the accuracy of intra-operative ultrasound in the detection of liver metastases at the time of primary colorectal resection. The second study consists of the evolution and assessment of an intra-operative colonic ultrasound technique.

The detection of colorectal hepatic metastases

The accurate staging of colorectal malignancy at the time of resection of the primary lesion allows appropriate planning of post-operative management. As the liver is the organ affected most commonly by blood borne metastases from colorectal cancer, staging must involve assessment of the liver. In patients who have undergone colorectal resection with an intent to cure (ie with no evidence of residual locoregional disease), subsequent resection of

isolated liver secondaries has been shown to improve survival in selected cases (Scheele et al 1990).

Assessment of liver involvement by colorectal malignancy has traditionally involved intra-operative inspection and palpation of the liver during laparotomy. Percutaneous ultrasound, computed tomography, angiography and more recently magnetic resonance imaging have all been investigated as possible pre-operative staging investigations (Alderson et al 1983, Schreeve et al 1984). Neither separately nor in combination do these techniques match the sensitivity of inspection and palpation at laparotomy by an experienced surgeon (Forster and Lundy 1981, Smith et al 1982).

The sensitivity of intra-operative ultrasound of the liver, at the time of resection of the primary colorectal cancer, in the detection of liver metastases has recently been the subject of several large series (Table 2.1.1). In all series, intra-operative ultrasound was the single most sensitive modality in the detection of these lesions. Between 4 and 14% of hepatic metastases from colorectal cancer were only detectable by intra-operative ultrasound (Table 2.1.2).

Laparoscopic techniques have been used to resect colon and rectum for malignancy in selected centres since 1991 (Schlinkert 1991). The inability of the laparoscopic surgeon to palpate the liver may increase the importance of laparoscopic hepatic ultrasound in the detection of liver metastases. Reports on the use of laparoscopic ultrasound for this purpose are, however, scarce. Hartley et al (1996) reported, without data, the use of a flexible tipped laparoscopic ultrasound probe, in conjunction with split image

video-laparoscopy, for hepatic assessment during laparoscopic surgery for colorectal cancer. This group was encouraged by their early results and is currently performing prospective studies.

TABLE 2.1.1:

Published series comparing the sensitivity (%) of pre-operative investigations, operative assessment and intra-operative ultrasound in the detection of hepatic metastases at the time of colorectal resection for adenocarcinoma.

Legend:
US = pre-operative percutaneous ultrasound
CT = computerised tomography
ART = arteriography
MRI = magnetic resonance imaging
OP = intra-operative inspection and palpation
IOUS = intra-operative ultrasound

TABLE 2.1.1

AUTHOR	No. patients	US	CT	ART	MRI	OP	IOUS
Castaing 1986	98	68	66	38	–	77	79
Boldrini 1987	86	76	76	–	–	86	100
Parker 1989	42	–	77	–	–	–	98
Clarke 1989	54	76	61	52	–	60	100
Olsen 1990	213	66	–	–	–	66	98
Machi 1991	186	41	47	–	–	66	93
Stewart 1993	100	58	65	–	–	76	94
Knol 1993	51	–	81	–	–	94	97
Machi 1996	250	41	49	–	–	66	94
Staren 1997	59	33	67	–	45	87	98

TABLE 2.1.2:

Published series reporting the percentage of hepatic metastases from colorectal cancer that were only detected by intra-operative ultrasound (IOUS).

TABLE 2.1.2

AUTHOR	YEAR	% IOUS ONLY
Russo	1989	7.1
Olsen	1990	9.9
Machi	1991	9.5
Stewart	1993	4.0
Stone	1994	5.4
Leen	1996	6.5
Staren	1997	14.0

Intra-operative ultrasound of the colon

The value of percutaneous ultrasound of the colon is limited by the inability of the sound waves to traverse gas. Despite this, its use has been reported to be of value in the diagnosis and assessment of acute diverticulitis (Scwerk et al 1992, Zielke et al 1997), the detection of strictures in inflammatory bowel disease (Sonnenberg et al 1982, Limberg 1990) and evaluation of the colonic changes of cystic fibrosis (Haber et al 1997).

The use of percutaneous ultrasound in the diagnosis of colonic neoplastic disease has also been reported in case reports (Schabel et al 1978, Sianesi et al 1984) and evaluated in small series (Price and Metreweli 1988, Shirahama et al 1994). Accurate results were only obtained when the cancer was advanced. The addition of retrograde installation of water into the colon for hydrocolonic ultrasonography has been reported in the detection of small colonic lesions (Ling et al 1995). Chui et al (1994), in a well designed, blinded trial, concluded that the usefulness of this technique appeared to be limited.

The introduction of high frequency, high-resolution ultrasound probes for intra-operative use allows placement of the transducer directly onto the serosa of the colon and compression of the colon to improve the quality of the image produced. Such a technique would allow the intra-operative assessment of colorectal neoplasia. The accuracy and potential role of this technique is yet to be defined. There is a theoretical role for this technique in the localisation and assessment of impalpable colonic lesions.

The majority of colonic neoplasms are either easily palpable at laparotomy or benign and amenable to colonoscopic resection. Between these extremes, there is a subset of large adenomata and small carcinomas that cannot be excised endoscopically but are impalpable at the time of surgery. If the lesion has been diagnosed by colonoscopy, there may be considerable disparity between the position where the lesion is thought to be situated and its actual position (Hancock and Talbot 1995). 'Blind' resection of the segment of colon thought to contain the lesion has been reported to lead to resection of the wrong section of colon (Monson et al 1992, Fielding et al 1997).

These lesions therefore require intra-operative localisation. If the resection is to be performed laparoscopically, the number of lesions requiring localisation is increased. Current strategies to deal with this problem include intra-operative colonoscopy (Sakanoue et al 1993), pre-operative localisation by contrast enema (Hill et al 1993) and marking of the colonic wall adjacent to the lesion at the time of pre-operative colonoscopy (Kitamura et al 1995). The use of intra-operative ultrasound to localise such lesions has not been reported.

Ultrasound is establishing a role during colorectal surgery for malignancy as it is the most sensitive technique in the assessment of the liver for metastases. It is therefore available in the operating theatre at this time. If ultrasound could be shown to be accurate in the localisation of impalpable colonic lesions, it would provide a most convenient localisation tool.

2.2 Laparoscopic Colorectal Surgery

Laparoscopic cholecystectomy, first performed in France in 1987 (Dubois et al 1990), has become the gold standard of treatment for symptomatic cholelithiasis. Many studies have shown improved post-operative comfort, earlier discharge from hospital, earlier return to work following surgery and a better cosmetic outcome in comparison to open cholecystectomy (Southern Surgeons Club 1991, Cuschieri et al 1992). Laparoscopic techniques have subsequently been applied to a wide range of intra-abdominal procedures and have become popular in the performance of appendicectomy (Attwood et al 1992), inguinal hernia repair (Corbitt 1993) and Nissen fundoplication (Hinder and Filipi 1992).

The use of laparoscopic techniques in the field of colorectal surgery followed soon after the early success of laparoscopic cholecystectomy, with the first case reports published in 1992 (Miller et al 1992, Berman 1992). All elective and many emergency colorectal procedures have been performed laparoscopically. In addition, laparoscopy has changed the management of selected colorectal patients with the evolution of techniques such as the laparoscopic management of colonoscopic perforation (Mehdi et al 1996, Miyahara et al 1996) and laparoscopic-assisted colonoscopic polypectomy (Beck and Karulf 1993, Averbach et al 1995).

The expected benefits of minimally invasive surgery are provided by laparoscopic colorectal procedures, although to a lesser extent than that seen with other procedures. This is thought to be because laparoscopic colorectal surgery requires dissection in more than one quadrant and, in the case of colon resection, a small

incision, usually of muscle-splitting or Pfannensteil type, is required for removal of the specimen. Nevertheless, a slight advantage to the laparoscopic groups in terms of reduced post-operative pain, earlier discharge from hospital and earlier return of bowel function has been reported (Phillips et al 1992, Milsom et al 1994). The difference in immediate post-operative patient benefit between open and laparoscopic techniques is most clearly shown in elective, non-resectional surgery such as mesh rectopexy for rectal prolapse (Darzi et al 1995), the creation of colostomy and ileostomy (Lyerly and Mault 1994, Ludwig et al 1996) and reversal of Hartmann's procedure (Gorey et al 1993).

Laparoscopic reversal of Hartmann's procedure

Sigmoid colon resection and formation of end colostomy (Hartmann's procedure) is commonly performed in the operative management of free perforation of the distal colon. Subsequent restoration of intestinal continuity can be challenging, due to adhesions from the original septic process and surgery. Most series report a significant morbidity and even mortality is associated with reversal of Hartmann's procedure (Sweeney and Hoffman 1987, Roe et al 1991, Mealy et al 1996). Such data has led some authors to advocate primary anastomosis with transverse colostomy as an alternative to Hartmann's procedure (Maddern et al 1995). Hartmann's procedure is however still the operation of choice of most surgeons in the presence of purulent or faeculent peritonitis (Wedell et al 1997).

A number of the complications of open Hartmann's reversal are wound related, including wound infection (7-16%; Mosdell and Doberneck 1991, Khan et al 1994) and incisional hernia (8-10%; Mealy et al 1996, Khoury et al 1996). The reported incidence of pulmonary complications (10%; Mosdell and Doberneck 1991) may also be attributable to the pain caused by a long midline abdominal wound leading to poor respiratory effort.

The use of laparoscopic techniques for reversal of Hartmann's procedure obviates the need for the midline abdominal wound and has the potential to reduce the incidence of wound related complications. Minimisation of manual handling of the bowel may also allow a more rapid return to full bowel function and earlier hospital discharge.

Laparoscopic-assisted colonoscopic polypectomy

Adenomatous polyps found at colonoscopy require excision for diagnosis and to prevent future malignant change. The majority of such polyps are successfully treated with a diathermy snare at the time of colonoscopy. Primary excision using the colonoscope has an unacceptable risk of perforation due to the size and/or location of the polyp in some cases (Webb et al 1985). In these instances it is usual to proceed to colectomy.

Observation of the serosal surface of the colon via laparoscopy at the time of polypectomy allows assessment of the perforation risk in difficult cases and may provide an alternative method of managing a select group of polyps unsuitable for primary

colonoscopic polypectomy.

Core temperature changes during open and laparoscopic colorectal surgery

The advent of laparoscopic surgery has led to a re-evaluation of peri-operative physiological changes and to an assessment of the differences in these parameters between open and laparoscopic surgery. Schauer and Schwesinger (1995) measured the cardiovasular changes associated with pneumoperitoneum and reported a decrease in cardiac output by as much as 30% with insufflation. Mansour et al (1992) measured the neuroendocrine stress response after minimally invasive surgery and found little difference in cortisol, insulin, glucagon and ACTH between the open and laparoscopic groups in a pig model. Senagore et al (1995) investigated the effects of earlier feeding on the nitrogen balance of post-operative patients and found that laparoscopic-assisted colectomy provides earlier return to pre-operative nitrogen balance. The incidence and significance of hypothermia during prolonged laparoscopic surgery has not been reported.

Inadvertent heat loss during surgery may have substantial pathophysiological sequelae. Patients who are subjected to peri-operative hypothermia have been reported to have an increase in peri-operative oxygen consumption (Makinen 1997), peripheral vasoconstriction (Frank et al 1995), impairment of coagulation capability (Burch et al 1997) and impairment of myocardial contractility (Frank et al 1994) in comparison to normothermic controls. Kurz et al (1996) showed, in a randomised, double-blind

trial that peri-operative hypothermia is an independent factor that increases the incidence of post-operative wound infection.

During open abdominal surgery without precautionary warming methods, it has been shown that inadvertent hypothermia occurs below 36.0°C in 50-70% of patients and below 35.0°C in up to one third of patients (Frank et al 1994). Multiple strategies have been employed to reduce intra-operative heat loss during laparotomy, including the warming of both intravenous and irrigation fluids. Forced-air warming devices, in particular the Bair Hugger™ (Augustine Medical, Eden Prairie MN), are currently recognised as the most effective tool in avoiding heat loss during open abdominal surgery (Giesbrecht et al 1994, Karayan et al 1996).

An anticipated advantage of laparoscopic surgery was a decrease in the incidence of hypothermia, because heat loss from the exposed abdominal contents is not a factor. Available data, although scarce, does not support this theory. Makinen (1997) could show no difference in the incidence of peri-operative hypothermia between non-randomised groups of patients undergoing open and laparoscopic cholecystectomy. Salzberg Moore et al (1997) stated that "hypothermia appears to be an even more common problem during laparoscopic surgery" although data to this effect are not provided. Bessell et al (1995) showed in a porcine model that pneumoperitoneum (using either cold or heated gas) caused significant temperature drop in comparison to anaesthesia alone. Comparison to laparotomy was not performed.

A direct comparison of the incidence of hypothermia in open and laparoscopic colorectal surgery has not been reported. There is also no report to date of the value or otherwise of the forced-air warming device in prolonged laparoscopic surgery.

2.3 Advanced prognostic techniques in colorectal cancer

Adenocarcinoma of the colon and rectum is the second commonest cause of death from cancer in the western world, accounting for 14 and 16 percent of cancer deaths in men and women respectively (O'Brien 1988). Whilst surgery is the mainstay of treatment, there is a role for chemotherapy and/or radiotherapy in selected patients. In order to plan an appropriate management plan for a patient with colorectal cancer, an estimate of the expected prognosis is required.

Staging systems

The extent of tumour invasion and spread (tumour stage) is established as the single most significant prognostic variable in colorectal cancer (Deans et al 1992). The relationship between extension of disease and prognosis was first noted by Lockhart-Mummery in 1927. Cuthbert Dukes incorporated this concept into a pathological staging system in 1932.

Dukes' original staging classification was for rectal carcinoma only and comprised three stages;

Dukes' A: Growth limited to the rectal wall

Dukes' B: Extension of growth to extra-rectal tissues but no metastases in regional lymph nodes

Dukes' C: Metastases in regional lymph nodes.

Stage C was subsequently subdivided into C_1, where only regional lymph nodes are involved and C_2 where nodal spread was to the level of the point of ligature of the blood vessels (Gabriel et al 1935). The classification was soon applied to colonic as well as rectal tumours (Simpson and Mayo 1939). There is a significant reduction in 5-year survival with increasing Dukes' stage and it has proved an excellent prognostic tool. Modifications of Dukes' system, by Kirklin et al in 1949 and Astler and Coller in 1954 have only served to complicate the pathological staging system and are rarely used in 1998.

The major deficiencies of the pathological classification proposed by Dukes are firstly that it does not take clinical variables into account and secondly that there is no separate stage for cancers that have produced distant metastases or are not completely resectable at the time of surgery. In an attempt to overcome these deficiencies, several clinicopathological staging systems have been developed. The most recognised of these is the Tumour-Node-Metastasis (TNM) classification (UICC committee on TNM classification 1966). This classification is considered by many to be too complex for routine use. In Australia, the Australian Clinico-Pathological Staging System (ACPS) was developed and published in 1983 by Davis and Newland. This is an elegant staging classification, which overcomes the above deficiencies in Dukes' classification, but it is rarely used internationally. In 1998, the staging classification of Dukes is still considered the 'gold standard' against which all other prognostic classifications in colorectal cancer should be assessed.

Early stage, but poor prognosis, colorectal cancer

Patients with Dukes' A or B tumours are potentially curable by surgery alone, as there is no pathological evidence of spread outside of the bowel. The 5 year survival figures for these patients is however not 100%, being approximately 90% for Dukes' A lesions and 70% for Dukes' B lesions (South Australian Cancer Registry 1996). This data suggests that there is a subset of patients with early stage colorectal cancer who have a poor prognosis.

Adjuvant chemotherapy has been shown to result in a 40% reduction in cancer recurrence and a 30% reduction in mortality for Dukes' stage C colorectal cancer (Moertel 1994). It is possible that patients with poor prognosis early stage colorectal cancer may also benefit from adjuvant chemotherapy, if they can be identified.

The prognostic significance of numerous pathological variables have been assessed in an attempt to improve on Dukes' classification and to sub-classify early stage lesions. These include tumour size (Cohen et al 1983), lymphatic invasion (Agrez et al 1988), mucinous tumours (Jass et al 1986), vascular invasion (Talbot et al 1980, Krasma et al 1988), histological grade (Halvorsen and Seim 1988), involvement of the lateral resection margin (Quirke and Dixon 1988), the presence of silver-binding nucleolar organising regions (Griffiths et al 1989) and tumour markers such as carcino-embryonic antigen (Blake et al 1982) and CA 19-9 (Kuusela et al 1984). Only histological grade, invasion of large extramural veins and, in the case of rectal cancer, involvement of lateral resection margins are consistently shown to have prognostic significance in addition to Dukes' classification in

a regression analysis model (Deans et al 1992).

Advances in molecular biology, coupled with an increasing knowledge of cancer genetics have encouraged research workers to attempt firstly to identify small numbers of malignant cells in peripheral blood (Eaton et al 1997), bone marrow (Soeth et al 1996) and lymph nodes (Noguchi et al 1994, Nakamori et al 1997) and then to assess the prognostic value of their findings. It is possible that advanced techniques such as these may hold the key to identifying patients with early stage, but poor prognosis colorectal cancer.

Immunobead reverse transcriptase-polymerase chain reaction (RT-PCR)

Research workers in the Division of Surgery and the Department of Haematology/Oncology at The Queen Elizabeth Hospital have developed a technique for identifying carcinoma cells in blood and other body fluids using immunomagnetic beads to enrich for epithelial cells and then reverse transcriptase-polymerase chain reaction to identify a tumour-specific or tissue-specific marker (Hardingham et al 1993). Immunobead RT-PCR is capable of detecting one tumour cell per 5-10 million white blood cells.

This technique was used in a pilot study of 27 colorectal cancer patients, whose tumour was positive for a K-ras mutation (Hardingham et al 1995). Nine of 27 patients were found to have cells carrying this marker in their peripheral blood. Seven of the nine relapsed and died within two years of diagnosis compared to

2/18 patients who were negative for tumour cells ($p<0.0001$). Five of the patients with circulating tumour cells were classified as early stage. Although encouraging, the technique cannot be used routinely because only 35% of colorectal cancers carry the K-ras mutation. Subsequent energies have been directed towards the identification of tissue-specific proteins which may be of use as markers of epithelial cells and the assessment of more specific tumour markers.

Tissue-specific markers (for epithelial cells)

1. CYTOKERATINS CK-19 AND CK-20

Cytokeratins are intermediate filament proteins and form a major component of the cytoskeleton. Messenger RNA for cytokeratins is found in epithelial tissues. CK-19 is found in a broad range of epithelial tissues including both normal and malignant colonic mucosa (Gunn et al 1996). CK-20 is reported to be restricted to the epithelial cells of the gastrointestinal tract, taste buds and Merkel cells (Burchill 1995, Denis 1997). It has not been reported in non-epithelial tissues.

Detection of cells by the presence of cytokeratins, in particular CK-20, will identify epithelial cells in bone marrow, lymph nodes or pre-operative blood samples, where epithelial cells are not usually present. In a patient with colorectal cancer, these cells are likely to be malignant cells.

2. MUCIN 2

Mucins are large molecular weight glycoproteins with branching carbohydrate side chains. Mucin 2 is synthesised by glandular epithelial tissue and is present in up to 40% of normal colon epithelium. It has been shown to be overexpressed in 100% of mucinous adenocarcinomas of the colon (Hanski et al 1997). Detection of Mucin 2 will identify epithelial cells from glandular tissue in distant sites. Detection of this marker from multiple sites in a patient with mucinous adenocarcinoma of the colon is highly suggestive of micrometastatic disease.

Tumour-specific markers (for colorectal cancer)

The use of epithelial cell markers as markers of malignancy requires the assumption that any epithelial cells present in the specimen are malignant. In pre-operative specimens of blood and bone marrow and in lymph nodes, this assumption may be sustainable. It would, however, be preferable to use a tumour marker known to be present in colorectal cancer cells. The use of a tumour marker would also allow the technique to be used for specimens likely to be contaminated with normal epithelial cells, such as post-operative blood samples and peritoneal washings taken at the time of surgery.

1. LAMININ 5 (GAMMA-2 CHAIN)

Laminins are a family of basement proteins with a role in cell differentiation, adhesion and migration (Tryggvason 1993). Laminin 5 is a laminin isoform that is a functional adhesion component for

epithelial cells and is composed of a heterotrimeric molecule of gamma-2, beta-3 and alpha-3 chains (Burgeson et al 1994). The gamma-2 chain of laminin 5 has been shown to be preferentially expressed in invading malignant cells in human colorectal cancer.

Pyke et al (1994) showed that 16/16 colorectal cancers were positive for laminin 5 gamma-2 chain expression by in-situ hybridisation. Expression was shown to be confined to tumour cells, with the highest expression at the invading front. The same group later confirmed this result using immunocytochemistry, which also showed that the marker was in the tumour cells and not in surrounding stromal cells (Pyke et al 1995).

2. MATRILYSIN

There is accumulating evidence that the matrix metalloproteinases, which degrade the extracellular matrix, play a causal role in tumour progression (Itoh 1996). Most matrix metalloproteinases have been shown to be present in surrounding stromal cells as well as tumour cells and are therefore not suitable for use as tumour markers in distant sites.

The exception appears to be matrixmetalloproteinase-7 or matrilysin. Matrilysin has been shown to be present in high levels in colorectal cancers but not in polyps, ulcerative colitis or normal colon (Itoh et al 1996). Yoshimoto et al (1993) studied expression of matrilysin using RT-PCR and found expression in 9/10 tumours and 0/10 adjacent normal colonic mucosa.

Detection of free malignant cells in the peritoneal cavity before and after resection of colorectal cancer

The association between large numbers of free intra-peritoneal colorectal cancer cells and reduced survival is well established. At its extreme, the presence of malignant ascites is considered evidence of disseminated disease. Lesser numbers of free malignant cells are also significant with inadvertent spillage of tumour cells at surgery for rectal cancer shown by Zirngibl et al (1990) to increase local recurrence rate from 21% to 51% ($p<0.001$) and to decrease 5-year survival from 70% to 44% ($p<0.01$). This data corroborated the earlier work of Slaentz (1984), who reported an increase in local recurrence from 23% to 73% ($p<0.001$) if the tumour was breached during surgery. This group also reported a decrease in 5-year survival from 54% to 13% under these circumstances, but did not subject this data to statistical analysis.

The significance of small numbers of free malignant cells in colorectal cancer is less well established. The main reason for this may be that a technique sensitive to detect small numbers of malignant cells has not been available. Conventional cytology has a low sensitivity in the detection of small numbers of malignant cells unless large volumes of peritoneal wash, such as the 400ml used by Leather et al (1994) are used. This necessitates several hours of centrifugation, and as such is somewhat impractical. Solomon et al (1997) avoided this pitfall by pressing cytology slides directly onto the serosal surface of the tumour. They reported 15/103 patients were positive for malignant cells. Whilst this technique has merit, it is not possible to assess for cells that are present only after completion of the resection.

The use of immunocytochemistry has been reported to be of value in diagnosing malignant cells in peritoneal fluid, particularly with the monoclonal antibodies Ber-EP4 and AUA-1 (Leather et al 1994). This technique required centrifugation, followed by the assumption that malignant cells only were in the heaviest layer of the specimen. Such an assumption raises concerns regarding the specificity of the technique.

It is possible that the technique of immunobead reverse transcriptase-polymerase chain reaction, using a panel of markers that includes tissue specific markers for epithelial cells and markers thought to be tumour specific for colorectal cancer, may be able to accurately assess peritoneal washings for malignant cells. The results of this investigation may identify a population of patients who have a worse prognosis than can be identified by staging alone.

2.4 Ambulatory anal surgery

The concept of ambulatory surgery (day surgery) is relatively new. Until recently, patients were kept in hospital after surgery until they achieved pre-operative activity levels. In the 1990's, there has been a re-evaluation of the appropriate length of the post-operative hospital stay for all procedures. This re-evaluation has been largely driven by economic considerations. As hospital budgets tighten, the expense of an acute care hospital bed cannot be justified for patients who have recovered from the immediate post-operative period and are convalescing.

All aspects of surgery, including anorectal surgery, have required reconsideration in the light of these economic constraints. Whether a condition can be appropriately alleviated by a less invasive procedure or even by medical means has been re-evaluated. In the case of haemorrhoidectomy, the efficacy of procedures such as rubber band ligation (Murie et al 1982), schlerotherapy (Santos et al 1993), infrared photocoagulation (Dennison et al 1988) and cryotherapy (Kaufman 1976) have all been compared to operative haemorrhoidectomy. The surgical management of high rectal adenomas and early carcinomas, which in the past would have required anterior resection, by trans-anal endoscopic microsurgery has been reported (Mentges et al 1996, Winde et al 1996).

Discussion of the gold standard management of anal fissure previously involved the relative merits of surgical procedures such as anal stretch or lateral sphincterotomy (Fischer et al 1978, Jensen 1984), the appropriate position for the sphincterotomy (lateral vs dorsal; Hawley 1969, Abcarian 1980) or comparison of the open and

closed techniques of sphincterotomy (Garcia-Aguilar et al 1996). The introduction of medications that can treat chronic anal fissure without surgery has revolutionised this argument. Most current research is directed at establishing the efficacy of botulinum toxin or glyceryl trinitrate paste in the management of this condition.

In conditions where the 'traditional' procedure is still considered the treatment of choice, clinical and research energies have been directed towards minimising the post-operative hospital stay. In the case of many minor procedures, the safety and feasibility of admission, operation and discharge on the same day have been evaluated. Successful day case projects for hernia repair (Gilbert 1995, Bessell et al 1996), varicose vein surgery (Dimakakos et al 1995) and laparoscopic cholecystectomy (Singleton et al 1996) have been reported.

Several aspects of the changing face of post-operative management in anal surgery are evaluated in this thesis. In the first section, the evolution and results of a day case haemorrhoidectomy project are reported and discussed. In the second section, the interim results of a randomised comparison between glyceryl trinitrate paste and lateral sphincterotomy in the management of chronic anal fissure is presented.

Day Case Haemorrhoidectomy

Haemorrhoidal disease is the consequence of the distal displacement of the anal cushions, which are normal structures with an important role in continence (Loder et al 1994). Symptoms

caused by haemorrhoids include bleeding, particularly with or after a bowel action, pain from thrombosis or strangulation, and prolapse. Haemorrhoids are classified according to the degree of prolapse (Dennison 1988). First degree haemorrhoids do not prolapse, second degree haemorrhoids prolapse with defaecation but reduce spontaneously, third degree haemorrhoids prolapse with defaecation and require manual reduction and fourth degree haemorrhoids are permanently prolapsed.

Ligation excision haemorrhoidectomy was first described by Milligan et al in 1937. Alternative treatment methods for haemorrhoids such as rubber band ligation (Murie et al 1982), sclerotherapy (Santos et al 1993), infrared photocoagulation (Dennison et al 1988) and cryotherapy (Kaufman 1976) have at times been successfully used for first and second degree haemorrhoids. All have been shown to be inferior to haemorrhoidectomy in the management of third and fourth degree haemorrhoids (Lewis et al 1988, MacRae and McLeod 1995).

The surgical technique for haemorrhoidectomy has also been modified in an attempt to lessen post-operative pain and allow earlier patient discharge. Suture haemorrhoidectomy was first reported by Farag in 1978 and was revisited as a day surgery alternative by Patel and O'Connor in 1996. Diathermy haemorrhoidectomy (Seow-Choen et al 1992, Andrews et al 1993) and the use of both the carbon dioxide (Hogson and Morgan 1995) and Nd:YAG (Senagore et al 1993) laser for haemorrhoid dissection have also been reported. None of these techniques have been shown to be superior to ligation excision haemorrhoidectomy.

Ligation excision haemorrhoidectomy is thus still considered by most surgeons to be the gold standard procedure in the management of prolapsing haemorrhoids. In order to achieve ambulatory management of haemorrhoids, the aspects of ligation excision haemorrhoidectomy which have to date precluded same day discharge require re-evaluation.

Analgesia for haemorrhoidectomy

It is the reputation of ligation excision haemorrhoidectomy as a procedure that produces severe post-operative pain, especially at the time of the first post-operative bowel action, that has caused it to remain an inpatient procedure in most institutions. An average post-operative inpatient stay of three to fours days is reported (Johnstone and Ibister 1992, Andrews et al 1993, Senagore et al 1993). The key to the successful introduction of haemorrhoidectomy into the day surgery setting is the control of post-operative pain.

Several innovative concepts have been evaluated in an attempt to control post-haemorrhoidectomy pain and allow same day discharge. Goldstein et al (1993) reported on the use of a subcutaneous morphine pump for haemorrhoidectomy patients. Kilbride et al (1994) showed that transdermal fentanyl improved the management of post-haemorrhoidectomy pain. Delivery of this medication in this fashion in the post-operative setting is not recommended because of a long half-life and the risk of respiratory depression (Bernstein and Klauser 1994). The non-steroidal anti-inflammatory medication ketorolac has also been reported to facilitate ambulatory haemorrhoidectomy as an intra-sphincteric

injection at the completion of surgery (Richman 1993, O'Donovan et al 1994).

Both spinal (Petros and Bradley 1990) and caudal (Pybus et al 1983) have been reported to achieve good control of immediate post-operative pain after haemorrhoidectomy. These techniques are reported to produce a high rate of post-operative urinary retention (up to 70%; Salvati and Kleckner 1957, Scoma 1975, Prasada and Abcarian 1978, Petros and Bradley 1990). They could not therefore be considered for a day surgery project.

Multi-modal analgesic regimes, the combination of two or more drugs and/or delivery systems, aim to improve analgesia and minimise side effects (Chung et al 1997). Michaloliakou et al (1996) reported the benefit of such a regime for laparoscopic cholecystectomy. In particular, the benefits of combining non-steroidal anti-inflammatory drugs and opioids have been recognised (Kehlet and Dahl 1993). The value of a multi-modal post-operative analgesic regime for haemorrhoidectomy, utilising standard medications and delivery systems has not been reported.

Wound infiltration with local anaesthesia also has been shown to improve post-operative pain relief (Dahl et al 1994), particularly in combination with post-operative non-steriodal anti-inflammatory medication. Perianal infiltration with local anaesthesia for haemorrhoidectomy has been reported with mixed results. Marsh et al (1993) demonstrated that bupivacaine infiltration after haemorrhoidectomy conferred no advantageous analgesic effect. Chester et al (1990) reported similar results. Morisaki et al (1996), however, did report a prolongation of

analgesia was produced by wound infiltration with lignocaine. This group used spinal anaesthesia for all patients, and as such the effect of the infiltration is difficult to assess.

All of the above authors used a technique involving infiltration of the haemorrhoidectomy wounds after completion of the procedure. Several other groups have suggested that peri-operative analgesia is more effective if it is started prior to the first incision. The theoretical basis of this 'pre-emptive' analgesia is that it alters the central processing that amplifies post-operative pain and inhibits the peripheral nociceptive response (Kissin 1996).

The afferent (sensory) nerve supply to the mucous membrane of the lower anal canal is via the inferior rectal branches of the pudendal nerve. The perianal skin is also supplied by these nerves and in addition by the perineal branch of S4 (McMinn 1990). All of these nerves pass through the ischio-rectal fossa lateral to the anal canal on each side. Injection of the pre-emptive local anaesthesic into the ischio-rectal fossae around these nerves as an anal block may increase its effectiveness in the control of post-operative pain. The use of such a pre-emptive local anaesthesic block for haemorrhoidectomy has not been reported.

The pain of the first post-operative bowel action has hitherto precluded early discharge after haemorrhoidectomy. It has been shown that this pain is less if the stools are soft and the initial bowel action is early in the post-operative period and that this can be achieved by the use of post-operative laxative medication (Johnson et al 1987, London et al 1987).

The ideal analgesic protocol for haemorrhoidectomy should thus include the use of pre-emptive local anaesthesia, possibly in the form of an ischio-rectal fossa block, a post-operative aperient and a multi-modal post-operative regime combining opioids, non-steroiodal anti-inflammatory drugs and simple analgesia.

Patient education for haemorrhoidectomy

Patient expectation is a major factor in determining the recovery from surgical procedures. In the past, surgeons have led their patients to expect haemorrhoidectomy to be painful and to require several days of post-operative hospitalisation. Friends or relatives' unpleasant experiences may reinforce these expectations. For day case haemorrhoidectomy to be successful, expectations must be altered. This requires appropriate and accurate pre-operative education.

Wallace (1985) showed that accuracy of expectations minimised post-operative pain and distress. In the case of haemorrhoidectomy, pre-operative patient education should focus on an honest appraisal of post-operative pain expectations, followed by pain management strategies.

Home care after haemorrhoidectomy

The trend towards earlier and even same day discharge after surgery has also necessitated reconsideration of the support given to patients once they leave hospital. Hospital-based home nursing services have been set up in many major institutions to provide delivery of traditional hospital services to patients at home

(Monalto and Dunt 1996). Such services have, in most cases been successful, with high levels of patient satisfaction (Monalto 1996).

The Division of Surgery at The Queen Elizabeth Hospital has provided a Hospital-at-Home Nursing Service in conjunction with the Day Surgery Unit since 1993. At approximately the same time, a separate convalescent ward for post-operative patients was opened. The creation of these services has allowed the safe introduction of day surgery to a wide range of procedures.

Glyceryl trinitrate versus lateral sphincterotomy in the management of chronic anal fissure

Anal fissure is defined as a split in the skin of the distal anal canal (Lund and Scholefield 1996). It usually occurs in the midline posteriorly but 10% of fissures in women and 1% in men occur in the anterior midline (Goligher 1984). The classic symptoms are anal pain that is worse with defaecation, and the presence of bright blood on the toilet paper. Many acute anal fissures heal spontaneously or with dietary fibre supplementation. If a fissure becomes chronic it will show induration at the edges of the fissure and a distal skin tag (sentinel pile). The white fibres of the internal anal sphincter may be visible at the base of the fissure. This usually occurs over a period of a few weeks. Most chronic anal fissures will not heal without intervention.

Aetiology and pathogenesis of anal fissure

Patients with anal fissure have long been recognised as having high resting pressure in the internal anal sphincter. Miles (1919) observed that anal fissure was associated with a 'pecten band' in the distal anal canal and advised division of this band as treatment. Eisenhammer in 1951 showed that this band was in fact the hypertonic internal anal sphincter. The role of this abnormality in the aetiology of anal fissure has until recently been unclear.

The advent of anal manometry has allowed accurate assessment of sphincter tone. The majority of published series have found that the resting anal pressure in patients with anal fissure is consistently higher than normal controls (Northmann and Schuster 1974, McNamara et al 1990, Xynos et al 1993. Farouk et al 1994). As the maximum voluntary squeeze pressure is no different from control, the high resting tone is likely to be due to hypertonicity of the internal anal sphincter. This has confirmed the clinical findings of earlier workers.

It was not until the late 1980's that the relationship between high resting anal tone and chronic anal fissure was elucidated. Klosterhalfen et al (1989) performed post-mortem angiography to follow the anatomy of the inferior rectal artery, from which the anal mucous membrane derives its vascular supply. They showed that divisions of these vessels must pass through the anal sphincters to reach the mucosa. This supply is most deficient at the posterior midline. It was suggested that, in patients with high resting anal tone, ischaemia at the posterior midline will cause an anal fissure.

The ischaemic theory of pathogenesis is supported by experimental work showing that there is an inverse relationship between anodermal blood flow and resting anal pressure. Gibbons and Read (1986) showed that a raised resting anal pressure could reduce the perfusion pressure of the anoderm to levels equivalent to a perfusion index of 0.29. Schouten et al (1994) confirmed the negative correlation between anal tone and blood flow and also demonstrated a reduced blood flow in the posterior commissure in comparison to the other three quadrants of the anus. This group subsequently showed that resting anal tone was lowered and blood flow to the anoderm was restored by lateral sphincterotomy (Schouten et al 1995).

Surgical management of chronic anal fissure

The principle of the surgical management of chronic anal fissure is to lower the internal anal sphincter pressure by either forced dilatation or a cut in the muscle (sphincterotomy). The current gold standard of treatment is lateral subcutaneous internal sphincterotomy. This procedure has been shown to be superior to maximal anal dilatation (Fischer and Hamalmann 1978, Jensen et al 1994) and dorsal internal sphincterotomy (Hawley 1969, Abcarian 1980) in many published series.

Lateral sphincterotomy does however have its complications. The procedure is unsuccessful in healing the fissure in between 1 and 6% (Hoffman and Goligher 1970, Lewis et al 1988) of cases, usually due to inadequate division of the internal sphincter (Farouk et al 1997). In addition there is a risk of faecal soiling or even incontinence which is usually temporary, but permanent

incontinence has been reported (Khubchandari and Reed 1989, Pernikoff et al 1994, Usatoff and Polglase 1995). The delay between diagnosis and definitive surgery is also of concern to patients suffering from this painful condition.

Medical management of chronic anal fissure

Experimental evidence suggesting an ischaemic aetiology for anal fissure based on a hypertonic internal anal sphincter has fuelled clinical research into the search for a medication which could reduce internal anal sphincter pressure without surgery. Most reports to date have concerned the use of botulinum toxin or topical nitrites for this purpose.

Botulinum toxin is a lethal biological toxin which acts by binding to presynaptic cholinergic nerve terminals and inhibiting calcium-dependent exocytosis of acetylcholine (Jankovic and Brin 1991). Paralysis usually occurs within a few hours. Small doses of botulinum toxin have been used in the management of blepharospasm and spasmodic torticollis (Albanese et al 1992). It is also under investigation as a treatment for achalasia (Pasricha et al 1995).

Small uncontrolled trials have shown healing of chronic anal fissures by a single injection of botulinum toxin into either the external (Jost and Schimrigk 1994) or the internal (Mason et al 1996) anal sphincter. There are however several concerns regarding this treatment. The long-term effects of paralysis of the external anal sphincter in this way are as yet unknown. The lethal nature of the toxin makes correct dosage vital and overdosage potentially

fatal. In addition, the drug is expensive. The use of botulinum toxin for anal fissures is likely to remain experimental for some time.

Nitric Oxide is now recognised as the principle inhibitory neurotransmitter in the internal anal sphincter, causing reversible relaxation via a non-cholinergic, non-adrenergic pathway (O'Kelly 1996). Glyceryl trinitrate is metabolised to nitric oxide, is available as a topical paste and has been shown to cause a decrease in resting anal tone when applied to the perianal region (Loder et al 1994, Lund and Scholefield 1997). This change of tone begins within 20 minutes of application and lasts for up to 9 hours.

Several pilot studies have reported excellent results using this technique in patients with anal fissure. Gorfine (1995) showed that 23/30 (77%) fissures healed at eight weeks using a 0.3% paste. Lund et al (1996) healed 18/21 (86%) fissures at six weeks with a 0.2% paste. This group subsequently published a randomised placebo controlled trial that showed conclusively that the observed response was not due to a placebo effect (Lund and Scholefield 1997).

Patients reported a decrease in pain within a few minutes of paste application (Gorfine 1995). This correlated with an increase in blood flow to the anoderm as measured by Doppler flowmetry (Schouten et al 1996). Faecal incontinence has not been reported by papers investigating this technique of temporary chemical "sphincterotomy". The principle reported side effect is a temporary headache.

The above studies detailing the use of glyceryl trinitrate paste for chronic anal fissure are most encouraging. It is possible that this medication may develop into the first line treatment for this condition. However, a large prospective randomised trial comparing the use of topical glyceryl trinitrate paste with the established surgical treatment of lateral internal sphincterotomy in patients with chronic anal fissure has not been reported in the international literature. Whilst the early reports are encouraging, the technique needs to be shown to have at least an equivalent success rate and a decreased complication rate to surgical sphincterotomy before it can be considered the treatment of choice in these patients.

2.5 Patient information by video

The provision of information prior to a medical or surgical procedure has two goals. This process should provide a mechanism for patients to participate in treatment decisions with full understanding of the factors relevant to their proposed care (Cassileth et al 1980). In addition, this opportunity should be taken to reduce the patient's anxiety regarding the pending procedure (Herrmann and Kreuzer 1989).

A high level of anxiety prior to a medical or surgical procedure can have deleterious consequences. In addition to being unpleasant, there is evidence that it produces an increased sympathetic outflow (Williams 1993) and a stress response with elevated cortocosteroid and catecholamine release (Fell et al 1985). Requirements for anaesthetic agents may be increased (Goldmann et al 1988). Kulik and Mahler (1987) showed that less anxious patients were more ambulant postoperatively and were released from hospital more quickly after coronary artery bypass surgery. Boyd et al (1973) reported that higher levels of pre-operative anxiety was associated with a slower post-operative recovery to an active lifestyle after reconstructive surgery for peripheral vascular disease.

Our understanding of the effect that information provided during the consent process has on anxiety is evolving. In the past, there was a belief that the provision of extra information, particularly about risks and complications, would cause the patient undue anxiety (Kerrigan et al 1993). There is now evidence that the converse is true. Wallace (1986) reported that patients with more

knowledge about surgery have fewer worries and recover faster. Elsass et al (1987) showed that patients given detailed information about their anaesthetic were less anxious. Situational stress has also been shown to decrease working memory capacity (Sorg and Whitney 1992), thereby intertwining knowledge and anxiety further.

The provision of information in a format that will maximise knowledge and minimise anxiety is therefore sought. The ideal medium with which to impart such information is as yet unclear. Several studies have investigated the use of leaflets to improve and standardise the information received by patients during the consent process (Olver et al 1995, Marteau et al 1996). These studies have shown mixed results. Many patients do not read such forms and the remainder often do not fully understand the information provided.

The efficacy of video in patient education has been evaluated in several studies. Cohen (1983) evaluated video information regarding knowledge of depression in volunteers, Black and Mitchell (1977) used video to teach emphysema patients about chronic obstructive airways disease and Fisher et al (1981) compared video information with information provided by the doctor in the understanding of beta thalessaemia trait. Uzark et al (1982) compared standard instruction with and without video in the preparation of children for cardiac catheterisation. In these studies, the imparting of information to patients by video was at least as good as, and often better than other educational methods.

The Australian Gastroenterology Institute has, in conjunction with Lederle Laboratories, recently released a video detailing colonoscopy as part of its Patient Education Video Series. The

video is directed at people about to have a colonoscopy for the first time. It is informative and details the requirements and risks of the procedure, but is narrated in layman's terms by a well-known Australian actor. It is possible that, in this "video age", such a medium may prove to be the best way of providing necessary information in a format which will allow it to be recalled more easily.

SECTION III

METHODS, RESULTS AND DISCUSSION

3.1 INTRA-OPERATIVE ULTRASOUND

(i) Ultrasound detection of colorectal hepatic metastases

(ii) Ultrasound of the colon

3.2 LAPAROSCOPIC COLORECTAL SURGERY

(i) Laparoscopic reversal of Hartmann's procedure

(ii) Laparoscopic-assisted colonoscopic polypectomy

(iii) Core temperature changes during laparoscopic and open colorectal surgery

3.3 ADVANCED PROGNOSTIC TECHNIQUES IN COLORECTAL CANCER

(i) Immunobead reverse transcriptase-polymerase chain reaction detection of free intra-peritoneal malignant cells at colorectal cancer resection

3.4 AMBULATORY ANORECTAL SURGERY

(i) Day case haemorrhoidectomy

(ii) Pre-emptive, local anaesthetic, ischio-rectal fossa block for haemorrhoidectomy

(iii) Glyceryl trinitrate paste *versus* lateral sphincterotomy in the management of chronic anal fissure

3.5 VIDEO INFORMATION

(i) The impact of visual information by video on pre-colonoscopy knowledge and anxiety levels

3.1 INTRA-OPERATIVE ULTRASOUND

In 1996, the Division of Surgery at The Queen Elizabeth Hospital purchased an Aloka 2000^{TM} (Aloka Co. Ltd, Mitaka-shi', Tokyo, Japan) mobile ultrasound machine. This machine has a 5/7.5 MHz endorectal probe that has been used extensively by the Colorectal Surgical Unit in the investigation of faecal incontinence, complex anal fistulae and rectal neoplastic disease. In addition, there are two sterilisable intra-operative probes, a 7.5 MHz hand-held 'finger' probe for use during open surgery and a 7.5 MHz laparoscopic probe with a flexible tip for use during laparoscopic surgery.

The use of intra-operative ultrasound in the field of colorectal surgery has been investigated using this instrument and is reported in this section. The first study involves intra-operative ultrasound assessment of the liver in patients who are undergoing resection of a primary colorectal malignancy. The accuracy of this technique is evaluated and compared to that achieved by intra-operative inspection and bimanual palpation of the liver by the surgeon. It is also compared to pre-operative computed tomography of the liver. This study was approved by the Ethics of Human Research Committee at The Queen Elizabeth Hospital.

The second study involves an evolving technique. Intra-operative ultrasound of the colon in the localisation and assessment of colonic neoplastic lesions for excision has not previously been reported. A preliminary study involving the imaging of colonic specimens resected for malignancy was performed to assess the potential value of this technique. The technique was then assessed

in the in-vivo, intra-operative setting. This study was also approved by the Ethics of Human Research Committee.

3.1.1 Intra-operative ultrasound detection of hepatic colorectal metastases: Comparison with intra-operative palpation and pre-operative computed tomography

Subjects

The subjects for this study were patients with a primary colorectal malignancy who were to undergo colorectal resection by laparotomy or laparoscopy at The Queen Elizabeth Hospital.

Patients in whom the presence of metastases on pre-operative computed tomography (CT) of the liver may have influenced management decisions were excluded from the study. The two groups affected by this exclusion criterion were patients being evaluated for pre-operative radiotherapy for rectal adenocarcinoma and elderly or infirm patients in whom significant liver metastases may have contraindicated resection of the primary lesion.

Methods

Potential subjects for this study were identified by consultant colorectal surgeons and the patient details given to the study organisers. Computed tomography of the liver was organised from the outpatients department. This scan was a component of the standard pre-operative protocol for all patients with colon and rectal cancer. The result of this scan was not released to the investigators until after the intra-operative ultrasound had been performed.

After admission to hospital on the day prior to or on the day of surgery, a study organiser approached the patient and discussed enrolment in the study. Full, informed consent was obtained in writing at this time.

In patients undergoing open colectomy, the surgeon inspected and then bimanually palpated the liver after completion of the abdominal incision. He did not verbalise his findings until after the intra-operative ultrasound had been performed. The findings of intra-operative inspection and palpation of the liver were documented on a data collection sheet. The intra-operative ultrasound was then performed.

In patients undergoing laparoscopic colectomy, pneumoperitoneum was created by a standard cutdown approach at the umbilicus and maintained at 12-mmHg maximum abdominal pressure. The laparoscope and camera were then inserted and the liver inspected for surface metastases. Results were recorded on the data collection sheet. The laparoscopic ultrasound probe was then introduced through a second 10-mm port and ultrasound of the liver was performed.

A standard ultrasound technique was used for all cases. This enabled the area of the liver that was being imaged to be identified when viewed subsequently on videotape. The technique was as described for laparoscopic ultrasound of the liver by Rothlin (1997). In this technique, the probe is placed to the back of the liver next to the right side of the falciform ligament. It is then slowly moved to the right on the posterior surface of the liver. When the right edge of the liver is reached, the probe is lifted and

again placed on the right edge of the falciform ligament, this time a little further forward. This process is repeated until a 'sweep' of the entire right lobe of the liver has been performed. If it is possible, the probe is then placed under the right side of the liver and this area of the liver is imaged from its inferior surface. The probe is then transferred to the left side of the falciform ligament and the process is repeated to obtain images of liver segments III and II.

All intra-operative ultrasounds were recorded on videotape. The videos were reviewed in conjunction with a radiologist who was blinded as to the results of computed tomography of the liver and the intra-operative findings of the surgeon. The intra-operative ultrasound reports were recorded on the data collection sheets.

At the completion of the study, all CT scans and ultrasound videotapes were reviewed by the same radiologist, who was again unaware of the results of the other detection techniques for individual patients. At this time, the case notes and any subsequent CT scans for all patients were reviewed. The details of follow up were documented on the data collection sheet, including the date of diagnosis of cancer recurrence and/or death where appropriate.

Results

Between May 1997 and September 1998, 57 patients were enrolled into this study. The final ultrasound video, computed tomography and case note review was performed in October 1998. The post-operative follow up for this study was therefore between 1 and 17 months.

The study was incomplete in 8 patients. In three patients it was not possible to perform intra-operative ultrasound without extending the operation solely for this purpose. This was not considered appropriate as the ultrasound was being used for research purposes. In two of these cases the ultrasound could not be performed because of extensive adhesions from a previous open cholecystectomy. In the third case, a lower midline incision revealed an unresectable rectal cancer in a patient who already had a defunctioning transverse colostomy. It was considered inappropriate to extend the incision to palpate and ultrasound the liver. In all three cases, computerised tomography of the liver was normal. These patients were excluded from further analysis.

Five patients did not have a peri-operative CT scan. The details of these patients are included in the analysis of this study as it is still possible to compare the findings of intra-operative inspection and palpation with those of intra-operative ultrasound. In addition, the follow up analysis of intra-operative ultrasound is still available for these patients.

According to Dukes' staging system, of the 54 patients remaining in the study, 12 patients (22%) were Stage A, 21 patients (39%) were Stage B, 14 patients (26%) were Stage C. The remaining 7 patients (13%) had residual macroscopic malignancy after colorectal resection and were considered to have Stage D disease. A subgroup of nine patients had their procedure performed laparoscopically. This group consisted of 5 patients (56%) with Stage A lesions, 2 (22%) patients with Stage B lesions and 2 patients (22%) with Stage C lesions.

Table 3.1.1.1 lists the follow up details of the 33 patients who had open colectomy and had no abnormalities found on peri-operative computed tomography, intra-operative inspection and palpation and intra-operative ultrasound. Three patients have died from causes other than disseminated adenocarcinoma. One of these was a post-operative death from aspiration pneumonitis. The other patients died from cardiac events at 2 months and 12 months after their surgery. Neither of the latter two patients had a post-mortem examination. The presence or absence of colorectal liver metastases is therefore uncertain. All three of these patients have been excluded from assessment of the sensitivity of intra-operative ultrasound in the detection of colorectal hepatic metastases.

Three patients have had locoregional disease diagnosed in the post-operative period. One of these patients had an unresectable primary lesion at the time of surgery and the other two have had pelvic recurrence of rectal adenocarcinoma. None of these patients have been shown to have liver metastases on repeat CT scanning. A further 26 patients continue to be free of both local and distant recurrent disease on clinical assessment. One patient, despite no metastases being detected by any technique at the time of surgery, had a repeat CT scan at 6 months post-operatively because of weight loss that showed extensive hepatic metastases. His primary tumour had been a poorly differentiated Stage B lesion. This patient died of his disease 8 months after his colorectal resection. This data represents a 96.7% negative predictive value (29/30) for intra-operative ultrasound in open surgery at the time of this report. The median follow up period for this group is 10 months (range 1-17 months).

Table 3.1.1.2 details the follow up findings for the 8 patients who had laparoscopic colectomy with no abnormality found in the liver during the peri-operative period by any modality. Seven patients have remained disease free on clinical assessment. One patient had a repeat CT scan 8 months after surgery because of vague abdominal pain. A new 1.5cm lesion was seen in segment IV of the liver. This lesion was followed with serial CT scans over the subsequent months and appeared to be a solitary liver metastasis that was increasing in size. Fourteen months after his colorectal resection, the patient had a laparotomy with the intention of resection of this lesion. At laparotomy he had widespread peritoneal and omental deposits. This data represents an 87.5% negative predictive value (7/8) for laparoscopic ultrasound at the time of this report. The median follow up for this group is 8 months (range 1-14 months).

Table 3.1.1.3 shows the investigation findings and follow up details of patients who had hepatic lesions that were thought to be benign detected on one or more modality. In this group of patients, intra-operative inspection and palpation of the liver was considerably less sensitive than either of the other modalities. Six patients were assessed by all three modalities. Blinded assessment of computed tomography and intra-operative ultrasound detected the same 13 benign lesions in these patients. Intra-operative assessment by the surgeon found 6 of these lesions, with a normal liver reported in 2 patients.

Intra-operative ultrasound of the liver proved to be superior to computed tomography in diagnosing the nature of these small liver lesions. In most cases, the CT report and review could not

definitely ascertain the nature of the lesion. Differentiation between benign and malignant was not always possible. Intra-operative ultrasound diagnosed most lesions in this group of patients as benign with confidence. The exception was the laparoscopic case, where poor views were obtained.

The findings of peri-operative liver assessment in patients where one or more of the investigations found a malignant deposit are seen in Table 3.1.1.4. Four of these six patients had widespread large liver metastases detected by all three methods. The lesions in the other two patients were more subtle. The first patient had a number of lesions that were reported on CT scan to be five cysts scattered throughout the liver parenchyma. Intra-operative assessment by the surgeon found three lesions. Again these were reported to be consistent with cysts. Intra-operative ultrasound detected all five lesions and showed that the patient in fact had two pathologies. Three of the lesions were cysts, but two lesions were solid metastatic deposits. The subsequent increase in the number and size of these deposits confirmed the ultrasound findings.

The other patient had a lesion that was superficially placed in segment VII of the liver. The pre-operative CT scan was inconclusive as to the nature of this lesion. It was thought to be a malignant deposit on palpation by the surgeon and this was confirmed by intra-operative ultrasound. Intra-operative ultrasound also suggested a further deposit near the duodenum in segment V. Serial CT scans continued to only show the single lesion in segment VII. This was resected 3 months after the primary surgery. A repeat CT scan 12 months later showed further lesions in the right lobe, including in the position where a lesion had been reported on the

original intra-operative ultrasound.

Discussion

This study raises several important issues regarding the value of intra-operative ultrasound in the assessment of the liver at the time of primary colorectal resection for malignancy. As documented in the introduction to this section, most series to date have found intra-operative ultrasound to be an invaluable screening tool and the most sensitive technique for detecting metastatic deposits. There are several deficiencies to these series that have been highlighted by the results of the current study.

It is somewhat surprising that in the myriad of previous studies, some with several hundred patients, there is no report of patients who were unable to have an intra-operative assessment of the liver because of practical difficulties at the time of surgery. In the current series there were three such patients. It is possible that these patients were simply excluded from analysis. It is important to discuss such patients when analysing the value of intra-operative ultrasound. In clinical practice, there will be patients in whom it is inappropriate to divide multiple adhesions or extend the incision for the sole purpose of ultrasound examination of the liver. This situation is clearly one in which computerised tomography is the investigation of choice. This should be considered and reported in the overall analysis of peri-operative hepatic assessment for metastatic colorectal carcinoma.

Most of the statistical data presented by the earlier series is based on comparison of the liver investigation techniques on a lesion by lesion basis. This approach does not reflect the true value of the various techniques as the detection of a greater number of lesions in a patient with multiple unresectable lesions, whilst impacting on the statistical analysis, will not change the surgical management or prognosis. Lesion by lesion analysis has also been criticised by other authors (Meijer et al 1995, John and Garden 1996).

In addition, previous studies have used the total number of lesions found by all techniques to represent the gold standard. In many cases, because intra-operative ultrasound detected the most lesions, this technique represented the gold standard. The use of the technique under investigation as its own gold standard is clearly not acceptable, a point also made by Stewart et al (1993).

If the data from this study are analysed in the same fashion, similar results to those published in other studies are produced. There were a total of 22 metastatic deposits detected in the liver in this study. Sixteen lesions were detected by peri-operative computerised tomography (sensitivity 73%), intra-operative inspection and palpation by the surgeon detected 14 lesions (sensitivity 64%) and intra-operative ultrasound found 22 lesions (sensitivity 100%). This data would allow a similar assessment of the value of intra-operative ultrasound as has been previously reported.

Eighteen of the 22 lesions were however detected in patients with widespread unresectable liver disease. The exact number of

lesions present in these patients is clinically unimportant. Of greater importance is the fact that intra-operative ultrasound confirmed secondary malignancy in two patients (2/54=3.7%) where this was undiagnosed or not diagnosed with certainty by other methods. Closer analysis of the published literature shows that the value of intra-operative ultrasound in diagnosing new patients with unsuspected hepatic metastases is closer to this mark. Machi et al (1987) detected metastases in 4/84 patients (4.8%) thought to be negative by other investigations. Olsen (1990) reported a rate of 9/213 (4.2%) for the same analysis and Stone et al (1994) detected occult hepatic metastases by intra-operative ultrasound alone in 3/56 patients (5.4%). Stone et al suggested that these figures would be improved by restricting intra-operative ultrasound of the liver to patients with T3 or T4 tumours. As the T stage of the lesion is not known at the time of surgery, this approach is impractical.

The only true gold standard is long-term follow up, that is the incidence of patients who develop hepatic metastases in the follow up period who were originally thought to have no liver involvement by disease. This rate has been variously reported to be 6.9% (Machi et al 1991, follow up 37 months), 16% (Paul et al 1996, follow-up 40 months) and 21% (Leen et al 1994, follow up 12 months). In the present series, there was only 1 patient who fitted into this category in the open surgery group (3.3%). It is probable that this figure will been shown to under-represent the true incidence of a false negative intra-operative liver ultrasound for two reasons. Firstly, follow up has thus far been by clinical assessment only in the majority of cases. Pre-clinical hepatic metastases may be detectable by CT scan in some patients. This would increase the above rate. Secondly, the follow up period, with a median of 10 months, is short in

comparison to other series. Stone et al (1996) reported that all of their missed liver metastases had become apparent by 24 months. A follow up CT scan is planned for all patients in this group if they are clinically disease-free 18 months after their colorectal resection.

It is worthy of note that, in this series, the results of peri-operative CT scanning and intra-operative ultrasound in the detection of abnormalities was similar. All patients with a normal CT scan had a normal intra-operative ultrasound. In the blinded detection of benign lesions tabled in Table 3, intra-operative ultrasound and computerised tomography detected the same 13 lesions in 6 patients. This is certainly at variance with the data published by other authors. It is possible that, because a surgeon learning the technique performed intra-operative ultrasound in this series, that other lesions were missed. These potential lesions were however also missed by an experienced radiologist on review of the ultrasound videotape and as such it is likely that this is not the case. It is more probable that the sensitivity of computerised tomography with oral and intravenous contrast in 1998 allows the detection of much smaller lesions than has previously been possible. Most of the published data is from the 1980's and early 1990's and the sensitivity data for computerised tomography may not represent that which is achievable on modern CT scanners.

Computerised tomography may have been shown to be equivalent to intra-operative ultrasound in the detection of small hepatic lesions in this series, but it is clearly inferior in the diagnosis of the nature of these lesions. It is in this situation that we found intra-operative ultrasound to be unparalleled. In the open

surgery group, there were 17 lesions found in eight patients on CT scan most of which were 0.5-1.5 cm in diameter. The CT reports and review by the radiologist could not confidently diagnose the nature of these lesions. Intra-operative ultrasound, on the other hand, enabled accurate diagnosis of these lesions, with 3 being diagnosed as metastatic deposits, 1 as a complex cyst requiring follow up and the remaining 13 lesions as small simple hepatic cysts. This information was invaluable in the planning of subsequent patient management. Several of the CT reports for these patients in fact requested percutaneous ultrasound to assess the nature of these small lesions. The availability and accuracy of intra-operative ultrasound in this setting makes it a valuable component of the liver assessment in such patients.

The only patient in which intra-operative ultrasound was unable to characterise lesions seen on computerised tomography was a patient who had their resection (and therefore their ultrasound) performed laparoscopically. The laparoscopic probe found the lesions but could not confidently assess them as being benign or malignant. Ultrasound of the liver during laparoscopic surgery was in fact considerably less satisfactory than in open surgery in all patients. The flexible probe was difficult to apply to the liver surface in order to provide an adequate image at all times and we were much less certain that all of the hepatic parenchyma had been imaged. This situation will improve with experience, but it is possible that laparoscopic ultrasonography will be less sensitive than open intra-operative ultrasonography even in experienced hands. The available literature does not reflect these difficulties (Marchesa et al 1996, Hartley et al 1996) but patient numbers are small and follow up data has not been reported at all.

Accurate intra-operative ultrasound in laparoscopic colorectal resection for malignancy is possibly more important than in open surgery, as the surgeon is unable to palpate the liver. Larger series with long-term follow up are required.

The findings of this study are somewhat different to published series reporting the superiority of intra-operative ultrasound over other peri-operative detection methods. There is no doubt that this technology has an important role to play in the peri-operative assessment of the liver at the time of colorectal cancer resection. It must however be recognised that there is a significant false negative rate and that a negative ultrasound should not be interpreted as indicating that the liver will be clear of disease for life. In patients where abnormalities are found, intra-operative ultrasound is superior to other techniques, however the lesion by lesion analysis performed by other authors considerably inflates the level of this superiority.

Intra-operative ultrasound was clearly the best available medium for the assessment of the nature of hepatic lesions when these were found. Modern computerised tomography was able to detect the vast majority of lesions but not to accurately characterise them. It is possible that the ideal peri-operative protocol, outside of the confines of a clinical trial, involves a combination of these technologies. Intra-operative ultrasound could then be directed by the findings of pre-operative computerised tomography.

Recommendations

In order to establish the most accurate hepatic staging assessment, a protocol comprising a screening pre-operative CT scan and a directed intra-operative ultrasound has been designed. The intra-operative ultrasound recommendations depending on the CT results are as follows;

OPEN COLECTOMY FOR CANCER

1. *CT shows multiple metastases that are not resectable.*

   Intra-operative ultrasound is not indicated.

2. *CT shows metastasis(es) that may be resectable.*

   Careful intra-operative ultrasound should be performed at the time of colorectal resection in the presence of an experienced liver surgeon, to assess resectability of the lesion(s) and to assess for other lesions.

3. *CT shows equivocal lesion(s).*

   Intra-operative ultrasound is essential in this situation. Lesion by lesion ultrasound analysis of all CT abnormalities should be performed as well as screening of the remainder of the liver.

4. *Normal pre-operative CT scan.*

   This situation is more controversial. A few patients may have occult metastases detected by intra-operative ultrasound, but whether this justifies widespread screening is less certain. A further study assessing the findings of intra-operative

ultrasound in the wake of a known normal CT scan, with long-term follow up, is recommended.

LAPAROSCOPIC COLECTOMY FOR CANCER

The value of laparoscopic ultrasound in the detection of hepatic colorectal metastases is not known. All patients having laparoscopic colectomy for cancer should have a laparoscopic liver ultrasound performed and recorded on videotape in order to improve the quality of the images produced and as part of the ongoing clinical assessment of this technique.

TABLE 3.1.1.1:

Follow up data for all open colectomy patients who had no abnormality detected on peri-operative assessment of the liver.

TABLE 3.1.1.1

AGE/SEX	STAGE	CT RESULT	FOLLOW UP (months)	FOLLOW UP DETAILS
66M	C	Normal	17	No recurrence
85F	C	"	16	"
86M	B	"	15	"
73F	C	"	15	"
76M	C	"	15	"
68M	D (locally advanced)	"	14	Alive with disease (No liver metastases)
66M	C	"	14	No recurrence
52M	A	"	13	"
45M	B	"	12	"
80M	C	"	12	Died (Unrelated cause)
70M	A	"	12	No recurrence
82F	B	"	12	Local and bony recurrence (No liver metastases)
76M	C	"	12	Local recurrence (No liver metastases)
62M	B	"	11	No recurrence
75F	A	None	10	"
67M	A	Normal	10	"
36M	A	"	10	"
46M	B	"	10	"
60M	B	"	9	"
59M	B	None	9	"
70M	B	Normal	9	"
72M	C	"	9	"
89M	B	"	8	Died (Liver metastases)
72M	B	"	8	No recurrence
79F	B	"	8	"
80M	B	"	7	"
78M	B	"	6	"
60F	C	"	6	"
68M	B	"	5	"
84F	B	"	2	Died (Unrelated cause)
75M	B	"	2	No recurrence
89F	B	None	1	"

TABLE 3.1.1.2:

Follow up data for all laparoscopic colectomy patients who had no abnormality detected on peri-operative assessment of the liver.

TABLE 3.1.1.2

AGE/SEX	STAGE	CT RESULT	FOLLOW UP (months)	FOLLOW UP DETAILS
70M	C	Normal	14	Liver metastasis seen on CT at 8 months. Widespread deposits at 14 months
47F	A	"	10	No recurrence
75M	A	"	10	"
80M	B	"	10	"
74M	A	None	6	"
62F	A	Normal	6	"
54M	A	"	2	"
73F	C	"	1	"

TABLE 3.1.1.3:

Investigation findings and follow up details for all patients who had benign liver pathology detected.

TABLE 3.1.1.3

AGE/SEX/ STAGE	CT RESULT	SURGICAL ASSESSMENT	IOUS ASSESSMENT	FOLLOW-UP (months)	FOLLOW-UP DETAILS
67F/C	1.5 cm hypodense lesion in right lobe (probably cyst)	No lesion seen or palpated	Lesion detected and confirmed as simple cyst. No other lesions	15	No recurrence
57M/B	2 small lesions in right lobe. Nature of lesions uncertain	One lesion palpated, thought to be simple cyst	Two lesions detected and confirmed as simple cysts. No other lesions	12	No recurrence
61M/C	5 hypodense lesions seen (probably cysts)	Three lesions palpated. Thought to be simple cysts	Five lesions detected and confirmed to be simple cysts. No other lesions.	11	Died of unrelated cause No post-mortem examination
79F/C	Fluid-filled lesion in left lobe. Uncertain nature.	Lesion in segment II, thought to be calcified haematoma	Single fluid-filled lesion in segment II with irregular back wall.	10	No recurrence. No change in size of lesion at 6 month follow up scan

TABLE 3.1.1.3 (continued)

AGE/SEX/ STAGE	CT RESULT	SURGICAL ASSESSMENT	IOUS ASSESSMENT	FOLLOW-UP (months)	FOLLOW-UP DETAILS
86F/B	Two hypodense lesions, 2 cm in segment IV and 1 cm in segment VII. Thought to be cysts.	Single cyst seen in segment IV on laparoscopy.	Lesions detected in segments IV and VII. Nature uncertain as poor views obtained.	10	No recurrence No change in lesions at 6 month follow up CT scan
77M/A	Two <5 mm hypodense lesions in segments III and IV. Nature uncertain	Liver clear at inspection and palpation	Lesions in segments III and IV detected and confirmed to be cysts. No other lesions.	8	No recurrence
74M/A	None	"Multiple hepatic haemangiomata"	Six lesions detected in total. All complex but benign cysts.	7	No recurrence

TABLE 3.1.1.4:

Investigation findings and follow up data for all patients who had liver metastases detected by one or more of the investigation modalities.

TABLE 3.1.1.4

AGE/SEX/ STAGE	CT RESULT	SURGICAL ASSESSMENT	IOUS ASSESSMENT	FOLLOW-UP (months)	FOLLOW-UP DETAILS
77F/D	Five lesions seen throughout liver. All reported as cysts	Three lesions palpated. All thought to be cysts	Five lesions detected. Three cysts; two lesions, 1 in segment V and 1 in segment III definitely metastases	16	Repeat CT scan at 14 months showed multiple liver and lung metastases. Alive with disease
73M/D	1.5 cm lesion in segment VII. Nature uncertain.	Lesion in segment VII thought to be metastatic deposit.	Lesion in segment VII detected and diagnosed as metastatic deposit. Second lesion (metastasis) in segment V	14	Segment VII lesion resected by wedge resection after 3 months. Repeat CT scan at 12 months shows three lesions in right lobe, including at site of lesion seen on IOUS
62M/D	Multiple metastases throughout liver. At least six lesions	Four large liver metastases palpated	Multiple liver lesions detected. Six lesions counted.	14	Alive with disease. No further investigation.

TABLE 3.1.1.4 (continued)

AGE/SEX/ STAGE	CT RESULT	SURGICAL ASSESSMENT	IOUS ASSESSMENT	FOLLOW-UP (months)	FOLLOW-UP DETAILS
75F/D	Three large lesions seen, on the dome of right and left lobes and deep in the centre of the right lobe	Lesions palpated on the dome of both right and left lobes	Three lesions detected 4 cm lesion on dome right lobe; 4 cm lesion on dome left lobe; 2.5 cm lesion in parenchyma of right lobe with portal vein bifurcating around it.	8	Alive with disease. No further investigations performed.
59M/D	Large metastasis in segment IV. Possibly smaller lesions in segment VI	Large metastasis palpated, but no other lesions	Large metastasis detected and two further metastases detected in segment VI	8	Died 8 months post-operatively from disseminated disease
51F/D	Large central mestastasis. Several (5) smaller metastases throughout liver	Multiple liver metastases palpated. Number not specified.	Large central mestastasis detected along with multiple others. Parenchyma replaced by cancer	2	Died 2 months post-operatively from disseminated disease

3.1.2 Intra-operative ultrasound of the colon

Methods

An in-vitro, bench-top method was used for initial analysis of this technique. The Aloka 2000^{TM} ultrasound machine was set up in a corner of the operating theatre in cases involving colorectal resection for neoplastic disease. Immediately after the specimen was resected and before it was placed in formalin, it was passed across to the ultrasound area. If the resection had been performed by open surgery, the specimen was imaged with the 7.5 MHz open intra-operative probe. If the resection had been performed laparoscopically, the specimen was imaged using the 7.5 MHz laparoscopic probe. This recreated the conditions that would have been present if the ultrasound of the colon had taken place intra-operatively in each case.

The colonic specimens were imaged under three sets of conditions, all of which could also be recreated in the intra-operative, in-vivo setting if they were shown to increase the sensitivity of the technique during the bench-top assessment.

1. Images were recorded with the colon empty and the probe placed directly on the serosal surface.

2. The empty colon was placed in a bowl containing saline, to allow a fluid interface between the transducer and the bowel.

3. The lumen of the colon was filled with saline, and the probe again placed directly on the serosal surface.

The anticipated positions of impalpable neoplastic lesions, as well as any unusual findings on ultrasound during the bench-top assessment, were marked with a suture. At the completion of the imaging the specimen was opened longitudinally along the anti-mesenteric border and the area of the suture examined for macroscopic pathology. The specimen was then fixed in formalin and sent for histopathological assessment.

The ultrasound images that were produced were stored in the hard drive of the ultrasound machine and reproduced on standard radiological film in the Department of Medical Imaging. The hard copies of the ultrasound images were reviewed in conjunction with a radiologist. The histopathological reports for all patients were recorded and compared with the ultrasound images.

After the initial series of in-vitro specimen ultrasounds had been assessed, the technique was attempted in the intra-operative setting in the localisation of an impalpable sessile polyp in the lower sigmoid colon.

Results

In-vitro study

Twenty-five separate specimens from 24 patients were imaged during the initial study period. One patient required a right

hemicolectomy and an anterior resection for synchronous cancers. Both specimens underwent ultrasound analysis. In one other patient, bench-top ultrasound of the specimen was intended, however resection was not possible because the transverse colon lesion had invaded the duodenum. Laparoscopic techniques were used in 6 resections and the flexible laparoscopic ultrasound probe was used in the assessment of these specimens.

In the images that follow, the wedge-shaped ultrasound images have been taken with the open intra-operative probe and the laparoscopic probe produced the rectangular images. There was little difference in the resolution or quality of the images produced by these probes in the bench-top ultrasound study.

The neoplastic lesion for which the colon was resected was found in all specimens. In several cases, unsuspected impalpable synchronous polyps were also detected by the ultrasound technique.

1. ULTRASOUND OF EMPTY COLON

With the colon empty and the ultrasound probe placed directly on its serosal surface, the five sonographic layers of the normal colon could be identified (Figure 3.1.2.1). These layers are the same as those seen in the rectum with the endorectal probe and alternate between a hyper-echoic layer, which appears white on the grey-scale ultrasound screen and a hypo-echoic layer, which appears black (Wong 1997). These layers are thought to represent the layers of the colon as follows, from the lumen outwards.

A) A hyper-echoic (white) inner layer, representing the probe/mucosa interface.

B) A hypo-echoic (black) layer, representing muscularis mucosae.

C) A hyper-echoic (white) layer, representing submucosa.

D) A hypo-echoic (black) layer, representing the two layers of the muscularis propria.

E) A hyper-echoic (white) outer layer, representing serosa and extra-serosal fat.

In a separate experiment, the benchtop ultrasound technique was used in an attempt to confirm the nature of the sonographic layers of the colon. After imaging the intact colon, the specimen was opened along the anti-mesenteric border. A large area of normal colon then had the mucosa excised in the submucosal plane and the specimen was placed lumen side down on a 1 litre bag of normal saline. Figure 3.1.2.2 shows the image produced at the junction of normal colonic wall (left) and the area denuded of mucosa (right). The normal colonic wall had the expected five layered pattern. The area without mucosa is left with three layers, an attenuated submucosa, muscularis propria and serosa/adventitial fat. Whilst this small experiment does not categorically prove that the five layers are as reported, the confirmation that the middle layer is indeed submucosa suggests it is highly likely.

Ultrasound imaging of the intact, empty colon in the area of the tumour was then performed. Large, palpable cancers were easily discernable from the normal colon (Figure 3.1.2.3). The nature of the cancer could occasionally also be seen. In Figure 3.1.2.3, there are dark areas in the cancer, which give the impression of being, at

least in part, fluid-filled. The histological report for this lesion described a mucinous adenocarcinoma with abundant mucin throughout the tumour. In retrospect, it is likely that the dark areas on the ultrasound image represent pools of mucous.

With the colon empty, small lesions tended to be compressed by the ultrasound probe and could not be localised with confidence. Figure 3.1.2.4 shows an area that was thought to be normal when examined with the laparoscopic probe and the colon empty, hence the label 'normal colon'. This area subsequently proved to be the site of the impalpable lesion for which the procedure had been performed.

2. ULTRASOUND OF EMPTY COLON SURROUNDED BY SALINE

With the addition of saline to surround the colon, image clarity was marginally improved, as seen in the large cancer in Figure 3.1.2.5. The detection of small colonic lesions was not facilitated by this technique.

3. ULTRASOUND OF COLON WITH THE LUMEN FILLED WITH SALINE

With the colonic lumen filled with saline, the layers of the normal colon for the entire circumference could be discerned more accurately. Of greater significance was that the lumen expanded, allowing the accurate assessment of all intraluminal pathology Figure 3.1.2.6 is an example of the ultrasound image produced by normal colon when there is fluid in the lumen. The edge of large

cancers can be accurately defined, as seen in Figure 3.1.2.7. This is the same lesion that was seen in Figure 3.1.2.3 when the lumen was empty.

Small lesions could also be localised with confidence. The small lesion that was missed with the colon empty (Figure 3.1.2.4) is easily seen when there is saline in the lumen of the bowel (Figure 3.1.2.8). Even smaller lesions can be visualised by the ultrasound probe under these conditions. Figure 3.1.2.9 shows a 9mm incidental polyp found during sonography of a specimen resected for a synchronous carcinoma. The position of this lesion was marked with a suture and confirmed when the colon was opened. Polyps can be differentiated from residual faeces because faeces cause acoustic shadowing.

The clarity of the image produced by colonic ultrasound when the colon was filled with saline was such that some staging assessments of the primary tumour can be made. In Figure 3.1.2.10 a small, impalpable cancer invades the muscularis propria. This small area of invasion was confirmed on histopathology. Enlarged lymph nodes were also recognised in several specimens. An example is seen in Figure 3.1.2.11. The sensitivity of lymph node staging was not assessed in this in-vitro pilot study.

No formal comparison of the accuracy of ultrasound with intra-operative colonoscopy, the most common technique in the localisation of impalpable lesions for resection, was undertaken. There were two specimens, however, in which benchtop ultrasound was able to find lesions which could not be localised confidently with intra-operative colonoscopy. Figure 3.1.2.12 shows a small

ulcer, the remains of a malignant polyp excised colonoscopically 6 days before colectomy. There was malignant invasion of the stalk of the polyp and colectomy was required. The ulcer was difficult to see at intra-operative colonoscopy, but was quickly recognised with the ultrasound probe.

Figure 3.1.2.13 also shows the remains of a malignant polyp excised at colonoscopy, but the patient was not referred for colonic resection for 5 weeks. This lesion could not be seen from the luminal surface at colonoscopy, nor by the naked eye when the specimen was opened. It could, however, be seen using ultrasound with the colonic lumen filled with saline. This area of submucosal derangement was marked with a suture and the presence of malignant cells in the submucosa was confirmed by histopathology.

In-Vivo Trial

After the pilot, benchtop study was complete, it was concluded that impalpable neoplastic lesions requiring resection by colectomy could be localised by intra-operative ultrasound of the colon if there was saline in the lumen of the bowel.

A 57-year-old woman with a sessile 3cm adenomatous lesion in the sigmoid colon 25cm from the anal verge was referred for sigmoid colectomy as the lesion was not considered amenable to colonoscopic polypectomy.

At laparotomy, the lower colon and rectum were palpated. A fullness in the lower sigmoid colon was thought to represent the lesion but confirmation was required. In this case rigid

sigmoidoscopy would have localised the lesion but the ultrasound technique was considered ready for *in vivo* trial. A 22F Foley catheter was inserted into the anus and the balloon inflated. A soft bowel clamp was placed across the large intestine at the junction of the descending and sigmoid colon and the distal bowel filled with sterile normal saline through the Foley catheter.

The lower bowel was then imaged using the hand-held intra-operative 'finger' 7.5 MHz probe. The image of normal colon created can be seen in Figure 3.1.2.14. The polyp was easily identified using this technique (Figure 3.1.2.15) and was confirmed to be the area of fullness felt at laparotomy. The level of the lesion was marked with a suture and the saline aspirated through the Foley catheter. The patient then underwent a sigmoid colectomy and made an uneventful recovery.

Discussion

The difficulties encountered in achieving good image quality in percutaneous ultrasound of the colon have been discussed in the introduction to this section. We have shown that these pitfalls can be avoided by placement of the probe directly on the serosal surface. The images so produced in this study are of exception clarity, especially when the lumen is filled with fluid. In the intra-operative environment, saline could be instilled via a Foley catheter placed in the anus for lesions thought to be on the left side of the colon. For lesions in the right colon, the appendix stump, or a small colotomy in the caecum could be used for introduction of fluid, in a similar fashion to an on-table colonic washout. This area of the

colon would normally be resected as part of a right hemicolectomy.

Evaluation of the true clinical value of intra-operative ultrasound of the colon in the localisation of colonic neoplasia will require considerably more in-vivo investigation, including direct comparison to the other available techniques of localisation. The technique described above, however, does have some theoretical advantages over the other available options, intra-operative colonoscopy, pre-operative contrast enema and pre-operative marking of the colonic wall at the initial colonoscopy.

Colonoscopic localisation of the lesion during laparotomy or laparoscopy is the most commonly used localisation strategy. This requires the availability in theatre of a trained endoscopist or a second surgeon with endoscopic skills as well as the colonoscope, a light source, a second suction apparatus and preferably a video screen to allow confirmation of the lesion by the operating surgeon. The colonoscopy itself can be cumbersome, as it must be performed with the patient in the unfamiliar lithotomy position. In addition, the colonoscopist is positioned under the sterile drapes of the perineum and between the sterile drapes of the legs. This may cause a breach of the sterile surgical field. Finally, the colonic insufflation required for colonoscopy can make subsequent resection more difficult, particularly in laparoscopic colectomy.

The use of contrast enema for pre-operative localisation of a potentially impalpable lesion exposes the patient to radiation during a second diagnostic investigation for a lesion that is already diagnosed. Definitive surgery is delayed by necessity in order to clear the bowel of the contrast agent. The major drawback of this

technique, however, is that it does not allow accurate real time confirmation of the exact position of the lesion at the time of surgery.

Marking of the normal colon in proximity to a lesion requiring resection has become a recognised technique with the advent of laparoscopic assisted colectomy. The marking agents reported are activated charcoal particles (Kitamura et al 1995), methylene blue (Hammond et al 1989) and India Ink (Gellmann et al 1996). Published reports with small numbers of patients have achieved excellent results. Methylene blue is however not the ideal tattooing medium as it will only last for 24 hours (Hill et al 1993). Concerns have also been raised regarding India ink as there have been reports of a colonic abscess with focal peritonitis at subsequent laparotomy (Part et al 1991) as well as fat necrosis, inflammation and fibroblast proliferation in the mesentery and omentum (Cormann et al 1991). In addition, the injection of foreign substances into the full thickness of the colonic wall immediately adjacent to a malignant lesion does have some potential oncological concerns, and long term follow up data is required before this method should gain widespread acceptance.

Intra-operative ultrasound of the colon has none of these drawbacks. No extra personnel are required as the surgeon can perform the ultrasound. No extra equipment is required as intra-operative ultrasound is used for liver assessment during colorectal resection for malignancy in many institutions. The probe is completely sterilisable, and poses no threat to aseptic technique. Ultrasound is a safe medium, exposing neither patient nor theatre staff to ionizing radiation. There are also no oncological concerns

in the use of ultrasound for this purpose.

The theoretical advantages of ultrasound as a localisational tool for impalpable lesions would come to nothing if the technique itself was not sensitive. The images produced in this pilot study and the success of the in-vivo trial suggest that, with refinement, the technique may be at least the equal of other methods in terms of sensitivity. The ability to detect the remnants of malignant polyps not visible at intra-operative colonoscopy, as seen in two cases in the in-vitro study, is particularly encouraging.

In order to become an accepted technique in the routine localisation of impalpable lesions however, intra-operative ultrasound of the colon must be shown to be to be as sensitive as the other techniques in the in-vivo, intra-operative setting. Of particular concern is the ability of the laparoscopic probe to produce images in the intra-operative setting equal to those seen with specimen ultrasound, especially if one considers the problems encountered whilst using this probe for liver ultrasound that were discussed in the preceding section.

The use of intra-operative ultrasound of the colon as a locoregional staging tool for colorectal malignancy has also not been reported previously. Intra-operative staging by ultrasound of gastric cancer prior to resection (Machi et al 1987) or of the specimen immediately after resection (DeManzoni et al 1994) has been shown to be of benefit in the planning of gastric resection for malignancy. Currently, such staging is not required in colonic malignancy, as surgery would not be modified. This situation may change in the future if intra-operative radiotherapy or hepatic artery

chemotherapy are shown to be of benefit in locally advanced colorectal malignancy. The images seen in this study suggest that ultrasound would be the intra-operative staging tool of choice.

This study has added a new technique to those available for the localisation and assessment of colonic neoplastic lesions during surgery. Further intra-operative investigation is required to confirm that the clarity of image and sensitivity of the findings seen in the pilot specimen ultrasound study can be translated into the intra-operative setting, particularly in laparoscopic surgery.

FIGURE 3.1.2.1:

Ultrasound image produced by the 7.5 MHz laparoscopic probe on normal colon with the lumen empty. The five sonographic layers of the normal colon can be seen.

Legend:	1	Mucosa
	2	Muscularis mucosae
	3	Submucosa
	4	Muscularis propria
	5	Serosa/ pericolic fat

FIGURE 3.1.2.1

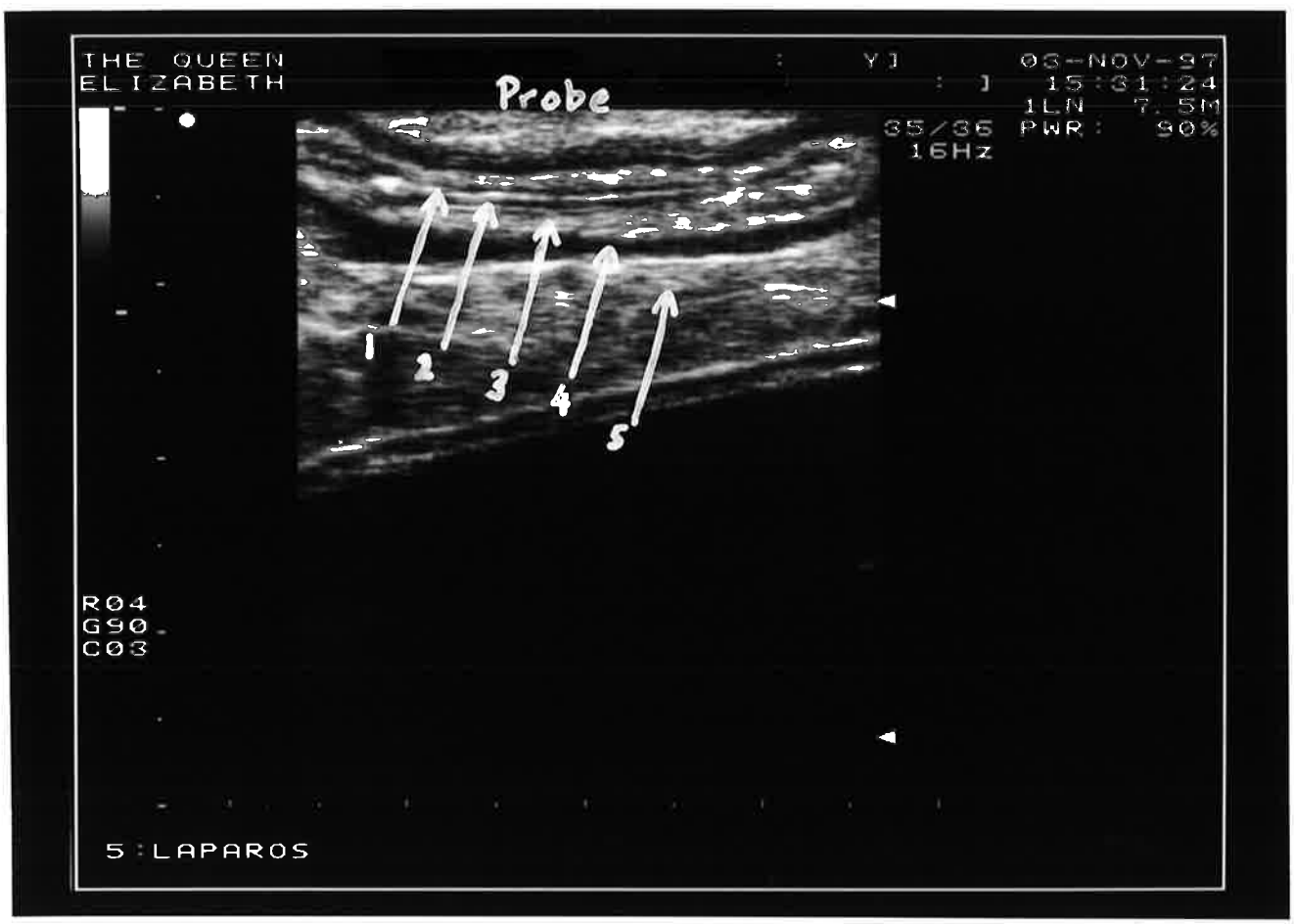

THE QUEEN
ELIZABETH
Probe
06-NOV-97
15:31:24
1LN 7.5M
35/36 PWR: 90%
16Hz
1
2
3
4
5
R04
G90
C03
5:LAPAROS

FIGURE 3.1.2.2:

Experimental assessment of normal colonic layers on ultrasound. The colon has been opened and laid lumen side down onto a bag of saline. The colon on the left (Arrow 1) has the expected five layers. The colon on the right (Arrow 2) has had the mucosa, muscularis mucosae and some submucosa excised in a submucosal plane. As expected, this leaves the colon with the two outer layers and an attenuated middle layer when imaged with ultrasound.

FIGURE 3.1.2.2

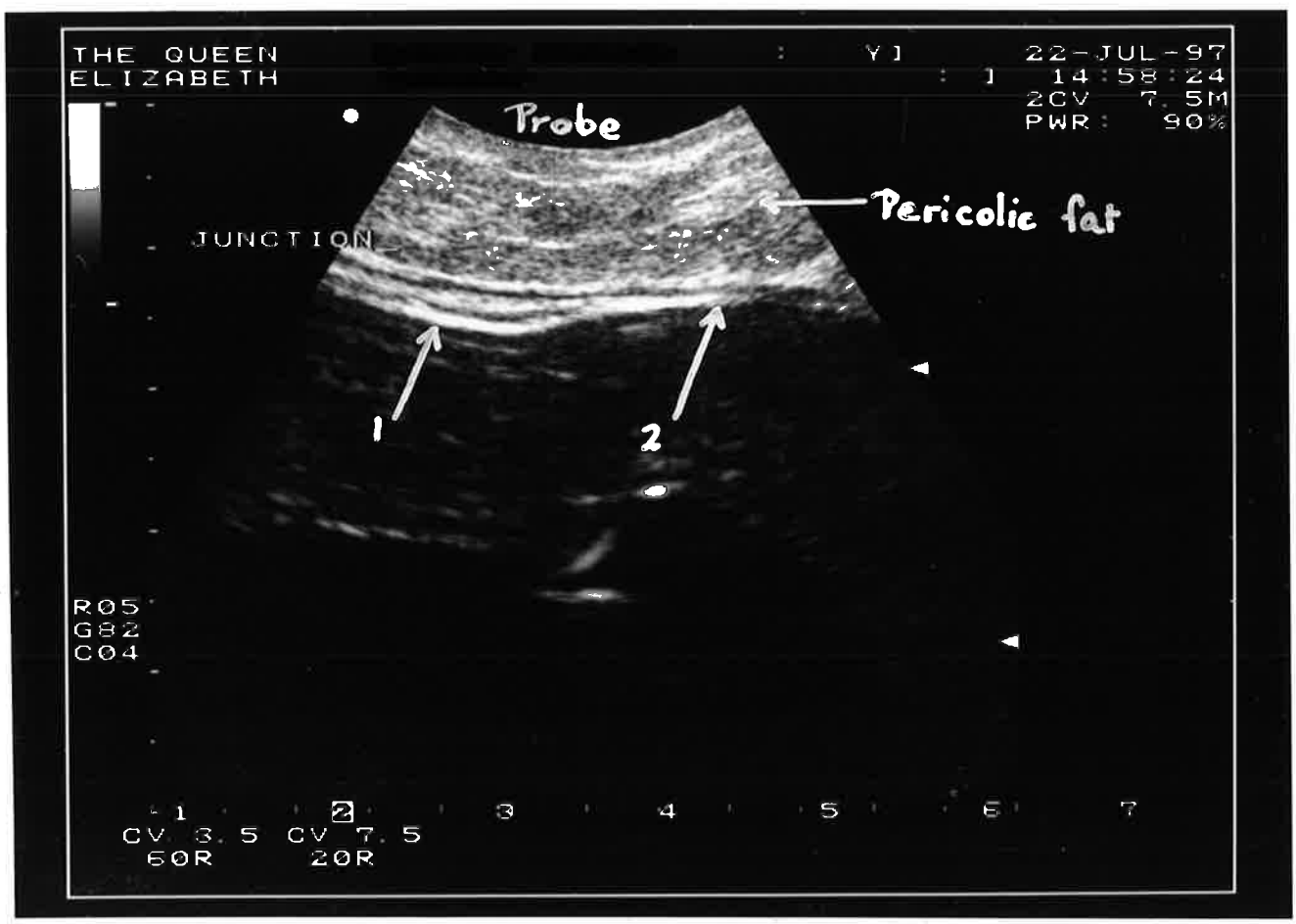

THE QUEEN
ELIZABETH
22-JUL-97
14:58:24
2CV 7.5M
PWR: 90%
Probe
Pericolic fat
JUNCTION
1
2
R05
G82
C04
1 2 3 4 5 6 7
CV 3.5 CV 7.5
60R 20R

FIGURE 3.1.2.3:

Ultrasound image of a large palpable cancer taken with the colon empty. The hypo-echoic (black) areas (Arrows 1 and 2) are thought to represent pools of mucin within the tumour.

FIGURE 3.1.2.3

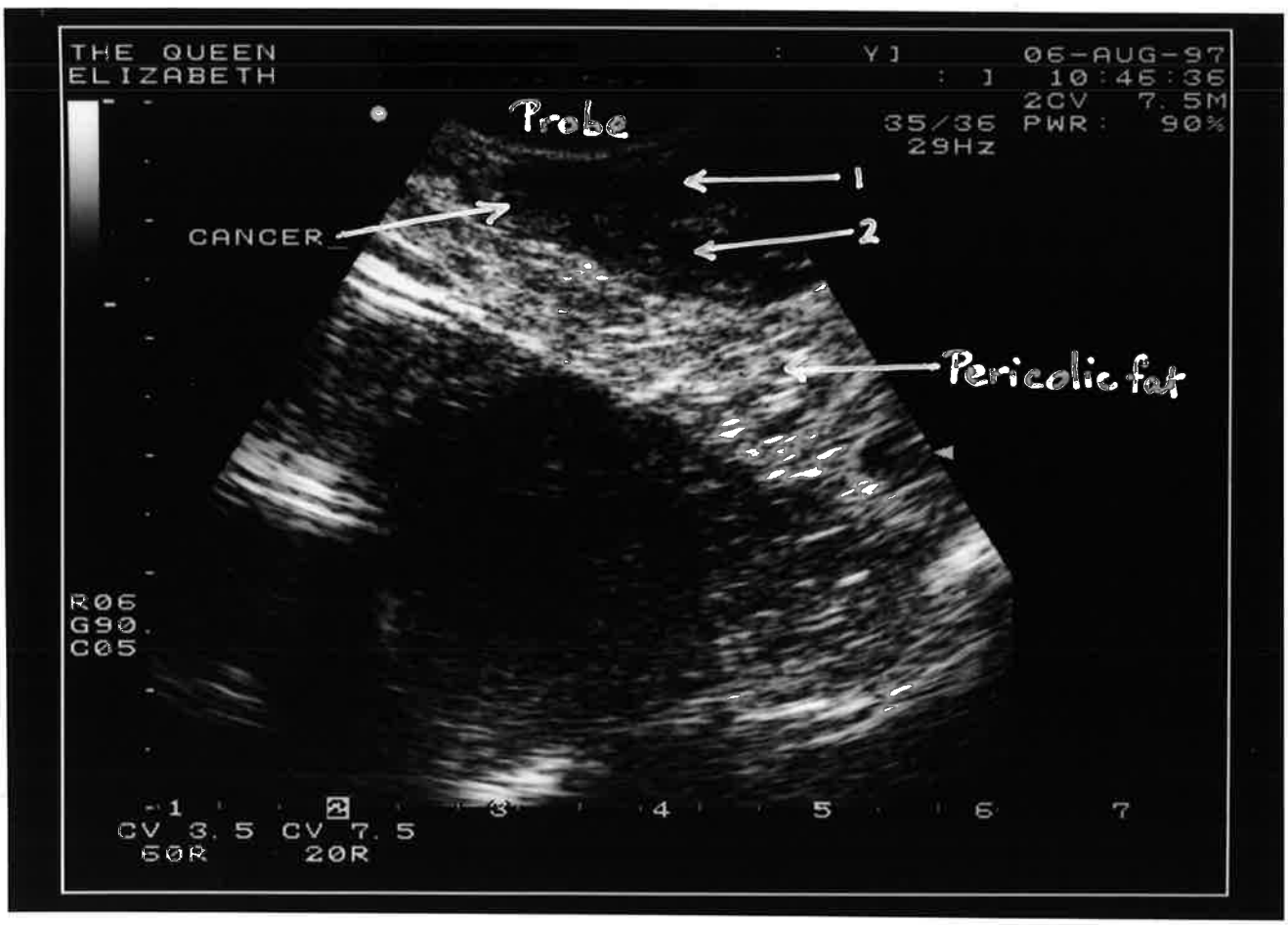

THE QUEEN
ELIZABETH
06-AUG-97
10:45:36
2CV 7.5M
35/36 PWR: 90%
29Hz
Probe
1
2
CANCER
Pericolic fat
R06
G90
C05
CV 3.5 CV 7.5
60R 20R

FIGURE 3.1.2.4:

Ultrasound image with the colon empty. This area was thought to be normal at the time of initial scanning, hence the label 'normal colon'. When fluid was placed in the lumen of the bowel (Figure 3.1.2.8), this was shown to be the site of the impalpable lesion for which the resection had been performed.

Legend:	1	Collapsed colonic lumen
	2	Submucosa
	3	Muscularis propria
	4	Pericolic fat

FIGURE 3.1.2.4

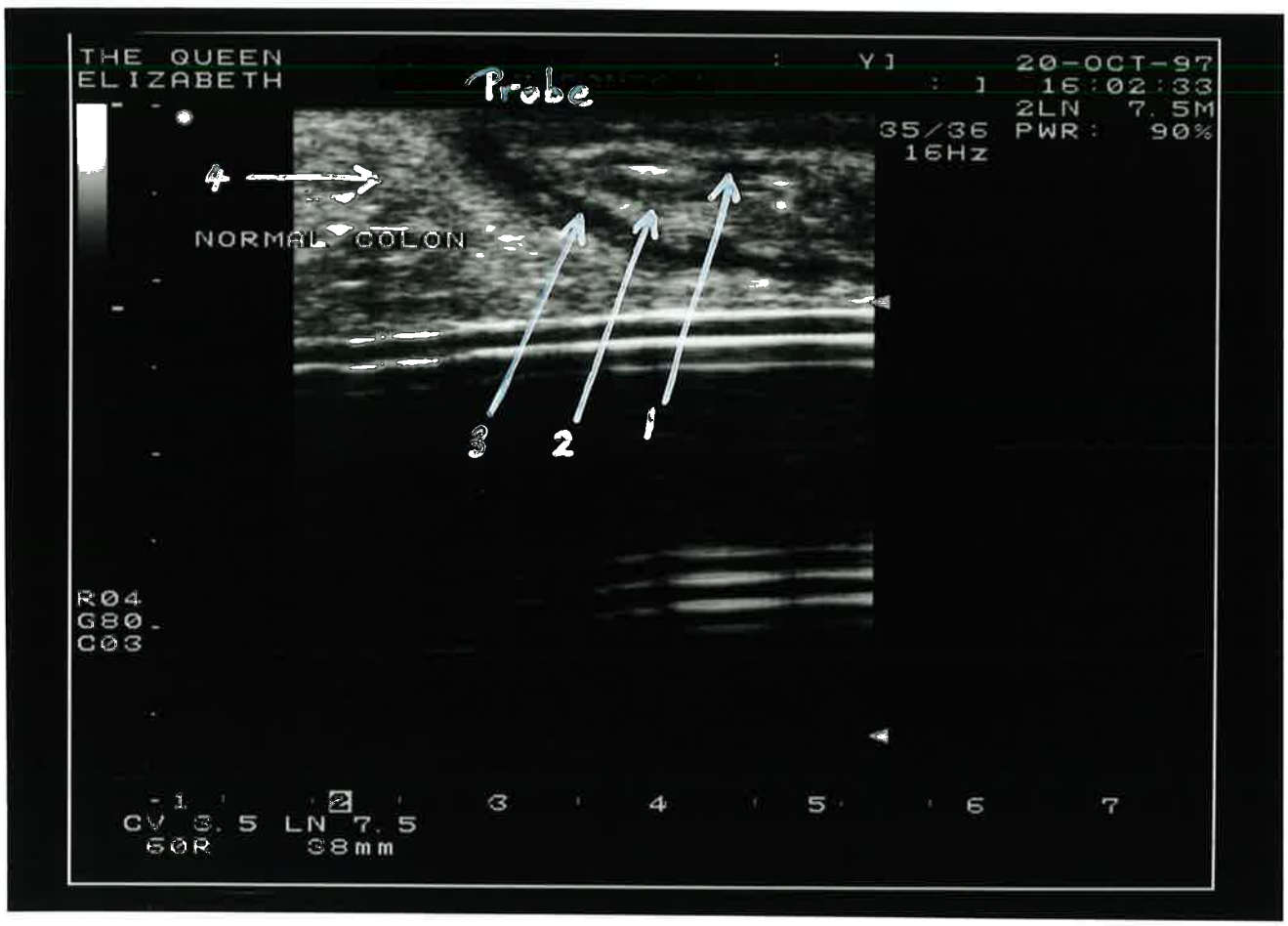

THE QUEEN
ELIZABETH
Probe
20-OCT-97
16:02:33
2LN 7.5M
35/36 PWR: 90%
16Hz
4
NORMAL COLON
3
2
1
R04
G80
C03
1
2
3
4
5
6
7
CV 3.5 LN 7.5
60R 38mm

FIGURE 3.1.2.5:

Ultrasound image of a large cancer taken with the empty colon immersed in a saline 'bath'. There is little improvement in image clarity when compared to the preceding images.

Legend:	1	Lumen
	2	Cancer
	3	Muscularis propria
	4	Pericolic fat

FIGURE 3.1.2.5

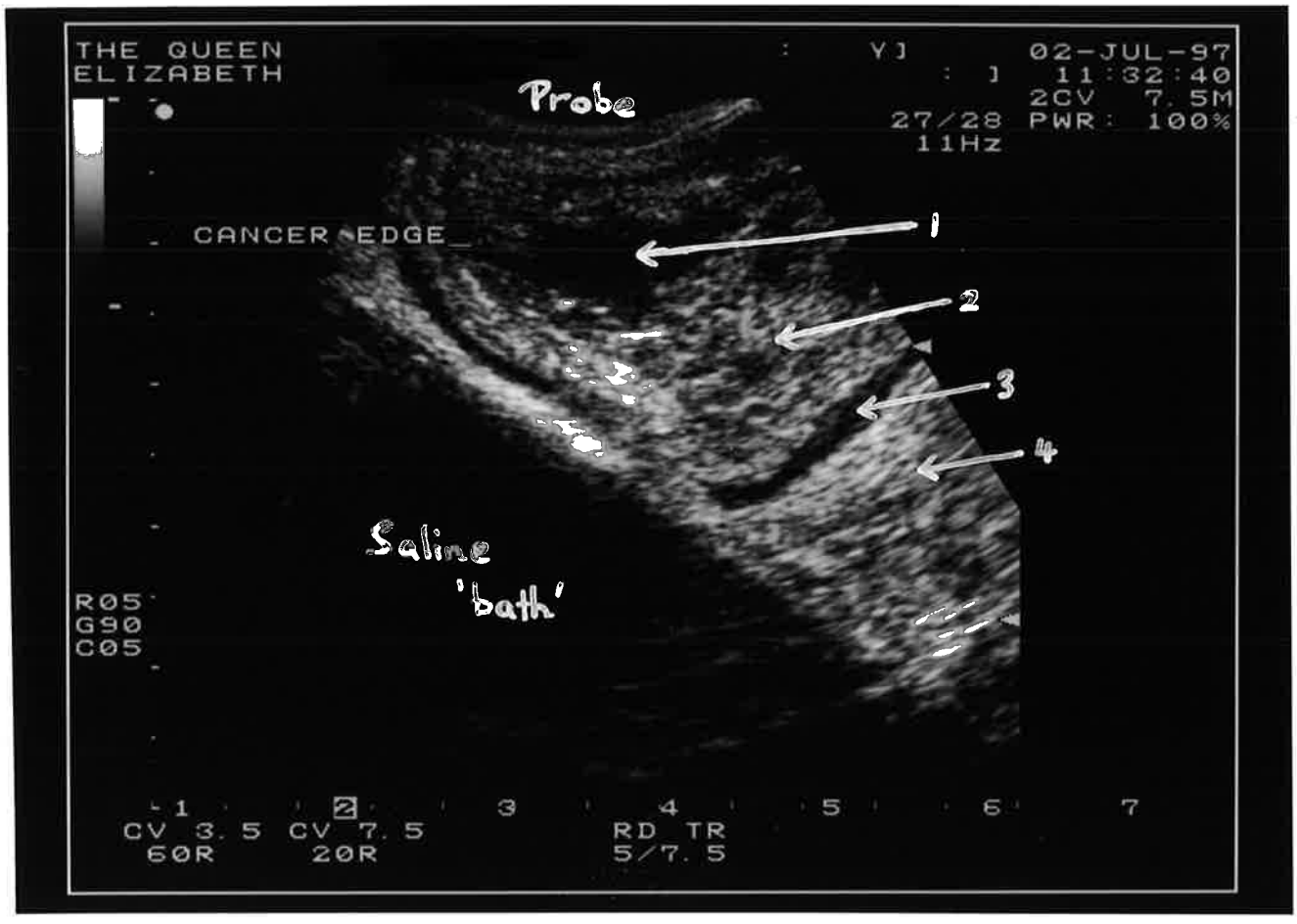

THE QUEEN
ELIZABETH
02-JUL-97
11:32:40
2CV 7.5M
PWR: 100%
27/28
11Hz
Probe
CANCER EDGE
1
2
3
4
Saline
'bath'
R05
G90
C05
1
2
3
4
5
6
7
CV 3.5 CV 7.5
60R 20R
RD TR
5/7.5

FIGURE 3.1.2.6:

Ultrasound image of normal colon with the lumen filled with fluid. The layers of the colonic wall can be easily discerned. The lumen has also opened up, allowing the assessment of intra-luminal and mural pathology.

Legend:	1	Lumen
	2	Mucosa
	3	Muscularis mucosae
	4	Submucosa
	5	Muscularis propria
	6	Pericolic fat

FIGURE 3.1.2.6

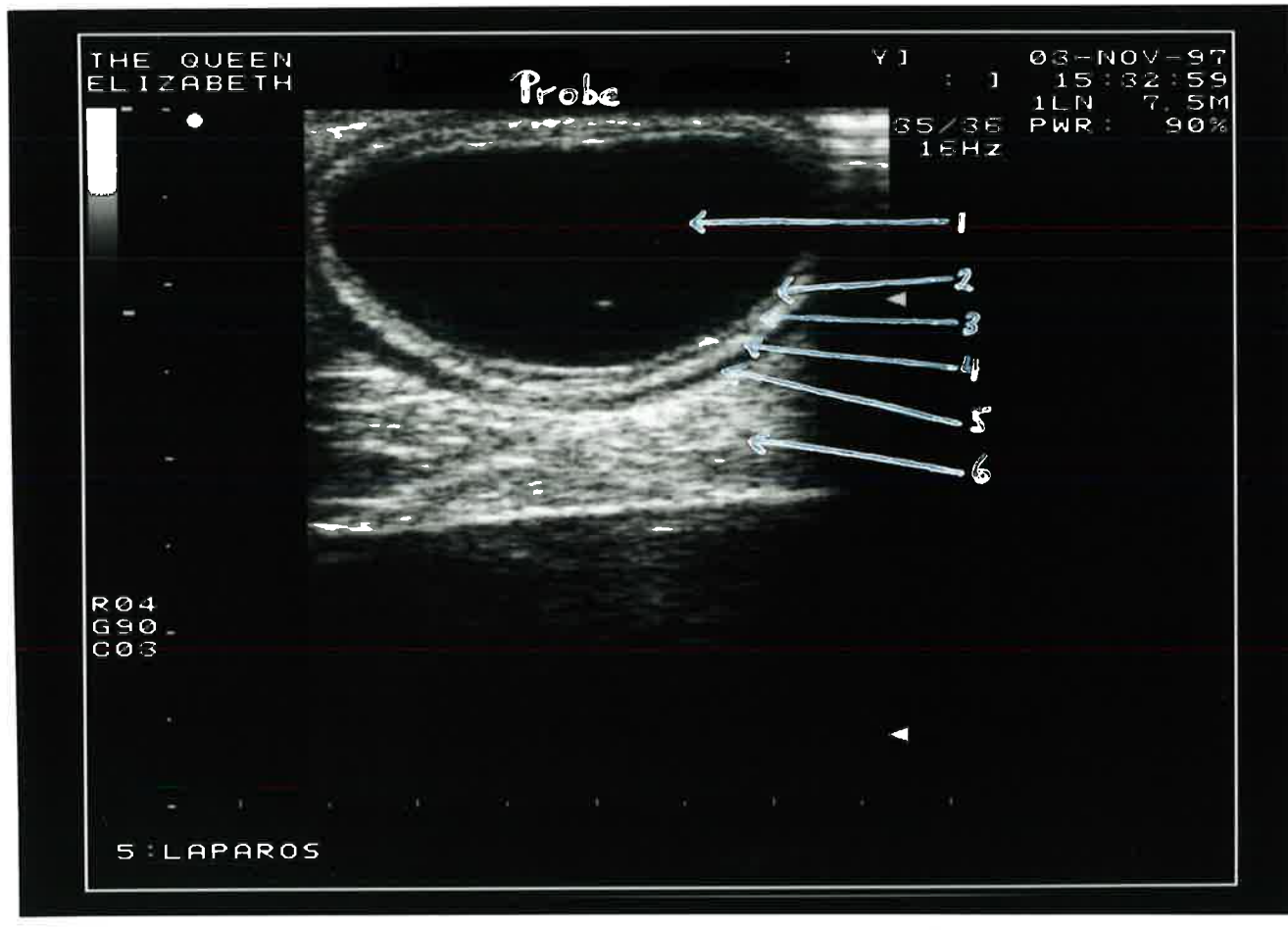

THE QUEEN
ELIZABETH
Probe
03-NOV-97
15:32:59
1LN 7.5M
PWR: 90%
35/35
15Hz
1
2
3
4
5
6
R04
G90
C03
5:LAPAROS

FIGURE 3.1.2.7:

Ultrasound image of a large cancer (Arrow 1) with the colonic lumen filled with fluid (Arrow 2). The edge of the cancer can be accurately defined (Arrow 3).

FIGURE 3.1.2.7

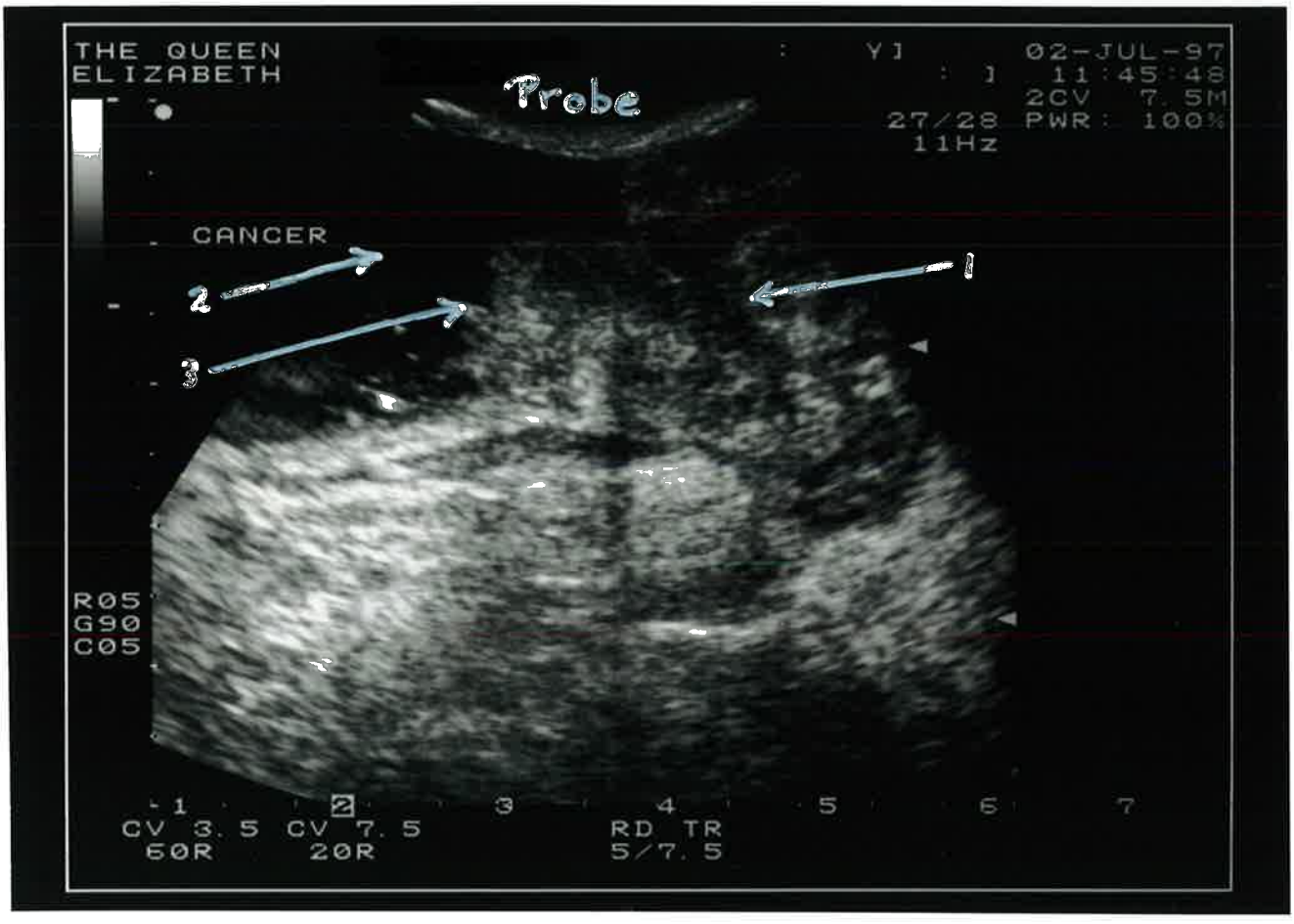

THE QUEEN
ELIZABETH
02-JUL-97
11:45:48
2CV 7.5M
27/28 PWR: 100%
11Hz
Probe
CANCER
1
2
3
R05
G90
C05
1 2 3 4 5 6 7
CV 3.5 CV 7.5
60R 20R
RD TR
5/7.5

FIGURE 3.1.2.8:

The small cancer, which could not be found with laparoscopic probe when the colon was empty (Figure 3.1.2.4), is clearly seen when there is intra-luminal saline.

FIGURE 3.1.2.8

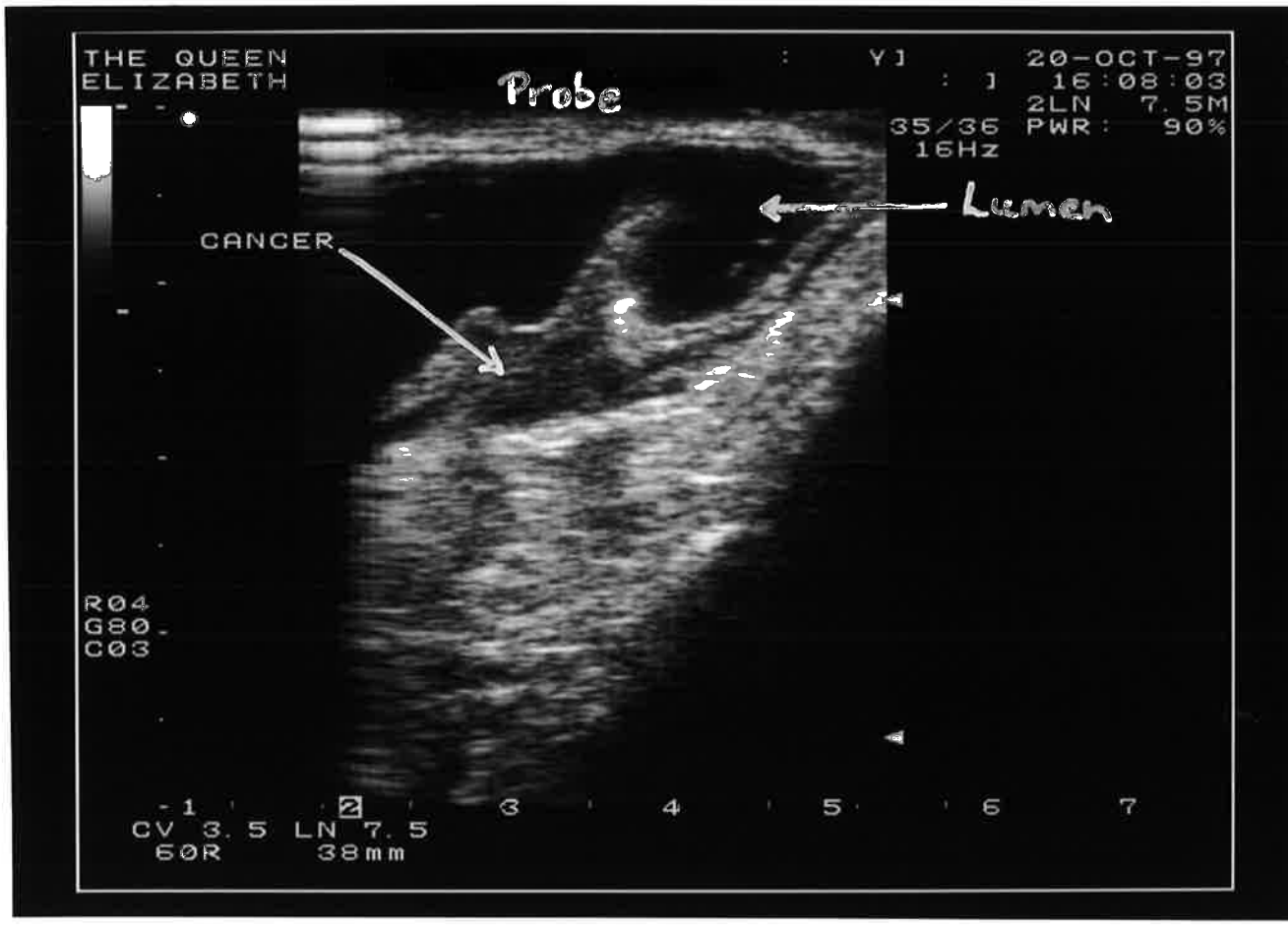

THE QUEEN
ELIZABETH
Probe
20-OCT-97
16:08:03
2LN 7.5M
35/36 PWR: 90%
16Hz
Lumen
CANCER
R04
G80
C03
1 2 3 4 5 6 7
CV 3.5 LN 7.5
60R 38mm

FIGURE 3.1.2.9:

Ultrasound image of a small (9 mm) polyp found incidentally in a specimen resected for a synchronous cancer.

FIGURE 3.1.2.9

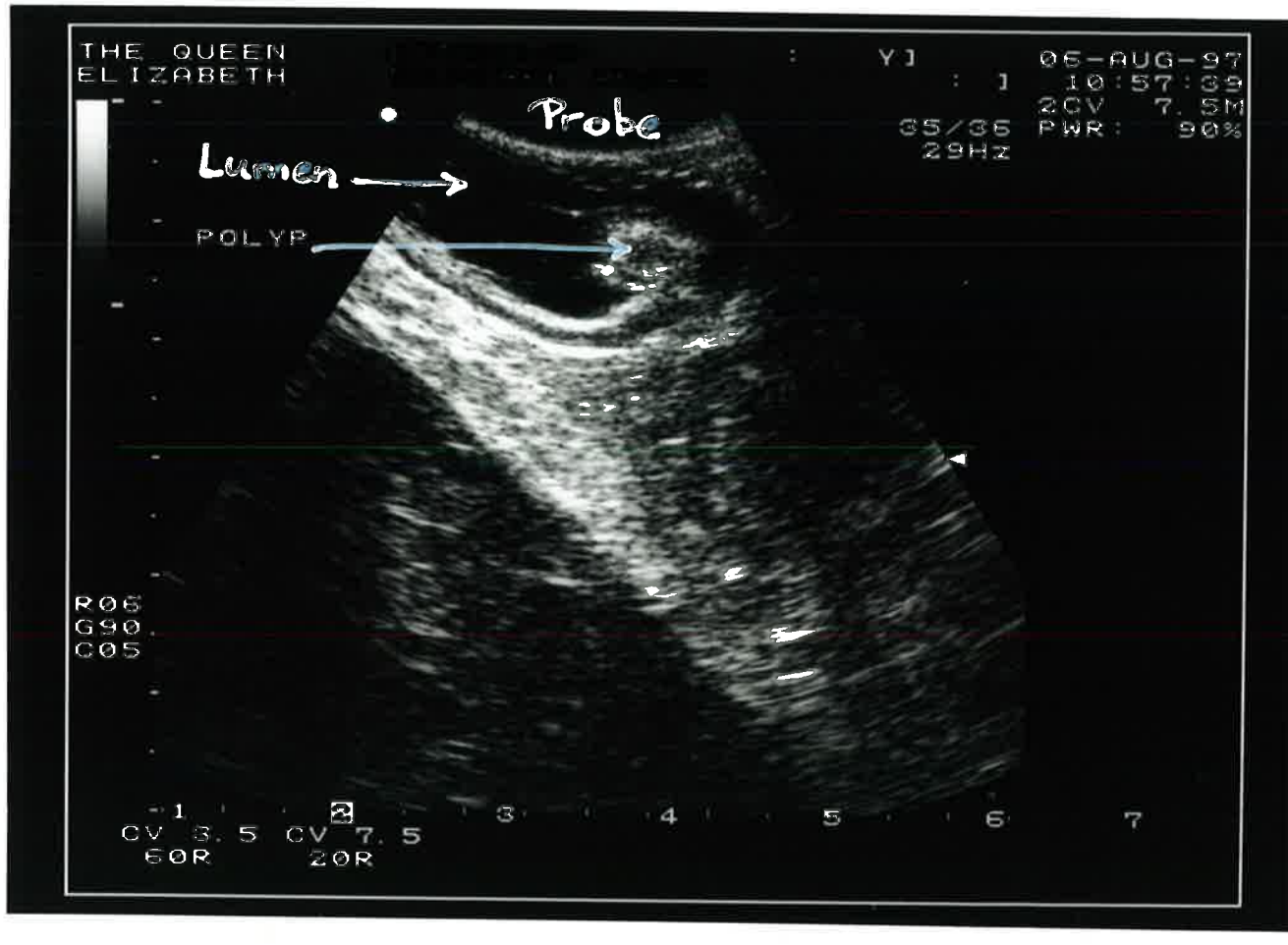

THE QUEEN
ELIZABETH
Y1
06-AUG-97
10:57:39
2CV 7.5M
65/65 PWR: 90%
29Hz
Probe
Lumen
POLYP
R06
G90
C05
1
2
3
4
5
6
7
CV 3.5 CV 7.5
60R 20R

FIGURE 3.1.2.10:

Ultrasound image of a small cancer with saline in the lumen of the colon. A small area of invasion through the muscularis propria can be seen.

FIGURE 3.1.2.10

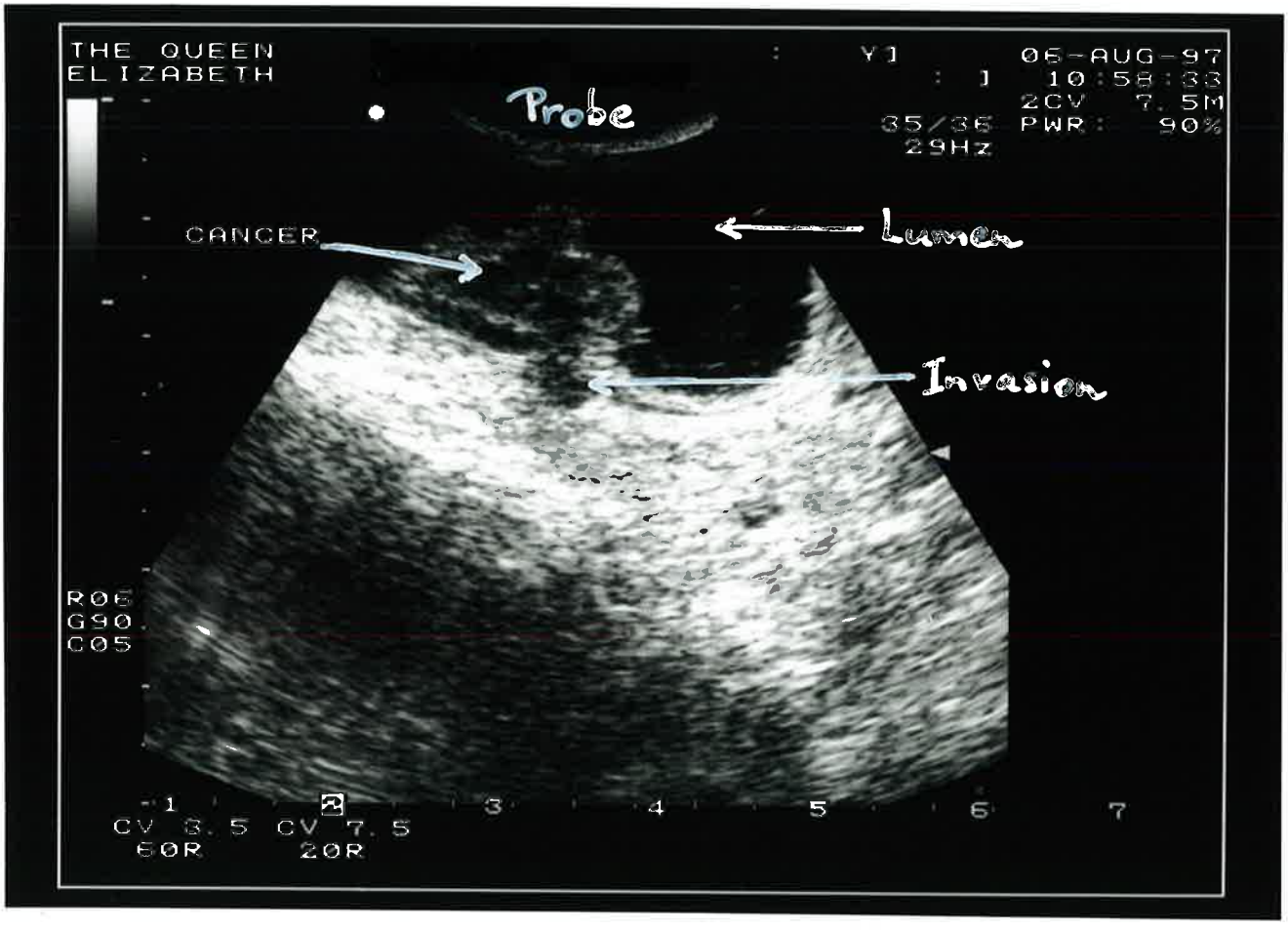


FIGURE 3.1.2.11:

Ultrasound of a large cancer with saline in the colonic lumen. A large para-rectal lymph node can be seen.

FIGURE 3.1.2.11

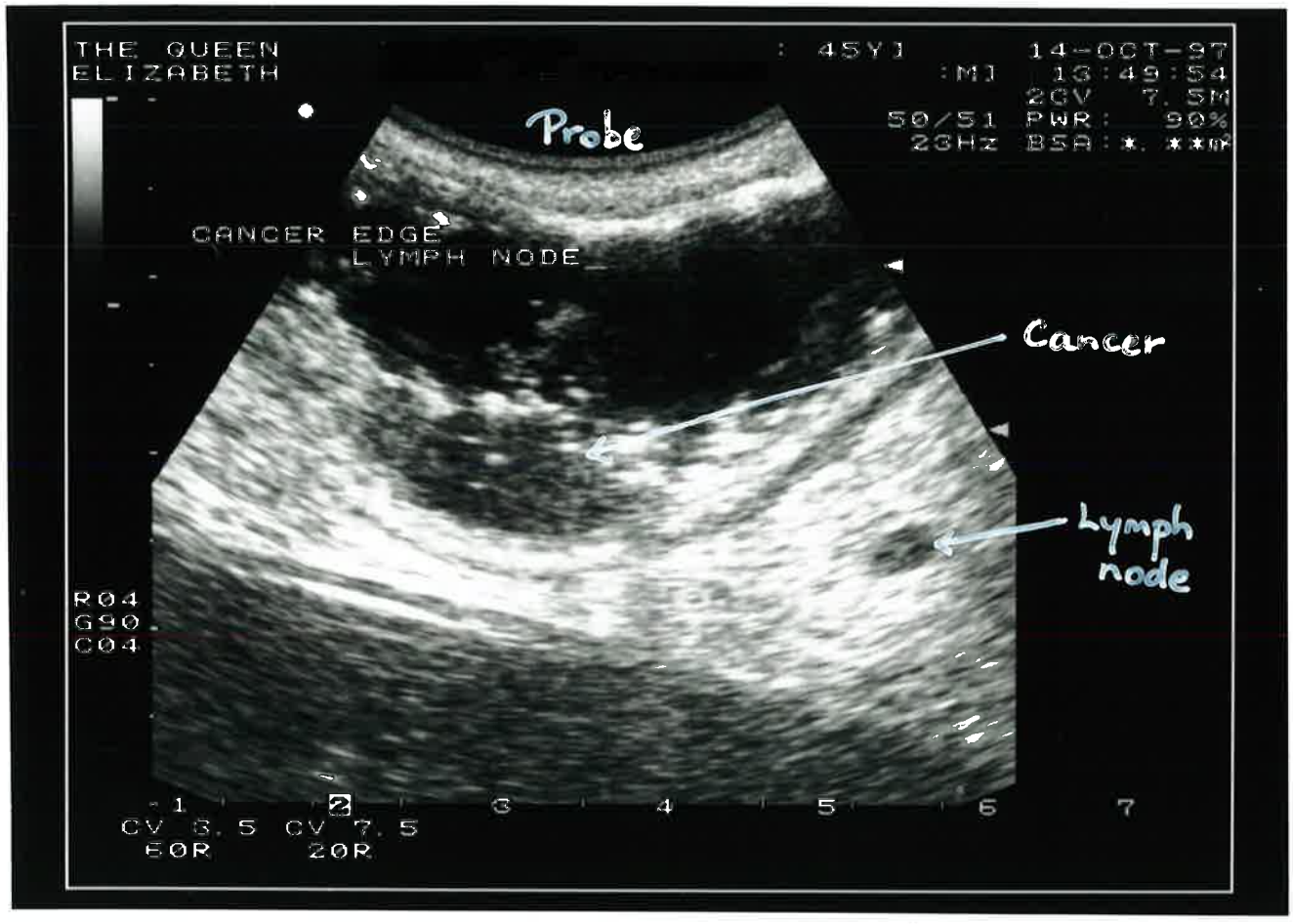


FIGURE 3.1.2.12:

Ultrasound image produced with fluid in the colonic lumen. There is a small ulcer, the remains of a malignant polyp that was excised six days previously by colonoscopic polypectomy.

Legend:	1	Colonic lumen
	2	Muscularis propria
	3	Pericolic fat
	4	Ulcer at site of previous polypectomy

FIGURE 3.1.2.12

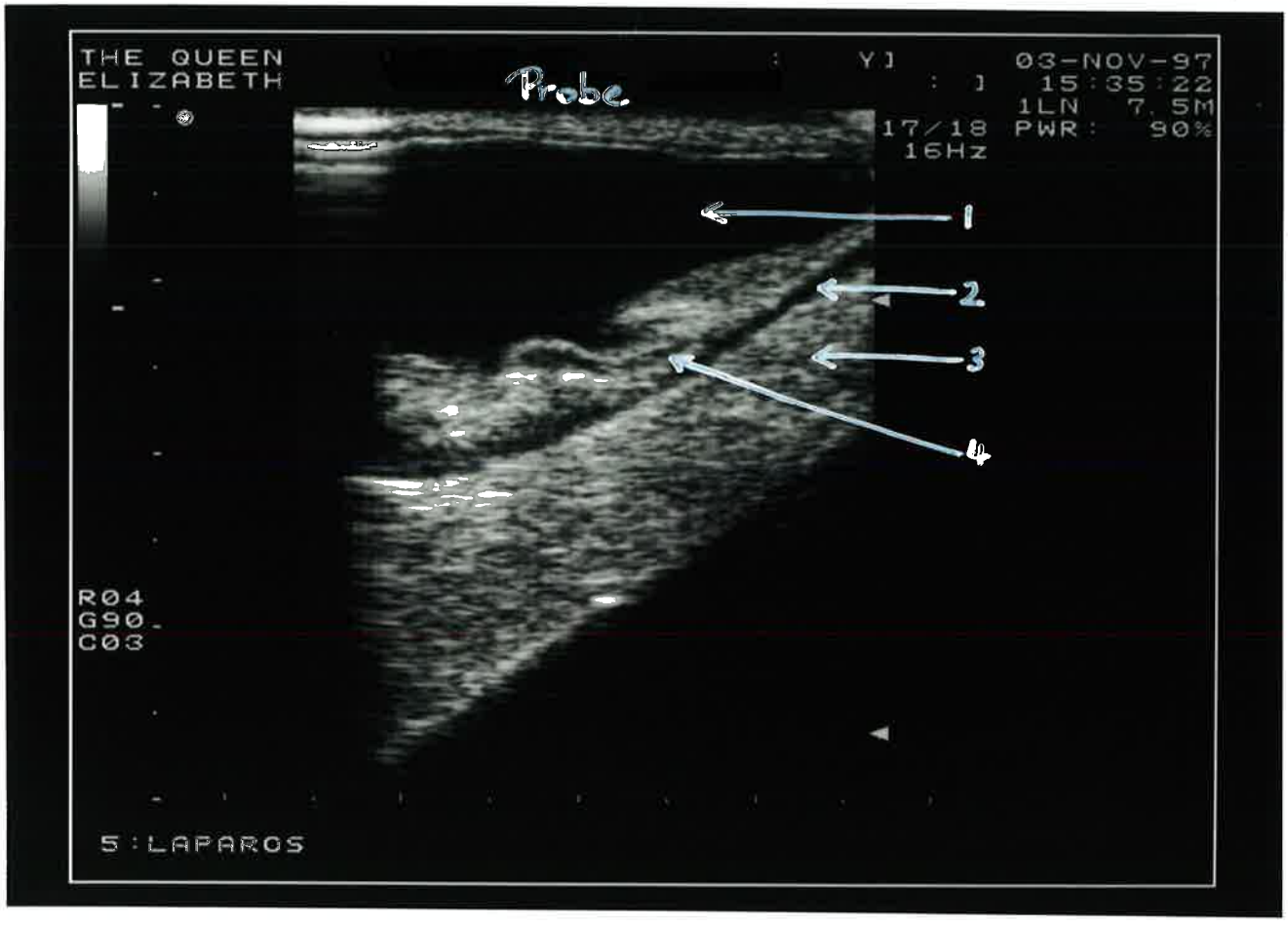


FIGURE 3.1.2.13:

Ultrasound image produced with fluid in the lumen of the colon. There is an area of submucosal derangement on the right edge of the image. This area was shown on histology to represent the remains of a malignant polyp excised 5 weeks before colectomy. This lesion could not be found by intra-operative colonoscopy.

Legend:	1	Colonic lumen
	2	Submucosa
	3	Muscularis propria
	4	Site of previous polypectomy

FIGURE 3.1.2.13

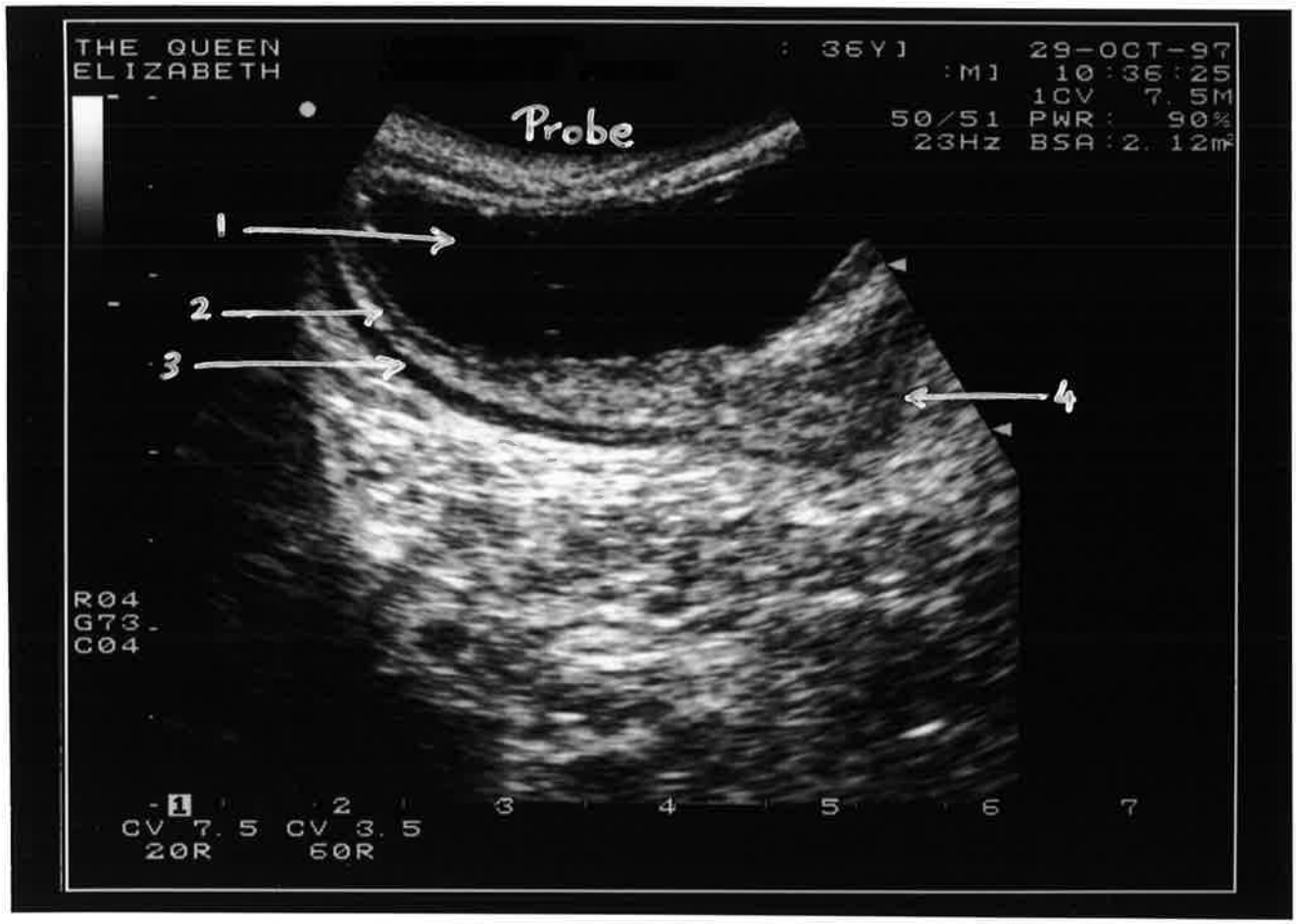


FIGURE 3.1.2.14:

In-vivo trial. Ultrasound of fluid-filled normal colon.

FIGURE 3.1.2.14

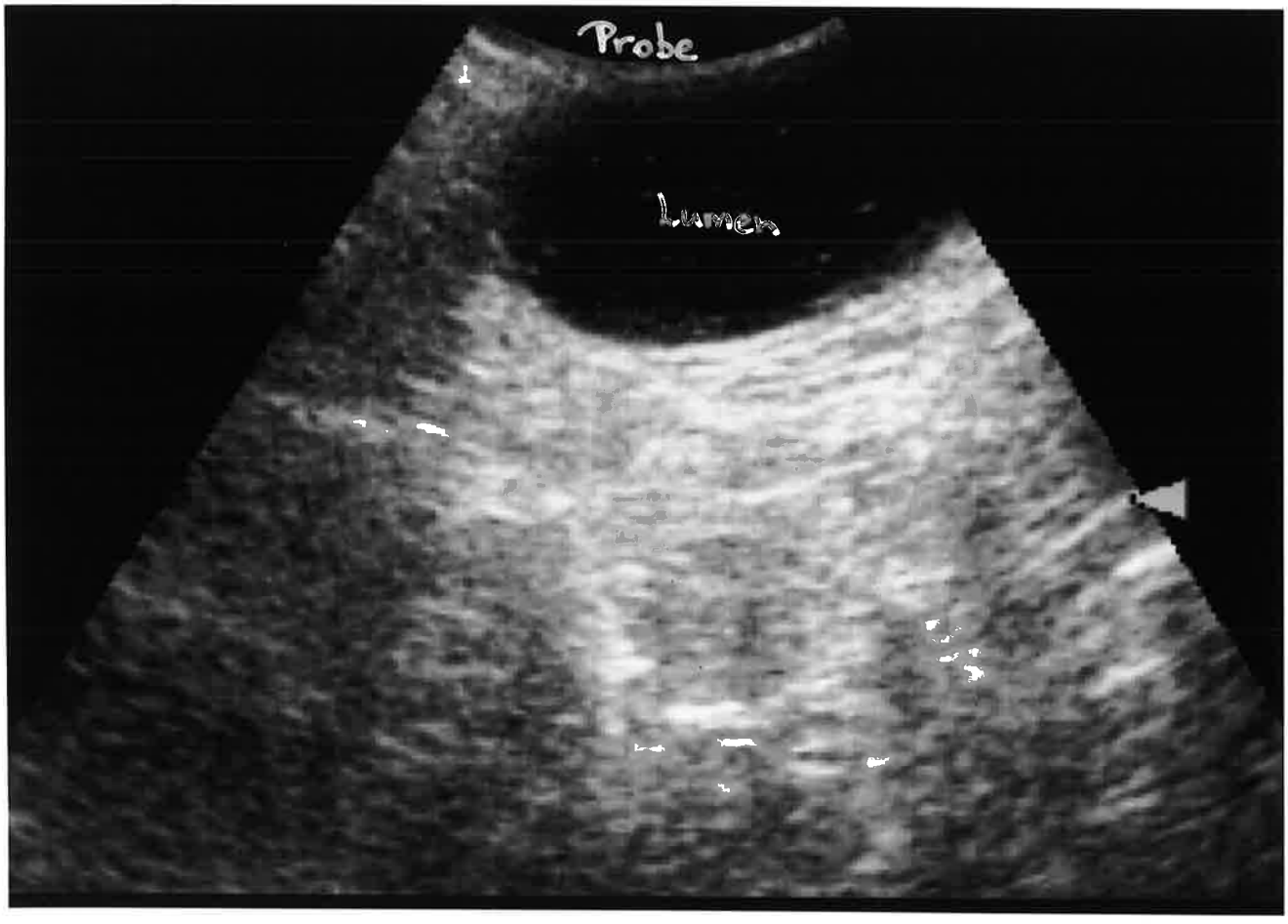
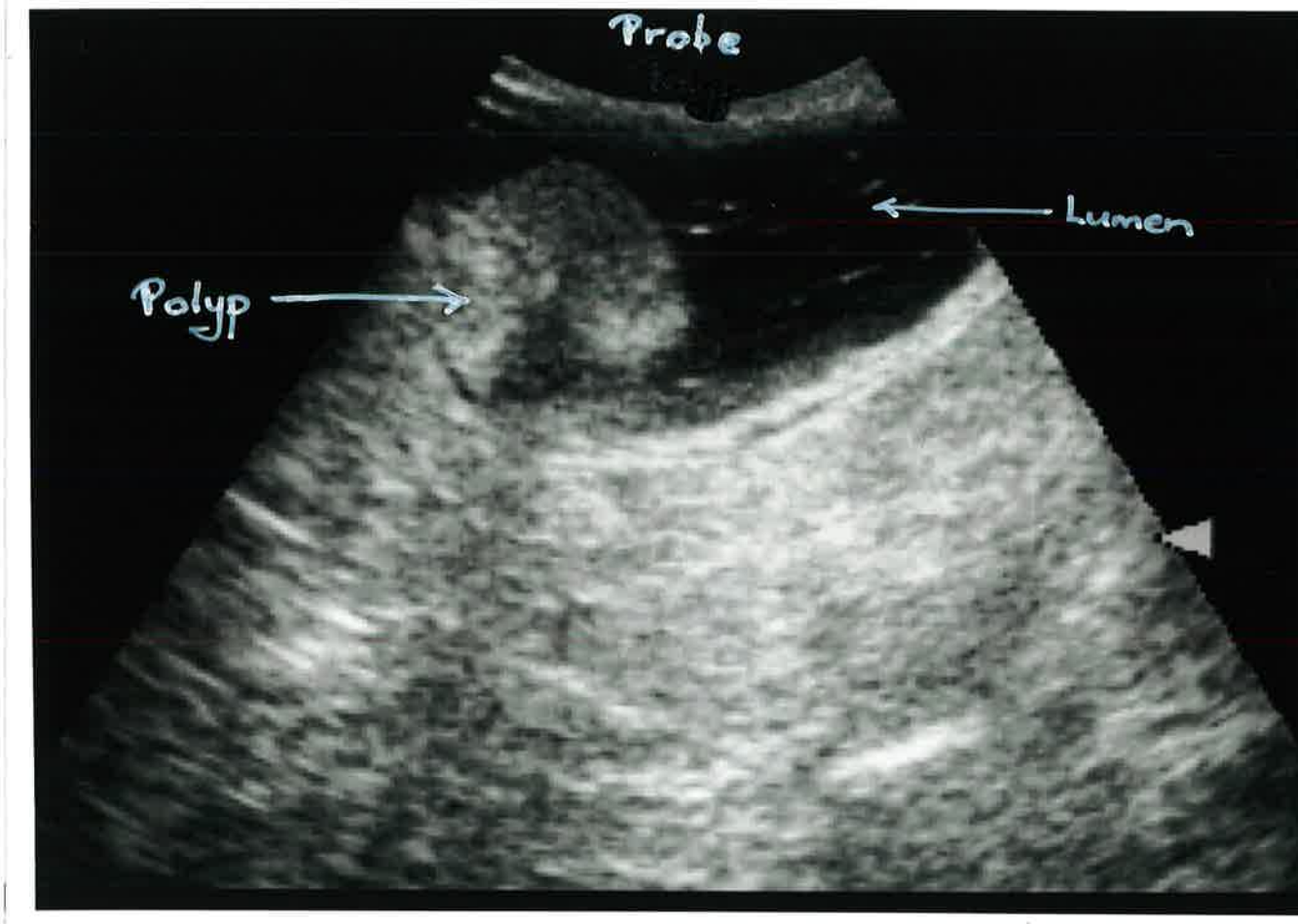


FIGURE 3.1.2.15:

In-vivo trial. Ultrasound of fluid-filled colon showing the impalpable polyp protruding into the lumen.

FIGURE 3.1.2.15



3.2 LAPAROSCOPIC COLORECTAL SURGERY

Laparoscopic surgery for colorectal conditions has been performed at The Queen Elizabeth Hospital since 1995. Most forms of elective colorectal surgery have been performed laparoscopically, including resection for both benign and malignant disease, mesh rectopexy for rectal prolapse, reversal of Hartmann's procedure and the creation of ileostomy and colostomy for faecal diversion. In addition, laparoscopy has been used to visualise the serosal surface of the colon during colonoscopic polypectomy in selected cases.

A prospective database of the progress of all patients undergoing laparoscopic colorectal surgery has been maintained. This has allowed the prospective evaluation of these procedures. As laparoscopic colorectal surgery is complex and often prolonged surgery, data collected from this patient group, particularly with regard to physiological variables, has also provided valuable information regarding the impact of laparoscopic surgery in general.

In this thesis, the technique and initial results of two procedures will be documented and discussed. These are laparoscopic reversal of Hartmann's procedure and laparoscopic-assisted colonoscopic polypectomy. In addition, the changes in core temperature of patients, which was recorded throughout surgery for this patient group, are analysed and compared to the changes recorded in a matched group of patients undergoing open colorectal surgery.

3.2.1 Laparoscopic reversal of Hartmann's procedure

Subjects

Patients who had undergone a Hartmann's procedure for the complications of benign sigmoid colon disease or (in one case) an anastomotic leak after elective anterior resection for a non-obstucting cancer were offered laparoscopic restoration of intestinal continuity. If a patient is considered suitable, from an anaesthetic point of view, for reversal of Hartmann's procedure, there is no contra-indication to the procedure being performed laparoscopically.

Technique

The patient has a polyethylene glycol bowel preparation and rectal washout on the day prior to surgery. A subcutaneous injection of low molecular weight heparin is given two hours before the procedure and prophylactic antibiotics are given at induction of anaesthesia. Under general anaesthesia, the patient is placed in the lithotomy position and sequential calf compression devices applied. An indwelling catheter and a nasogastric tube are inserted and a povidone-iodine soaked ribbon gauze is placed in the colostomy.

The positions of the surgical team, television monitors and ports are shown in Figure 3.2.1.1. Initial access to the camera port is by open insertion of a Hasson cannula in the right upper quadrant. Insufflation of carbon dioxide to a maximum intra-

abdominal pressure of 12mmHg is followed by insertion of a 0^{o} laparoscope. Subsequent ports are inserted under direct vision.

All adhesions to the anterior abdominal wall are divided to allow a clear view of the pelvis. In the last case of this series, adhesions were divided with the Ultracision^{TM} ultrasonic dissector (Ethicon Endosurgery Australia, North Ryde, N.S.W). The patient is then placed in a steep Trendelenburg position and the small bowel is mobilised out of the pelvis. The rectal stump is then mobilised. The assistance of a rigid sigmoidoscope placed in the rectal stump has at times proved invaluable in rectal mobilisation.

The surgeon then moves between the patient's legs and the position is changed to reverse Trendelenburg for full mobilisation of the splenic flexure and any remaining descending colon. The patient is then returned to a neutral position and the abdomen is desufflated.

The stoma is mobilised from the abdominal wall to the peritoneal cavity via an elliptical incision. The mucocutaneous junction is excised and an 0 polypropylene pursestring inserted. The anvil of an end-to-end stapler is inserted and the pursestring suture tied. The bowel is then dropped back into the abdominal cavity. The colostomy wound is closed with interrupted nylon sutures.

The abdomen is then reinsufflated, the patient placed in the Trendelenburg position and the small bowel retracted from the pelvis. If the left colon fails to reach the rectal stump without tension, further mobilisation is performed. A standard stapled end-to-end anastomosis is performed under laparoscopic vision.

The pelvis is then washed out with normal saline and a suction drain inserted. Port-sites are closed under vision with a suture through all layers. The skin is closed with staples.

At the completion of surgery, patients are sent to a standard recovery area and then observed overnight on the high-dependency ward. Removal of the drain, nasogastric tube and staples, the introduction of a liquid and then solid diet and the time of hospital discharge are at the discretion of the operating surgeon.

Results

Laparoscopic reversal of Hartmann's procedure has been performed on eight patients at The Queen Elizabeth Hospital between January 1996 and June 1998. There were 5 men and 3 women. The median age was 61 years (range 27-74 years) and the median weight was 72.5 kg (range 49-105 kg).

In 7 patients, the indication for the initial Hartmann's procedure was free perforation of a sigmoid diverticulum. The remaining patient required a Hartmann's procedure because of anastomotic dehiscence following anterior resection for cancer. The median time between the Hartmann's procedure and the restoration of intestinal continuity was 7 months (range 3-12).

The median operating time was 210 minutes (range 150-250 minutes). No patient required conversion to an open procedure and there were no intra-operative complications. Post-operative return of bowel function and hospital stay is detailed in Table 3.2.1.1.

One patient had a post-operative chest infection requiring intravenous antibiotics. The same patient required a two-unit blood transfusion post-operatively. She was discharged, well, on the eighth post-operative day. There were no other post-operative complications.

The median post-operative follow-up is 11 months (range 1-30 months). In this series, there have been no late complications of laparoscopic reversal of Hartmann's procedure.

Discussion

The morbidity of end colostomy closure by laparotomy is well documented. Complication rates between 24% and 35.2% have been reported (Sweeney and Hoffmann 1987, Mosdell and Doberneck 1991, Roe et al 1991, Keck et al 1994, Khan et al 1994, Mealy et al 1996, Khoury et al 1996).

A number of the complications of open Hartmann's reversal are wound related, including wound infection (7-16%; Mosdell and Doberneck 1991, Khan et al 1994) and incisional hernia (8-10%; Mealy et al 1996, Khoury et al 1996). In addition, the pain of a long mid-line wound may contribute to other complications. Pain causes decreased respiratory effort that may lead to atelectasis of lung bases and pneumonia. The incidence of pulmonary complications after open reversal of Hartmann's procedure is reported to be 10% (Mosdell and Doberneck 1991, Khan et al 1994).

Laparoscopic reversal of Hartmann's procedure is essentially the same operation as the open procedure, except that the long mid-line wound is not required. In theory therefore, this procedure has the potential to decrease the incidence of some of the aforementioned wound related complications. The decrease in post-operative analgesic requirements and the minimisation of manual bowel handling during the procedure may also impact on the length of the post-operative ileus.

The absence of wound infection or incisional hernia from this series, the rapid return of intestinal function and the median post-operative stay of 4 days give encouraging evidence that the proposed advantages of laparoscopic reversal of Hartmann's procedure can be delivered. This data corroborates that reported by other authors. Vernava et al (1995) reported two cases, without complications and with discharge of both patients on the fourth post-operative day. Sosa et al (1994) reported 14 completed procedures with 1 wound infection and a mean post-operative stay of 4.3 days. Regadas et al (1996) reported a series of 20 cases. Bowel movements recommenced within an average of 2.5 days and the mean post-operative stay was 4 days. In comparison, average length of stay for the open procedure is reported as being between 9 and 18 days post-operatively (Sweeney and Hoffmann 1987, Roe et al 1991, Khan et al 1994, Khoury et al 1996).

In order to analyse the results of this series of patients undergoing laparoscopic reversal of Hartmann's procedure, however, consideration must be given to several factors. It is a small series and, as such, the low complication rates seen thus far may not be indicative of the morbidity of the procedure. In

addition, comparison of the length of post-operative ileus and inpatient stay with historical control series may introduce bias, in that differences may have occurred because of changing clinical practices over time, rather than a real difference between the procedures (Binderow et al 1994, Reissman et al 1995).

Performance of Hartmann's reversal laparoscopically is at least as technically demanding as the open procedure. The median operating time of 210 minutes in this series is evidence of the challenging nature of the surgery, with much of the time taken to divide adhesions. Non-wound related complications such as anastomotic leak (Sosa et al 1994), anastomotic stenosis (Anderson et al 1993), peritonitis (Regardas et al 1996) and small bowel obstruction (Anderson et al 1993), whilst not seen in this series, have been reported in other series published to date. Extensive laparoscopic experience, including experience with laparoscopic colectomy is required before this procedure is introduced into a surgeon's armamentarium.

Even with consideration given to the above caveats, the early results of laparoscopic reversal of Hartmann's procedure are most encouraging. The clinical setting lends itself to a laparoscopic approach, as the pathology is benign, there is no intestinal resection and the healthy, elective patient can fully appreciate the benefits of the minimal access procedure. The above data adds to growing evidence that it is a feasible and safe technique and that it may produce a reduction in both the post-operative hospital stay and the rate of wound related complications reported with the open procedure.

FIGURE 3.2.1.1:

Positions of operating theatre equipment and personnel and laparoscopic ports for laparoscopic reversal of Hartmann's procedure.

FIGURE 3.2.1.1

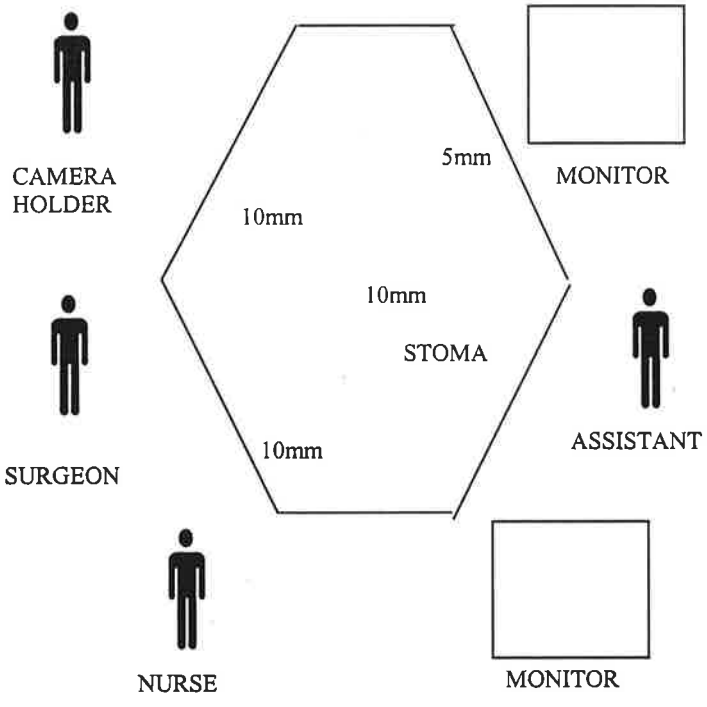

CAMERA
HOLDER
5mm
MONITOR
10mm
10mm
STOMA
SURGEON
ASSISTANT
10mm
NURSE
MONITOR

TABLE 3.2.1.1:

Post-operative progress of patients after laparoscopic reversal of Hartmann's procedure.

TABLE 3.2.1.1

Post-operative days until:	Median	Range
Passage flatus	2	1-3
Passage bowel action	3	2-5
Tolerating oral fluids	2	1-4
Tolerating solid food	3.5	2-5
Discharge	4	3-8

3.2.2 Laparoscopic-assisted colonoscopic polypectomy

Subjects

Patients with colonic polyps that, because of their size and/or location were considered to be unsuitable for primary colonoscopic polypectomy were referred for consideration of laparoscopic-assisted colonoscopic polypectomy. Initial assessment had, in all cases, been performed by an experienced colonoscopist, and biopsies had been taken to exclude overt malignancy.

Technique

The patient is admitted on the day of surgery following standard polyethylene glycol bowel preparation. A subcutaneous injection of low molecular weight heparin is given two hours before the procedure and prophylactic antibiotics are given at induction of anaesthesia. Under general anaesthesia the patient is placed in the lithotomy position. Pneumatic calf compression devices are applied and an indwelling urinary catheter is inserted.

Pneumoperitoneum is established with carbon dioxide to a pressure of 12 mmHg via a standard cutdown approach at the umbilicus. A Hopkins II zero degree telescope (Storz, Tuttlingen, Germany) coupled to a video display system is used to perform a thorough laparoscopy including inspection of the liver. Accessory 5mm ports are placed to aid in manipulation and mobilisation of the colon.

Colonoscopy is then performed using minimal insufflation. The location of the polyp is identified colonoscopically, and the abdominal operator confirms the position. Vascular clips can be used to mark the position of the lesion. A video colonoscope with a picture-in-picture device is advantageous because it allows the colonoscopist to visualise the colonic lumen and peritoneal cavity simultaneously. The relevant colonic segment is mobilised, if required, to allow the serosal surface of the colon in the area of the polyp to be visualised laparoscopically.

The colon proximal to the polyp is controlled using either an atraumatic grasper (Storz, Tuttlingen, Germany) or detachable intestinal clamps to prevent over-insufflation of the small intestine.

Prior to excision of the lesion, a trial of snare engagement of the polyp is performed. The polyp is encircled by the snare and manoeuvred into the lumen. This process is observed laparoscopically to ascertain if the snare includes a full thickness segment of the colonic wall.

If it is considered safe to proceed, colonoscopic excision of the lesion using an electrosurgical snare is then performed. Careful observation of the serosal surface over the polyp is maintained at all times to monitor the occurrence of any thermal injury during this process. The laparoscopic surgeon can manipulate the colon to optimise presentation of the polyp to the colonoscopist.

The excised polyp is removed and sent for histopathological assessment. The colonoscope is withdrawn while maintaining suction to deflate the colon. All ports greater than 5mm are closed

under vision to include all layers. The skin is closed with staples.

The patient is then admitted to the hospital for overnight observation.

Results

Between November 1996 and September 1997, six patients were referred with polyps deemed unsuitable for conventional colonoscopic resection. There were five men and one woman and the ages ranged from 32 to 68 years.

Two patients were referred with a sessile polyp in a thin walled caecum. Four patients had large polyps (3-7cm). Three were in the left colon and one in the caecum. Laparoscopic-assisted colonoscopic polypectomy was further indicated in a patient with a large caecal polyp because of frequency of stool after a previous anterior resection. He was reluctant to consent to another colonic resection.

Laparoscopic-assisted colonoscopic polypectomy was successfully achieved in all cases with complete excision of the polyp. All patients were able to tolerate oral intake 2-4 hours following the procedure and all patients were discharged the following day. There were no complications and all of the excised polyps were confirmed as benign on histopathology.

Twelve-month colonoscopic follow-up has been performed on the first three patients. There is no evidence of recurrence at the

site of the initial polypectomy.

Discussion

Since the advent of colonoscopy, as first reported by Wolff and Shinya in 1970, most colonic polyps have been managed by colonoscopic polypectomy with an acceptable outcome and low complication rates. However, in some instances colonoscopic polypectomy is unsafe due to the size or location of the polyp. The incidence of complications such as perforation increases with polyps greater than 3-4 cm in size particularly in the thin walled caecum and ascending colon (Webb et al 1985). These polyps are usually treated by colectomy.

With the widespread use of minimal access techniques, recent reports have indicated that laparoscopically assisted colonoscopic polypectomy is safe and feasible for selected patients with left-sided colonic lesions (Averbach et al 1995, Smedh et al 1997). This series shows that the technique is also applicable in patients with sessile polyps in a thin-walled caecum. The addition of laparoscopy enables the polyp to be presented optimally for colonoscopic snare polypectomy, via either mobilisation or manipulation of the bowel. This is particularly helpful in polyps located at acutely angulated locations such as the rectosigmoid junction and the splenic and hepatic flexures.

Direct laparoscopic visualisation of the bowel prior to snare polypectomy allows a trial capture of the polyp followed by traction to assess the degree of tethering and ascertain whether full

thickness injury will result during polypectomy. If the polyp is deemed unsuitable for excision via the laparoscopic-assisted approach a colectomy could be performed using either a laparoscopic or open approach. The choice should be discussed with the patient pre-operatively.

Laparoscopic visualisation provides an added degree of safety because the abdominal operator can visualise the serosal surface of the bowel to monitor any thermal effects of snare polypectomy. In the event of an injury laparoscopic intracorporeal suturing, or placement of an Endo-GIA stapler (Ethicon Australia, North Ryde, N.S.W.) can be utilised to control the breach.

In a report of a variation of this technique, a colotomy was performed in the region of the previously localised lesion. The polyp was delivered intraperitoneally and resected using an Endo-GIA stapler followed by intracorporeal suture closure of the colotomy (Beck and Kraulf 1993). There are concerns that tumour cells might be seeded by this technique if the polyp was malignant.

Laparoscopic-assisted colonoscopic polypectomy has the potential to provide significant advantages to the patient when compared to the alternative of colectomy. In this series, the patients treated using this technique were discharged one day following the procedure, and returned to full activity within a few days.

Polyps resected in this manner that subsequently show features of malignancy require colectomy. The patient must be fully informed of this possibility prior to laparoscopic-assisted colonoscopic polypectomy.

Laparoscopic-assisted colonscopic polypectomy is an alternative to colectomy in the management of large or difficult colonic polyps. It is safe and provides the post-operative advantages associated with minimal access surgery including early discharge from hospital and early return to full activity. In a select group of such patients, laparoscopic-assisted colonoscopic polypectomy may become the procedure of choice.

3.2.3 Core temperature changes during laparoscopic and open colorectal surgery

Subjects

Core temperature data was collected for all patients undergoing laparoscopic colorectal surgery at The Queen Elizabeth Hospital as part of a prospective database, commencing in November 1996. In June 1997, it was decided to collect similar data from patients undergoing open colorectal surgery in order to compare the results of this group with the data provided by the laparoscopic database.

Methods

In view of the fact that core temperature data had been collected for patients undergoing laparoscopic colorectal surgery for some eight months prior to the commencement of data collection in open surgery, it was decided to perform a case-controlled series rather than a randomised trial. The access technique for the surgery, that is whether it was to be an open or a laparoscopic procedure, was the choice of the operating surgeon.

Pre-operative preparation for all patients was standardised according to the Colorectal Surgical Unit protocol. Mechanical bowel preparation using polyethylene glycol was administered on the day prior to surgery. The patient was fasted from all food and

fluids for at least six hours prior to surgery. A subcutaneous dose of low molecular weight heparin was given as prophylaxis against deep venous thrombosis two hours prior to the scheduled commencement of surgery.

At induction of anaesthesia, a dose of prophylactic broad-spectrum antibiotics was given. The remainder of the anaesthetic details were at the discretion of the anaesthetic consultant in charge of the case. All intravenous fluids, including blood, were warmed to 37°C with a standard blood warmer prior to being infused into the patient.

The Bair Hugger™ forced-air warming device (Augustine Medical, Eden Prairie, MN) is a large disposable paper sheet which is attached by an adhesive device to the skin over the patients' lower sternum and costal margins. It covers the upper torso, the head and both arms. A specially designed pump forces air into the space between the two layers of the sheet. The temperature of the forced air can be adjusted according to requirements, up to 41°C. The Bair Hugger™ had been used in a non-randomised fashion for several of the laparoscopic cases before this case control series was commenced. The use of the Bair Hugger™ for the remainder of the cases was therefore not randomised, but was at the discretion of the anaesthetic team.

After induction of anaesthesia, a trans-oesophageal temperature probe was inserted via the nasal route and fixed in position at the estimated junction between the middle and lower thirds of the oesophagus. The initial core temperature was recorded prior to the commencement of surgery. The temperature was then

taken at 15-minute intervals throughout the procedure. The temperature probe was removed after the completion of the procedure but prior to extubation.

Data collected included age, sex, body surface area (calculated from weight and height), procedure performed, type of surgery (open or laparoscopic), operating time and the use or otherwise of the forced air warming device.

Two types of statistical analysis were carried out. Firstly, the minimum temperature recorded for each patient was classified as either normothermia (>36.0°C), mild hypothermia (35.5°C-35.9°C), moderate hypothermia (35.0°C-35.4°C) or severe hypothermia (<35.0°C). This data was then analysed using the Pearson Chi Square test of homogeneity.

Secondly, the graphic trend of temperatures during the procedure was analysed by using a repeated measures analysis of variance. This allowed for a prediction of the expected temperature value at the completion of surgery for each sub-group. Program 5V from the BMDP statistical software package was used for analysis (Ed W Dixon UCLA Press 1993).

Results

Between November 1996 and November 1997, 33 patients had laparoscopic colorectal surgery. Between July and November 1997, 27 patients underwent open colorectal surgery. The operations performed in each group are listed in Table 3.2.3.1. The groups

were well matched in terms of sex, age, body surface area and initial trans-oesophageal temperature (Table 3.2.3.2). The median time taken in the laparoscopic group was 180 minutes (range 60-285) which was significantly longer than the open operations (median 150 minutes, range 90-240; $p<0.05$).

The Bair Hugger^{TM} forced air warmer was used in 17 of the 33 patients (52%) who had laparoscopic surgery and 19/27 (70%) of those undergoing open surgery. The groups who did and did not have the Bair Hugger^{TM} applied were also well matched for sex, age, body surface area and initial transoesophageal temperature.

The minimum temperature recorded for each patient during surgery was used for the initial analysis. Table 3.2.3.3 shows the comparison of minimum temperatures between patients undergoing open and laparoscopic surgery. There was no significant difference between the groups ($p=0.8232$).

Table 3.2.3.4 shows the comparison of minimum temperatures between patients who did or did not have the Bair Hugger^{TM} applied during surgery. The use of the forced air-warming device was associated with a significant decrease in hypothermia during surgery ($p=0.0146$).

Table 3.2.3.5 shows the distribution of minimum temperature values after dividing the patients into subgroups. This analysis enabled an assessment of the incidence of hypothermia between subgroups whilst holding one of the variables, either the type of surgery (open or laparoscopic) or the use or otherwise of the forced-air warming device, as a constant. Chi square analysis of

this data shows that, in open surgery, there was no difference in minimum temperature between patients who had the use of the Bair Hugger™ and those who did not (p=0.0702). In the laparoscopic surgery group, however, the use of the Bair Hugger™ was associated with a significantly lower incidence of hypothermia (p=0.0264). Subgroup analysis to compare the incidence of hypothermia between open and laparoscopic surgery in patients who had the Bair Hugger™ showed no difference between the groups (p=0.3572). There was also no difference in the incidence of hypothermia between open and laparoscopic colorectal surgery in those who did not have the Bair Hugger™ applied (p=0.4730).

The final analysis was an estimate of linear combinations of regression parameters, allowing an estimate of the expected temperature change for each subgroup over time. The end-points were at 150 minutes in the open surgery group and 180 minutes in the laparoscopic surgery group, as these were the median operating times for each type of surgery. The predicted change in temperature was significantly different between males and females, necessitating separate analyses for each gender. The results are illustrated graphically in Figure 3.2.3.1 and Figure 3.2.3.2.

No difference in predicted final temperature could be seen in male patients (Figure 3.2.3.1) when comparing open and laparoscopic surgery, nor when comparing patients who had the use of the Bair Hugger™ with those who did not. In female patients (Figure 3.2.3.2), however, the Bair Hugger™ allowed significantly less temperature drop in both the laparoscopic and open surgery groups. In addition, laparoscopic surgery in females had a significant slowing of temperature drop in comparison to open

surgery, both in the group who had the Bair Hugger™ and in those who did not.

Discussion

The results of this study have raised several points for discussion concerning the incidence of hypothermia in open and laparoscopic colorectal surgery, the efficacy of the Bair Hugger™ forced-air warming device in the prevention of hypothermia and the role that a patients' gender may play in the response to the hypothermic stimulus of surgery.

The minimum temperature data for the small patient cohort who underwent open colorectal surgery without the warming device in this study is similar to that which has been reported in the literature which was presented in the introduction to this section. A minimum temperature below 36°C was recorded in 6/8 patients (75%), and below 35°C in 2/8 patients (25%). In laparoscopic surgery without the Bair Hugger™ the figures are similar (13/16 [81%] below 36°C and 3/16 [19%] below 35°C).

Similarly, there was no significant difference in the incidence of hypothermia between open and laparoscopic surgery in the patients who did have the forced-air warming device applied during surgery. The overall comparison of all patients, both with and without the Bair Hugger™, also showed no difference between the open and laparoscopic surgery groups.

Laparoscopic surgery in this series was performed using unheated carbon dioxide for pneumoperitoneum. The use of heated, humidified gas, as suggested by Bessell et al (1995), or gasless laparoscopy (Kawamura et al 1995) may cause less hypothermia and requires further investigation.

The value of forced-air warming devices in open abdominal surgery is well established. They have been shown in randomised trials to prevent hypothermia in this setting (Onik et al 1993, Karayan et al 1996). In this study, however, the difference in the incidence of hypothermia between the patients who did and did not have the Bair Hugger^{TM} applied during open abdominal surgery did not reach statistical significance ($p=0.0702$). This finding is possibly due to the small size of the patient cohort (eight patients) who did not have the device applied during open abdominal surgery.

A significant decrease in the incidence of hypothermia, as shown in this series, of a forced air-warming device during laparoscopic colorectal surgery has not been previously reported. Seitzinger et al (1993) did report that a lesser degree of hypothermia was seen with the use of the Bair Hugger^{TM} during prolonged laparoscopic gynaecological surgery, however this data was not subjected to statistical analysis. If the results of the current study are reproduced by a randomised, controlled trial, it is likely that the use of forced-air warming devices should be recommended for prolonged laparoscopic surgery as well as open abdominal surgery.

A difference in the hypothermic response of males and females has been previously reported. Bush et al (1995) showed, in a multivariate analysis that female gender was an independent predictor of intra-operative hypothermia during elective abdominal aortic aneurysm repair. The scarcity of corroborative data is more likely to be due to any gender difference not being fully assessed, rather than the difference not being present.

This study, however, does not show that females have a higher incidence of hypothermia per se. According to the presented data, females have greater inter-group variability, with laparoscopic surgery and the use of the forced-air warmer both providing significant protection from hypothermia. These differences were not seen in men. Indeed, from the data presented by this study, there is no statistical evidence that the use of the Bair Hugger™ provides protection from hypothermia in men, in either laparoscopic or open colorectal surgery. It is possible that the protection from hypothermia seen in other studies may be attributable solely to differences between the female patients in the study groups.

The finding of a possible gender difference in the temperature response to surgery, combined with the need for randomised data to accurately assess the role of the forced-air warming device in prolonged laparoscopic surgery has prompted further research. The protocol for a randomised trial has been written and has recently obtained approval from the Ethics of Human Research Committee at The Queen Elizabeth Hospital.

Statistical analysis this trial will concentrate on the overall results, in order to reassess the apparent value of the Bair Hugger™

in prolonged laparoscopic surgery. In addition, there will be separate statistical analyses for male and female patients. It is anticipated that the results of this trial will allow a conclusion to be reached regarding the effect that a patients' gender has on the hypothermic response to surgery. Nevertheless, it must be strongly encouraged that the authors of other publications investigating peri-operative hypothermia report the effect of gender in their statistical analyses.

TABLE 3.2.3.1:

Comparison of open and laparoscopic operations performed in the core temperature study.

TABLE 3.2.3.1

	Open Group	Laparoscopic Group
Right hemicolectomy	5	7
Left/sigmoid colectomy	7	5
Anterior resection	9	8
Abdominoperineal resection	5	-
Total colectomy	1	1
Rectopexy	-	5
Reversal of Hartmann's procedure	-	5
Colostomy formation	-	2
Total	**27**	**33**

TABLE 3.2.3.2:

Comparison of patient details between open and laparoscopic surgery groups in the core temperature study.

Data are recorded as median (range)

TABLE 3.2.3.2

	Open Group	**Laparoscopic Group**
Sex (M:F)	16:11	16:17
Age (Years)	70 (36-88)	68 (19-89)
Height (m)	1.70 (1.57-1.85)	1.68 (1.52-1.86)
Weight (kg)	72 (55-95)	73 (45-114)
Initial temperature (°C)	36.3 (35.3-36.7)	36.3 (35.5-37.1)
Operating time (min)	150 (90-240)	180 (60-285)

TABLE 3.2.3.3:

Overall comparison of the minimum temperature values recorded between patients undergoing open and laparoscopic colorectal surgery.

Statistical analysis has been performed using the Pearson Chi square test of homogeneity. Significance is considered to be a p value of less than 0.05.

TABLE 3.2.3.3

	Normothermia >36.0°C	Mild Hypothermia 35.5-35.9°C	Moderate Hypothermia 35.0-35.4°C	Severe Hypothermia <34.9°C	TOTAL
Open Group	8	11	4	4	27
Laparoscopic Group	13	13	3	4	33

p=0.8232

TABLE 3.2.3.4:

Overall comparison of the minimum temperature values recorded between patients who did and did not have the Bair Hugger™ forced-air warming device applied during surgery.

Statistical analysis has been performed using the Pearson Chi square test of homogeneity. Significance is considered to be a p value of less than 0.05.

TABLE 3.2.3.4

	Normothermia >36.0°C	Mild Hypothermia 35.5-35.9°C	Moderate Hypothermia 35.0-35.4°C	Severe Hypothermia <34.9°C	TOTAL
Bair Hugger™ Group	16	16	1	3	36
No Bair Hugger™ Group	5	8	6	5	24

p=0.0146

TABLE 3.2.3.5:

Subgroup analysis of the minimum temperature values recorded whilst holding one of the variables, either the type of surgery (open or laparoscopic) or the use or otherwise of the Bair Hugger^{TM} as a constant.

Statistical analysis has been performed using the Pearson Chi square test of homogeneity. Significance is considered to be a p value of less than 0.05.

*Statistically significant.

TABLE 3.2.3.5

	Normothermia >36.0°C	Mild Hypothermia 35.5-35.9°C	Moderate Hypothermia 35.0-35.4°C	Severe Hypothermia <34.9°C	TOTAL
A Open, Bair Hugger™	6	10	1	2	19
B Open, No Bair Hugger™	2	1	3	2	8
C Lap, Bair Hugger™	10	6	0	1	17
D Lap, No Bair Hugger™	3	7	3	3	16

Chi Square subgroup analysis

Open surgery;	Bair Hugger vs No Bair Hugger (A vs B)	p=0.0702
Laparoscopic surgery;	Bair Hugger vs No Bair Hugger (C vs D)	p=0.0264*
Bair Hugger;	Open vs laparoscopic surgery (A vs C)	p=0.3572
No Bair Hugger;	Open vs laparoscopic surgery (B vs D)	p=0.4730

FIGURE 3.2.3.1:

Trend of core temperature change during surgery for male patients as calculated by linear regression analysis.

Legend:

Op	=	Open surgery
Lap	=	Laparoscopic surgery
BH	=	Bair Hugger™ applied during surgery
No BH	=	Bair Hugger™ not applied during surgery

FIGURE 3.2.3.1

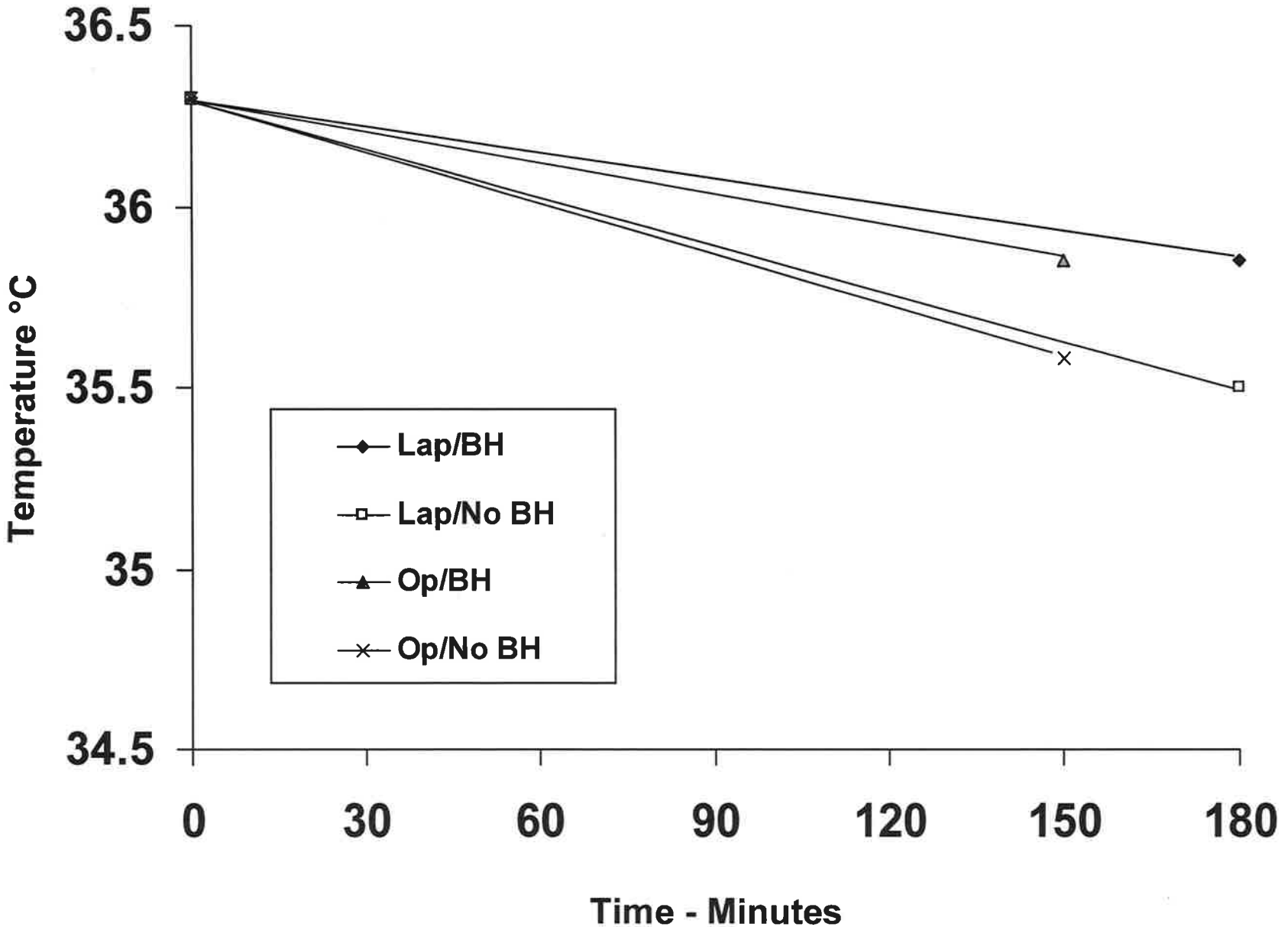

36.5
36
35.5
35
34.5
Temperature °C
Lap/BH
Lap/No BH
Op/BH
Op/No BH
0
30
60
90
120
150
180
Time - Minutes

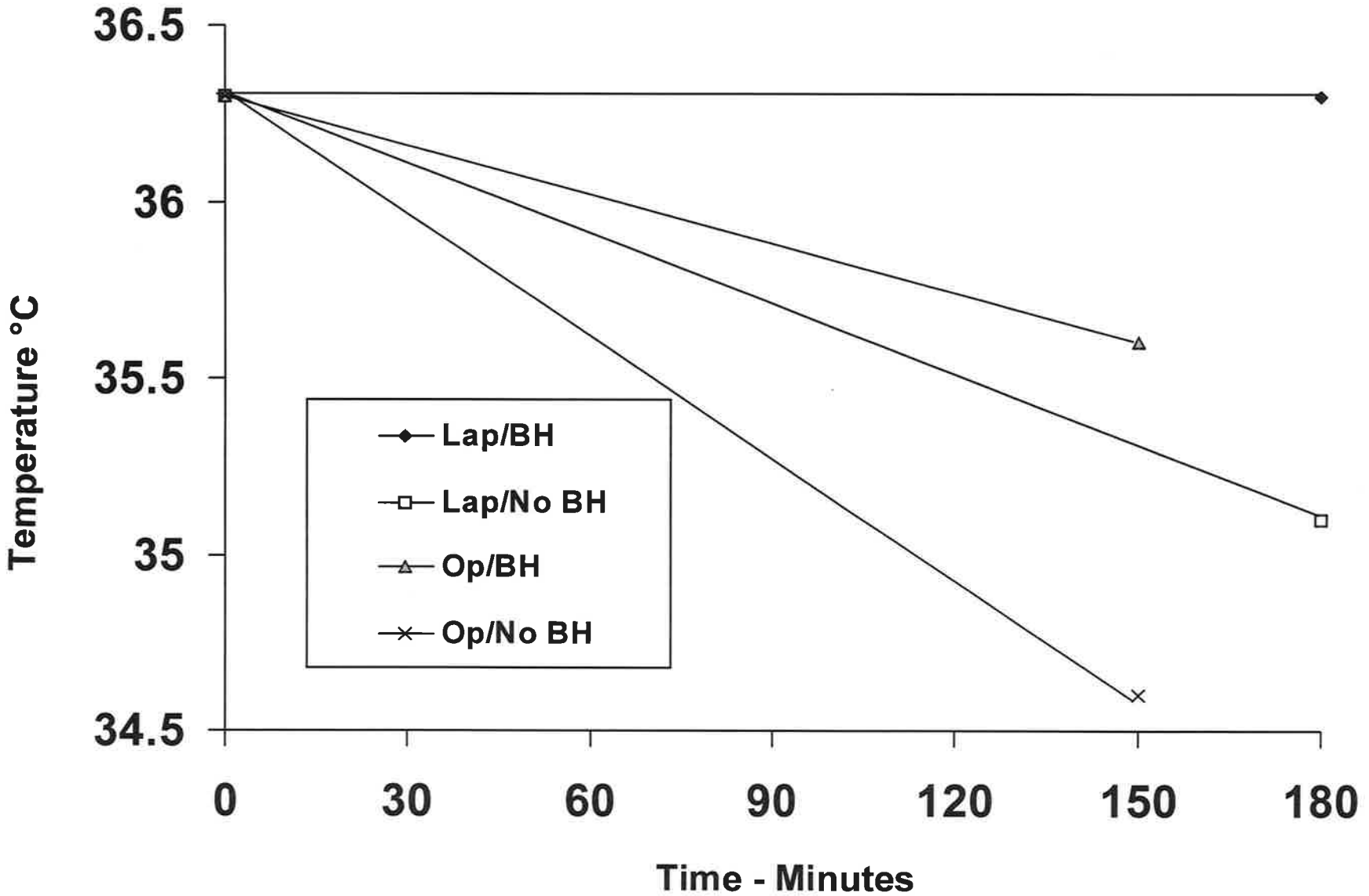
FIGURE 3.2.3.2:

Trend of core temperature change during surgery for female patients as calculated by linear regression analysis.

Legend:

Op	=	Open surgery
Lap	=	Laparoscopic surgery
BH	=	Bair Hugger™ applied during surgery
No BH	=	Bair Hugger™ not applied during surgery

FIGURE 3.2.3.2


36.5
36
35.5
35
34.5
Temperature °C
Lap/BH
Lap/No BH
Op/BH
Op/No BH
0
30
60
90
120
150
180
Time - Minutes

3.3 ADVANCED PROGNOSTIC TECHNIQUES IN COLORECTAL CANCER

3.3.1 Immunobead reverse transcriptase-polymerase chain reaction (RT-PCR) detection of free intra-peritoneal malignant cells at colorectal cancer resection

The aim of this study was to assess the efficacy of three techniques; conventional cytology, immunocytochemistry and immunobead RT-PCR in the detection of free intra-peritoneal colorectal cancer cells at the time of resection of the primary lesion. The laboratory work for this section was performed by hospital scientists in the Department of Pathology (cytology and immunocytochemistry) and research workers from the Department of Haematology/Oncology (immunobead RT-PCR). These workers have been acknowledged in the appropriate section of this thesis.

Although the technique of immunobead RT-PCR will be described in the Methods section of this paper, the development and validation of this technique is not a component of this thesis, as this aspect is the subject of other works, including theses, written by the designers of the technique. This study concentrates on the applicability of this technique to a clinical situation, namely the detection of small numbers of intra-peritoneal malignant cells, and a comparison of the results with those of two other techniques that have been used for this purpose in the past.

This study was approved by the Ethics of Human Research Committee at The Queen Elizabeth Hospital.

Subjects

The subjects for this study were patients with a primary colorectal malignancy who were to undergo colorectal resection by laparotomy or laparoscopy at The Queen Elizabeth Hospital. There were no exclusion criteria from this subject group. A control group of patients having colorectal surgery for benign conditions was also included.

Methods

The patients were approached on the ward on the day prior to surgery and asked if they would consider enrolment in the study. A written information sheet was provided and informed consent was obtained in writing. This study required no changes to the standard pre-operative preparation for colorectal resection.

Collection of specimens

A total of fifteen specimens were collected from each patient. These consisted of three identical saline wash specimens from five sites. One specimen from each site was sent for cytology, one for immunocytochemistry and one for immunobead RT-PCR. The specimen containers for the former two techniques were sterile plastic bottles. The containers for immunobead RT-PCR were sterile plastic tubes that had been pre-treated with EDTA (ethyline diamine tetra acetic acid). This was to stop thrombosis of the specimen if it contained blood. Extraction of epithelial cells by immunobeads is not possible if the specimen has coagulated.

The sites from which specimens were taken are as follows;

1. Pelvis pre-resection: After completion of the abdominal incision and a thorough laparotomy, warmed sterile normal saline was placed in the pelvis. This saline was gently agitated and 60ml of the fluid was aspirated into a sterile plastic syringe. This aspirate was then divided equally between the three specimen containers (i.e. 20ml in each). In the case of laparoscopic colectomy, the saline was placed in the pelvis after creation of pneumoperitoneum. It was then aspirated into a suction specimen trap, from which 20ml fluid specimens were placed in each of the three containers. The remainder of the pelvic fluid was then aspirated into the suction apparatus and discarded.

2. Tumour bed pre-resection: Warmed sterile normal saline was then placed around the area of the tumour. 60ml of this fluid was then aspirated and distributed as above. If the patient had benign disease, the 'tumour bed' specimens were taken from around the site of proposed operation. In the case of rectal cancers, because the tumour was in the pelvis, a second set of specimens was taken from the pelvis.

3. Pelvis post-resection: After resection of the specimen and reanastomosis of the bowel, but before the use of any washout fluid, saline was again placed in the pelvis. Specimen collection was as for the pelvis pre-resection specimens.

4. Tumour bed post-resection: After the pelvis post-resection specimens had been collected and the residual pelvic saline aspirated and discarded, saline was placed in the area from which the tumour had been resected. Specimen collection was as for the tumour bed pre-resection specimens.

5. Wound protector: In all cases of open surgery, a sterile plastic wound protector was placed in the abdominal wound at the commencement of surgery and removed after resection of the tumour-containing colon and reanastomosis. In all cases of laparoscopic surgery, a sterile plastic wound protector was placed in the wound prior to extraction of the specimen. After removal of the wound protector, it was washed with approximately 200ml of warmed, sterile normal saline. 60ml of this fluid was aspirated and divided evenly between the three specimen bottles.

Cytology

The specimens for cytology were sent to the Cytology Department immediately upon completion of the procedure. The specimen was prepared by centrifugation using a standard cytocentrifuge for 10 minutes. The cell layer spun down by this process was stained using a Papanicoloau stain on a standard cytology slide.

Each prepared slide was examined cytologically by a senior hospital scientist and separately by a senior consultant pathologist from the Department of Pathology. Slides were classified as either containing or not containing malignant cells. Equivocal or

suspicious cells on cytology were considered non-diagnostic of malignancy. The hospital scientist who assessed the cytology slides was unaware of the results of immunocytochemistry or immunobead RT-PCR.

Immunocytochemistry

The immunocytochemistry was performed using a cell block technique. The peritoneal washing fluid was fixed in buffered formal acetone for 30 seconds and then rinsed with distilled water. The endogenous peroxidase was blocked with 0.5% hydrogen peroxide in methanol for 20 minutes, after which it was rinsed with phosphate buffered saline (PBS). The antibody (either Ber-EP4 or AUA1) was then added, diluted 1:100 in 33ul normal horse serum to 2.5ml of PBS and incubated overnight at 4°C in a humid tray.

The following morning, biotinylated antibody (DAKO LSAB) was applied for 15 minutes, followed by rinsing with PBS and the application of streptavidin peroxidase (DAKO LSAB) for a further 15 minutes. After rinsing with PBS, 0.05% diaminobenzidine substrate solution was applied for 7 minutes. Further rinsing with PBS was followed by staining with haematoxylin for 30 seconds and washing in distilled water. The specimen was then dehydrated, cleared, mounted and reported. The pathologist reporting the results of immunocytochemistry was unaware of the immunobead RT-PCR results.

Immunobead reverse transcriptase-polymerase chain reaction

The peritoneal washing specimens for immunobead RT-PCR were collected immediately upon completion of the procedure by research staff from the Clinical Development and Research Centre at The Queen Elizabeth Hospital. The details of the immunobead RT-PCR process have been described in detail in the literature by the designers of the technique (Hardingham 1998). As previously stated, the technique itself is not the subject of this thesis. A brief outline of the technique is included to allow analysis and discussion of its value.

Each specimen was spun down and then re-suspended to a total of 10ml using phosphate buffered saline (PBS). This sample was incubated with 4 x 10^6 immunomagnetic beads (Dynal, Oslo, Norway) labeled with the antibody Ber-EP4 (Dakopatts, Gestrop, Denmark). Ber-EP4 is a monoclonal antibody that has been shown to detect both neoplastic and non-neoplastic epithelial cells but not mesothelial or haemopoietic cells (Latza 1990). Incubation was for four hours or overnight with gentle mixing at room temperature. Bead-rosetted cells were isolated using a magnetic array. This isolate should consist only of non-neoplastic and neoplastic epithelial cells.

The isolated cells are then lysed in a volume of 15ul containing 0.1% Nonidet P-40, 10mM DTT and 10 units Rnasin (Promesa, WI, USA) to release RNA. Following a 70°C denaturation for 3 minutes, reverse transcription was carried out by the addition of 5 x First Strand Buffer, 300 units of M-MLV reverse transcriptase (both from Life Technologies, MD, USA), 750 ng

random hexamers (Pharmacia, Uppsala, Sweden), 0.6 mM of each deoxynucleotide triphosphate (Boehringer Mannheim, Mannheim, Germany) with sterile ultra-pure water to a volume of 30 ul. The reverse transcriptase reaction was incubated at 37°C for 60 minutes.

A separate PCR was performed for each of the markers CK-19, CK-20, mucin 2, laminin 5 (gamma 2 chain) and matrilysin. Seven microlitres of the RT product was taken as a substrate for the PCR in a final volume of 50 ul. The other components of the PCR were as follows: 100ng of each primer, 0.75 units of Taq polymerase (Amplitaq gold, Perkin Elmer Ca, USA), 10 units PCR buffer (Perkin Elmer), 1.5 mM $MgCl_2$, 200 uM of each deoxynucleotide triphosphate and sterile ultra-pure water. The PCR cycling parameters varied for each marker.

The PCR product was then run on a 1.5% agarose gel, transferred by Southern blotting to nylon membrane (Hybond N+, Amersham) and hybridised to a ^{32}P end-labelled internal oligoprobe. After washing twice at 42°C in 2 x standard saline citrate, autoradiography using Hyperfilm^{TM}-MP (Amersham) was carried out for 6-72 hours before assessment. The research workers who performed and reported the immunobead RT-PCR were unaware of the results of cytology or immunocytochemistry.

Results

Between May 1997 and August 1998, peritoneal washing specimens were collected from 59 patients. Forty-seven patients had colorectal cancer, 6 patients had large adenomata requiring colonic

resection and 6 patients required colorectal resection for benign disease. Four of the patients with benign disease had sigmoid diverticular disease, 1 had ileocaecal Crohn's disease and 1 patient had an ischaemic sigmoid stricture after an emergency abdominal aortic aneurysm repair. In two patients (one with a Dukes' B colorectal cancer and one with benign disease), immunobead RT-PCR was not possible because of failure of equipment. These patients have been excluded from further analysis.

Eight of the 46 patients (17%) with colorectal cancer had Dukes' Stage A disease, 23 patients (50%) had Dukes' Stage B disease and 11 patients (24%) had Dukes' Stage C disease. The remaining 4 patients (9%) had residual overt malignancy at the completion of surgery and are considered to have Stage D disease. Forty of the patients (87%) with malignant disease underwent open resection; the remaining 6 patients had a laparoscopic-assisted colectomy. Six of the 12 patients (50%) having colorectal resection for benign disease had open surgery and 6 had laparoscopic surgery

Conventional cytology was performed on specimens from all 59 patients. The 20ml peritoneal wash specimens collected from these patients were paucicellular, particularly those collected prior to resection. No overtly malignant cells were detected in any specimen from any patient.

Immunocytochemistry, using the monoclonal antibodies Ber-EP4 and AUA1 was performed on the first 18 patients. Sixteen of these patients had colorectal cancer (4 Stage A, 8 Stage B, 2 Stage C and 2 Stage D) and the other 2 patients had benign disease. The immunocytochemistry specimens also suffered from the

paucicellular nature of the specimens. No malignant cells could be confidently diagnosed by this technique on the first 18 patients. After interim analysis of this data, it was considered inappropriate to continue both conventional cytology and immunocytochemistry due to the low yield and the considerable expense of the latter. The peritoneal washing specimens from the remaining 41 patients did not undergo analysis by immunocytochemistry.

Immunobead RT-PCR was performed on the wound protector specimens of the 33 patients who were analysed to the end of 1997. A single positive result was reported, that being for CK-19. All other results were negative. At this time there had been numerous positive results from the intra-peritoneal washing specimens of the same patients. The wound protector results were thus considered non-representative. The 26 patients analysed in 1998 did not have wound protector specimens collected.

In the five patients who had colorectal resection for benign disease and in whom immunobead RT-PCR was successful, there were no positive results from the peritoneal washings using any of the markers. Immunobead RT-PCR of the peritoneal washings from the 6 patients with colonic adenomata were negative in all but one case. This patient was a 47-year-old woman who had a laparoscopic-assisted anterior resection for an adenoma in the sigmoid colon. The post-resection pelvic washings were positive for CK-19.

The immunobead RT-PCR results for the peritoneal washings of the patients with colorectal cancer fall broadly into three categories;

1. Negative to all markers - Twenty-four of the 46 colorectal cancer patients (52%) were shown to be negative to all of the five markers in all pre- and post-resection peritoneal washes. This group consisted of 5 patients with Stage A disease, 13 patients with Stage B disease, 4 patients with Stage C disease and 2 patients with Stage D disease. The latter 2 patients were thought to have macroscopic clearance of the locoregional disease at the time of resection, but were known to have liver metastases. Five of the 6 patients (83%) who underwent laparoscopic colectomy for cancer were negative to all markers in all specimens.

2. Positive to epithelial markers only - Eleven patients (24%) had a positive result to one or more of the tissue-specific markers for epithelial cells, CK-19, CK-20 or mucin 2, but were negative in all specimens to the markers of colorectal malignancy. This group consisted of 2 patients with Stage A colorectal cancer, 5 patients with Stage B disease and 4 patients with Stage C disease. None of the Stage D patients were in this group.

The details of the immunobead RT-PCR results in these patients is shown in Table 3.3.1.1. Five patients were positive to CK-19, 2 patients were positive to CK-20 and 7 patients were positive to mucin 2. There were 3 patients who registered positive results to more than one of the epithelial specific markers. One patient had positive results in the pre-resection peritoneal washings but was negative after resection. Five patients had negative pre-resection peritoneal washings and positive washings after resection. The remaining five patients had epithelial cells detected by immunobead RT-PCR in both the

pre- and post-resection specimens. In three patients epithelial cells were found in the pelvic washings but not around the tumour. The converse was found in a further 2 patients, with the remaining 6 patients having cells detected in both sites. Of particular note are the last two patients on this table who had mucin 2 detected in all specimens, both before and after resection and in both the pelvis and the area of the tumour. The histopathology for both of these patients showed mucinous adenocarcinoma with abundant extracellular mucin.

3. Positive to malignant markers - Due to the expense of the markers of colorectal malignancy, only one of either laminin 5 (gamma 2 chain) or matrilysin was used in each patient. The remaining eleven patients (24%), consisting of 1 patient with Stage A disease, 5 patients with Stage B disease, 3 patients with Stage C disease and 2 patients with Stage D disease, had one or more positive result using the malignant marker. Some of these patients also had positive results with the epithelial-specific markers. One of the 6 patients (17%) having laparoscopic-assisted colectomy for cancer had positive results with the markers of malignancy.

The results of immunobead RT-PCR and the details of follow up are shown in Table 3.3.1.2. Four patients had cells that were thought to be malignant detected in a single site (2 in the pelvis, 2 in the tumour bed) after resection. All of these patients are alive without evidence of recurrence at 4 to 17 months after resection. In a further 2 patients, laminin 5 was detected in the pre-resection specimens but not after resection. One of these patients died of unrelated causes 2 months after

surgery, the other is alive without evidence of recurrence 15 months after surgery.

The remaining five patients had cells that were considered to be malignant detected by RT-PCR in both the pelvis and the area of the tumour, either only after the resection was completed, or both before and after resection of the cancer. Two had known Stage D disease, one of whom has since died from his disease. There were also two Stage B patients in this group. Both of these patients have had locoregional recurrence of their malignant disease, one 8 months after surgery and the other 9 months after surgery. The latter patient has required a defunctioning colostomy due to obstruction from recurrent cancer. The final patient in this group had a laparoscopic-assisted anterior resection for a Dukes' C adenocarcinoma of the sigmoid colon. He developed a solitary liver metastasis that was thought to be amenable to resection. At laparotomy, 14 months after his primary resection, he had widespread omental and peritoneal malignant deposits.

Discussion

Accurate identification of patients with early stage, but poor prognosis colorectal cancer is vital for two reasons. Firstly, when such a patient is identified, they can be offered appropriate chemo- or chemoradiotherapy, which produces a documented improvement in terms of both recurrence and survival in more advanced disease. Secondly, patients who are not at high risk of recurrence will not receive unnecessary adjuvant treatment, thereby avoiding its risks

and complications.

The myriad of techniques that have been reported in an attempt to accurately identify these patients is detailed in the introduction to this section. The techniques that have been successful in this quest are pathological variables, namely histological grade, malignant invasion of extramural veins and involvement of the lateral resection margins by tumour cells. All of these variables are now taken into consideration when assessing a patient with Dukes' B colorectal cancer for adjuvant treatment. The addition of these variables to the Dukes' staging assessment is, however, unlikely to identify all patients with early stage, poor prognosis colorectal cancer.

This study investigates the use of the new technique of immunobead isolation of epithelial cells, followed by reverse transcription and polymerase chain reaction in an attempt to identify small numbers of malignant cells in the peritoneal cavity at the time of colorectal resection for malignancy. It is too early to make a final assessment of this technique and its potential impact on the task of accurately identifying patients with early stage but poor prognosis disease. In fact, because both conventional cytology and immunocytochemistry provided no positive results in this study and there is currently no other technique capable of confirming the results of immunobead RT-PCR, there is no gold standard with which to compare our results. Long-term follow up is therefore required not only to assess the value of the technique in terms of assessment of prognosis, but also to establish whether or not the cells that we have identified are in fact malignant cells.

In an attempt to provide a standard with which to compare the results of immunobead RT-PCR of peritoneal washings, biopsies of normal colonic mucosa and colonic cancer were taken from each of the 26 patients analysed in 1998. These specimens have also been subjected to immunobead RT-PCR using the same markers as those used the peritoneal washings. In theory, if a patient had normal colonic mucosa that was negative for matrilysin expression but a colon cancer that was positive for matrilysin, then the presence of peritoneal washings that are positive for this marker would be almost diagnostic of free intra-peritoneal malignant cells. This data will provide a case-by-case analysis of the peritoneal washings results that will allow a more confident prediction of the presence or absence of free intra-peritoneal colorectal cancer cells than is currently possible. The results of this project will be included in the Ph.D. thesis of one of the principal research workers and, as such, are not available for discussion in this thesis.

With the above limitations taken into account, this project still provides considerable data for discussion. The absence of any positive results with conventional cytology or immunocytochemistry is of interest. The design of the study is partially responsible for this result, in that it was set up to be applicable in the clinical setting outside of the confines of the study. Therefore, the cytology and immunocytochemistry results are based on small samples that can be spun down within a single centrifugation. In addition, equivocal or suspicious cells were not recorded because in clinical practice these results would not be acted upon. Solomon et al (1997) encountered a similar problem. This group washed the peritoneal surface of the tumour with 20ml of buffered phosphate solution, then immediately centrifuged,

smeared and stained the specimen with a Papanicolaou stain. They were unable to identify any cells, either malignant epithelial or reactive mesothelial. They abandoned this technique after the first 20 patients. Leather et al (1994) used 400ml of peritoneal fluid and identified malignant cells in 4/35 patients prior to resection, with a further 7 patients having equivocal cells identified. Centrifugation of such a large volume of fluid is time-consuming and impractical outside of a research setting. The results of this study suggest that both conventional cytology and immunocytochemistry of peritoneal washings are not sensitive enough to be used for comparison with newer techniques such as immunobead RT-PCR, and are certainly inadequate for assessment of the presence of free intra-peritoneal malignant cells in clinical practice.

The results of immunobead RT-PCR of the wound protector specimens were disappointing. Given that several patients had cells thought to be epithelial or even malignant in nature in their peritoneal cavity, the almost universally negative results provided by the wound protector specimens are not likely to be representative. As there is currently considerable interest in the mechanism of wound metastases, particularly after laparoscopic surgery, accurate results from the wound protector specimens would have been most informative. It is assumed that, even if malignant cells were attached to the wound protector at some time during the procedure, they had dried out or were otherwise denatured by the time of washing and their RNA was therefore not available for immunobead RT-PCR.

The value of the cytokeratin markers, CK-19 and CK-20, to the clinical application of a project such as this is likely to be

minimal. There is no evidence, either from the current study or the literature, that positive results, even in selected patients, represent the presence of neoplastic rather than non-neoplastic epithelial cells. The cytokeratin markers, especially the more specific CK-20 may provide accurate data in pre-operative peripheral blood specimens or lymph nodes, where positive results can be confidently assumed to be malignant cells. This assumption cannot be made in the case of peritoneal washings at the time of surgery, because of the high likelihood of contamination by non-neoplastic epithelial cells.

In most patients, the results of the mucopolysaccharide marker mucin 2, would also be insufficiently specific to consider a diagnosis of malignant intra-peritoneal cells. Two patients in this series suggest a possible exception to this rule. These patients, who had mucinous adenocarcinoma with abundant extracellular mucin on histopathology, had washings positive for mucin 2 both before and after colorectal resection, from both the pelvis and around the site of the tumour. It is possible that the cells positive for mucin 2 may have come from another site, such as the normal colonic epithelium (which can be mucin 2 positive in up to 40% of cases - Hanski et al 1997). Positive findings in all sites at all times in patients with mucinous carcinoma of the colon, however, must be considered strongly suggestive, if not actually diagnostic of free malignant cells in the peritoneal cavity. The long term prognosis of these patients will be watched with interest, as will the results of the immunobead RT-PCR results of normal and malignant colonic mucosa in patients with mucinous adenocarcinoma of the colon or rectum and peritoneal washings that are strongly positive for mucin 2. It is possible that, in the future, it may be considered appropriate

to recommend chemotherapy to Dukes' B patients with mucinous adenocarcinoma who are strongly positive with immunobead RT-PCR for mucin 2 in peritoneal washings and/or peripheral blood during the peri-operative period.

The positive results found with immunobead RT-PCR using the gamma 2 chain of laminin 5 or matrilysin as the markers are more straightforward to analyse, as there is no evidence in the literature to suggest that there is a non-neoplastic source. Until there is evidence to the contrary, it is assumed that these patients had free intra-peritoneal malignant cells either before or after resection of their cancer. It will not be possible to assess the significance of this finding without long-term follow up, particularly in those patients with a single positive result, none of whom have been diagnosed with recurrence as yet.

The short-term follow up of the five patients with positive results to a marker of malignancy in multiple peritoneal washing specimens provides strong evidence, albeit somewhat anecdotal, that the cells detected are in fact free malignant cells with the potential to cause recurrence. This is highlighted by the two patients with Dukes' B adenocarcinoma with multiple positive results to the markers of malignancy, both of whom were diagnosed with local recurrence within 9 months of their 'curative' surgery. This suggests that immunobead RT-PCR of peritoneal washings may be able to identify some members of the subset of colorectal cancer patients who have an early stage lesion but a poor prognosis and may provide data that leads to the more appropriate use of adjuvant therapy in this group of patients.

TABLE 3.3.1.1:

Immunobead RT-PCR results for patients who had positive results to markers of epithelial cells but not to markers of colorectal malignancy in peritoneal washings at the time of colorectal resection.

*Tumours had abundant extracellular mucin when examined histologically.

Legend: CK-19 = cytokeratin 19
CK-20 = cytokeratin 20
Muc 2 = mucin 2

TABLE 3.3.1.1

Age/Sex	Stage	Marker	Pre- or Post-Resection	Pelvis or Tumour bed
86M	A	Muc 2	Post	Pelvis
77F	C	Muc 2	Post	Tumour bed
62M	C	CK-19	Pre and post	Both
46M	B	Muc 2	Post	Pelvis
62M	C	CK-19 & CK-20	Pre and post	Both
71M	B	CK-20	Pre	Tumour bed
74M	B	CK-19 & Muc 2	Post	Pelvis
86F	B	CK-19	Pre and post	Both
74M	C	CK-19 & Muc 2	Post	Both
52M	A*	Muc 2	Pre and post	Both
71M	B*	Muc 2	Pre and post	Both

TABLE 3.3.1.2:

Immunobead RT-PCR results and follow up details of patients who had positive results to markers of malignancy in peritoneal washing specimens taken at the time of colorectal resection.

Legend: Lam = laminin 5 (gamma 2 chain)
Mat = matrilysin

TABLE 3.3.1.2

Age/Sex	Stage	Marker	Pre-or Post-Resection	Pelvis or Tumour bed	Follow up (months)	Follow up details
80M	B	Lam	Pre	Both	2	Died (unrelated cause)
70M	A	Lam	Pre	Both	15	No recurrence
62M	D	Lam	Post	Both	15	Alive with liver metastases
82F	B	Mat	Post	Both	14	Local and bony recurrence at 8 months
73F	C	Mat	Post	Pelvis	17	No recurrence
61F	B	Mat	Post	Tumour bed	4	No recurrence
67F	C	Lam	Post	Pelvis	16	No recurrence
76M	B	Lam	Pre/post	Both	13	Local recurrence at 9 months
61M	B	Mat	Post	Tumour bed	10	No recurrence
69M	C	Mat	Pre/post	Both	14	Laparotomy at 14 months - widespread intraperitoneal metastases
68M	D	Lam	Pre/post	Both	14	Died of disease

3.4 AMBULATORY ANAL SURGERY

3.4.1 Day Case Haemorrhoidectomy

At the beginning of 1996, a protocol was designed to allow the performance of ligation excision haemorrhoidectomy in the Day Surgery Unit of The Queen Elizabeth Hospital. Since this time all patients requiring operative haemorrhoidectomy have been considered for the day surgery project. The results of this project, recorded prospectively over a thirty-month period, are reported.

Subjects

Patients were referred for ligation excision haemorrhoidectomy in the Day Surgery Unit if they had third or fourth degree haemorrhoids or if their second degree haemorrhoids had failed to respond to rubber band ligation or sclerotherapy. Patients presenting to the Emergency Department with thrombosed or strangulated haemorrhoids were treated in the emergency general theatre and were not included in this study.

Patients were excluded from day case haemorrhoidectomy if they did not fulfil standard day surgery inclusion criteria; patients that were considered Grade 4 or 5 according to the American Society of Anesthesiologists (ASA), those with a history of bleeding or clotting problems and those with inadequate social support following surgery. Additional specific exclusion criteria for this project were chronic renal failure or peptic ulcer disease,

because of the use of non-steroidal anti-inflammatory drugs as a component of the analgesic regime, and symptoms of bladder outlet obstruction because of the historically high incidence of urinary retention after haemorrhoidectomy.

Methods

In the outpatient department, an investigator discussed with the patient the study requirements and obtained informed consent in writing. The patient was also provided with written information describing the management plan. Patients underwent anaesthesia assessment and were seen by a member of the Hospital at Home nursing service approximately one week prior to surgery in the Day Surgery pre-admission clinic. Interpreter services were provided for patients from a non-English speaking background.

On the day of surgery all patients were allowed to continue clear oral fluids until three hours prior to the scheduled surgery. Admission to the Day Surgery Unit was at 0700 hours. At this time patients were given a sodium citrate/ sodium lauryl sulfoacetate/ sorbitol (Microlax^{TM}, Pharmacia & Upjohn, Pty. Ltd., Rydalmere, N.S.W., Australia) enema and all exclusion criteria were reviewed. If a new reason for exclusion from the study was identified, the operation went ahead as scheduled, but no attempt was made at same day discharge. Patients were scheduled to a morning operating list.

A standardised anaesthetic technique was used. Patients received a propofol induction and anaesthesia was maintained using

an inhalational agent via spontaneous ventilation through a laryngeal mask. The anaesthetist administered an intravenous dose (4mg) of the antiemetic ondansetron hydrochloride at induction of anaesthesia. An intravenous dose of the short acting opioid fentanyl citrate was also given at induction. The dose of fentanyl citrate varied in accordance with the patient's weight. Intravenous fluids were not given routinely during the procedure.

The operation was a standard ligation excision haemorrhoidectomy. Prior to commencement of the procedure, a mixture of 20ml 0.5% bupivacaine plain, 10ml 1% lignocaine plain and 10ml normal saline was prepared. A pre-emptive, ischio-rectal fossa block was then created by injection of this mixture into the ischio-rectal fossae at the four and eight o'clock positions, with the patient in the lithotomy position. The block was supplemented by perianal infiltration of all haemorrhoidal complexes with the same solution. At the completion of the procedure, the wounds were infiltrated with the remainder of the local anaesthetic mixture and an indomethacin suppository (100mg) was inserted into the anal canal. A pad dressing was then gently laid onto the perineum.

The patients were transferred to the day surgery recovery room and then to a convalescent ward when standard recovery discharge criteria were met. Nursing staff assessed pain and nausea at 30 minutes, 2 hours and 4 hours post-operatively using a Visual Analogue Scale (VAS Scale 1-10, where 1 represented no pain [or no nausea] and 10 represented the worst pain imaginable [or severe nausea and vomiting]). Bleeding was also assessed at these times and analgesic and anti-emetic requirements were documented.

Once in the convalescent ward, patients were encouraged to be self-caring, ambulant and to commence on a normal diet. Patients were reassessed by the nursing staff for discharge at no later than 1800 hours. If the patient had voided urine and pain and nausea were well controlled, they were discharged home to the care of a responsible adult. Prior to discharge all patients were further educated with respect to both the regular and as required post-operative medications and were provided with a 24-hour contact number for emergencies. They were told to expect a visit from the Hospital at Home nursing service the following day.

At home, the patients were instructed to take oral indomethacin (25mg tds) and sorbitol (15ml bd). They had available to them a range of as required analgesic medications including paracetamol and dextropropoxyphene/paracetamol for mild to moderate pain and oxycodone for severe pain. Metoclopramide was self-administered for nausea. Patients were encouraged to take at least twice daily warm salt baths. A registered nurse visited each patient daily until at least the time of the first bowel action and assessed pain and nausea (VAS), bleeding, analgesic and anti-emetic requirements and urinary or bowel problems. The patient also recorded pain scores and analgesia requirements at the time of the first bowel action.

The surgeon reviewed all patients at 10 days and 30 days post-operatively. At the 30-day visit the patient completed a questionnaire with an independent assessor to ascertain the level of satisfaction with their general management, with the pain management and with the information and education provided. In addition all patients who went home on the night of surgery were

asked if they were satisfied with this arrangement and if they would recommend this protocol of post-operative care for haemorrhoidectomy.

Statistical analysis was performed in three ways. Repeated measures analyses for pain scores, nausea scores, analgesia used and antiemetic used were conducted using generalised estimating equations. Categorical analyses were conducted using the Chi-square test of homogeneity. Non-parametric analyses were conducted for patient satisfaction with pain management and pain at first bowel action using the Wilcoxon rank sum test.

Results

Between February 1996 and September 1998, 107 patients were referred for day case haemorrhoidectomy. Of these, 13 were excluded from the study on the day of surgery, 9 because of inadequate social support to allow same day discharge, 3 did not require ligation excision haemorrhoidectomy following examination under anaesthesia and 1 patient developed rapid atrial fibrillation in the immediate pre-operative period. The remaining 94 patients underwent ligation excision haemorrhoidectomy with the intention of discharge from hospital on the day of surgery.

The study group consisted of 58 male patients and 36 female patients. They had a median age of 45 years (range 23-82 years) and a median weight of 72kg (range 41-110kg). Ten patients (10%) had second degree haemorrhoids, 71 patients (76%) had third degree haemorrhoids and 13 patients (14%) had fourth degree

haemorrhoids. Sixteen patients (17%) had undergone a total of thirty attempts to control their haemorrhoidal symptoms with rubber band ligation or sclerotherapy. Most patients (86%) reported symptoms attributable to haemorrhoids for at least twelve months, with 31 patients (33%) complaining of such symptoms for over 5 years.

Of the 94 patients included in the study, 45 were considered ASA Grade 1, 47 were ASA Grade 2 and 2 were ASA Grade 3. The median dose of fentanyl citrate given at induction of anaesthesia was 100mcg (range 50-250mcg). Eighty-five patients (90%) did not have any intravenous fluid during or after their haemorrhoidectomy. Of the remaining 9 patients, 5 had less than 100ml of intravenous fluid, 1 had between 100 and 500ml and 3 had greater than 500ml.

Eight patients (8.5%) had a one complex haemorrhoidectomy, 23 patients (24%) had two complex haemorrhoidectomy and 63 patients (67%) underwent three complex haemorrhoidectomy. All operations were performed or supervised by a consultant surgeon from the Colorectal Surgical Unit, with most (77%) being performed by a single colorectal surgeon.

Eighty-three of the 94 patients were discharged on the day of surgery, giving a same-day discharge rate of 88%. All of the remaining 11 patients were discharged early on the day after surgery, with the longest post-operative hospital stay recorded being 28 hours. Several patients were discharged as early as 3 hours post-operatively. The median post-operative hospital stay was 7 hours.

The reasons recorded for requiring overnight admission were post-operative nausea and/or vomiting (4 patients), a delay in post-operative voiding of urine past a reasonable hour for discharge (3 patients), post-operative pain (3 patients) and delay in the delivery of post-operative medications from pharmacy (1 patient). All three of the patients who did not void early enough to achieve same day discharge subsequently voided without difficulty and were not considered to have suffered post-operative urinary retention.

Seven patients (7.4%) had minor complications in the first 10 days post-operatively. Two patients had post-operative bleeding requiring admission to hospital; one was a reactive bleed on day 1 and the other was a secondary bleed on day 10. Both patients were admitted for observation but neither required further operative intervention or blood transfusion. Another patient had a secondary bleed on day 6 but did not require admission.

Two patients required admission to hospital for parenteral opioid analgesia, one after his first post-operative bowel action on day 7 and one because of on-going severe pain on day 10 post-operatively. Both of these patients had been non-compliant with the post-operative regimen of anti-inflammatory medications and aperients.

Two patients had post-operative urinary retention; one had primary retention requiring catheterisation (but not admission) on the first night and the other had voiding difficulties for seven days before this was recognised as urinary retention with overflow. The post-operative urinary retention rate for this series was thus 2/94 or 2.1%.

A further two patients were diagnosed with an anal stenosis at the 30 day outpatient appointment. Both patients underwent gentle digital dilatation under general anaesthetic and have had no further problems.

The mean pain scores and the range of pain scores recorded at each of the designated post-operative times is shown in Table 3.4.1.1. A wide range of pain scores was seen at all times in the post-operative period. All mean pain scores were low, being between 2 and 3.

Closer analysis of the mean pain scores however, as shown graphically in Figure 3.4.1.1, shows two definite trends in the amount of pain experienced after haemorrhoidectomy. Firstly, the pain scores recorded in the first four hours post-operatively were significantly lower than those recorded on day 2 ($p<0.02$) and day 3 ($p<0.05$). Secondly, whilst the pain scores decreased significantly between day 3 and day 5 post-operatively, pain subsequently increased, with scores recorded on the tenth post-operative day being significantly higher than those recorded on day 5 ($p<0.05$). A similar pattern is seen when analysing the proportion of patients who reported pain scores of 3 or greater (Figure 3.4.1.2). Peaks are again seen on this graph at Day 2 and Day 10.

Figure 3.4.1.3 shows the analgesic requirements after day case haemorrhoidectomy. All analgesia used was recorded prospectively on the data sheets. This graph, however, records only the strongest analgesia required by each individual patient in a given time period. Analgesia is classified, in this instance, as parenteral opioid analgesia (fentanyl), oral opioid analgesia

(oxycodone), simple analgesia (dextropropoxyphene/paracetamol or paracetamol) or no analgesia. Twelve patients (13%) required parenteral opioid analgesia in the first 30 minutes post-operatively, but none required it subsequently. Oral opioid requirements peaked on the second, third and fourth post-operative days, whereas the use of simple analgesic medication was steady throughout the post-operative period. The majority of patients did not require any analgesia in the first twenty-four hours after their operation.

The mean pain score recorded at the time of the first post-operative bowel action was 4.9 (range 1-10). This was significantly higher than at any other time in the post-operative period ($p<0.0001$). Forty-six patients (49%) required oxycodone for pain relief at this time, 23 patients (24%) used simple analgesia and 24 patients (26%) needed no analgesia at all. One patient had pain that was severe enough to require admission to hospital for parenteral opioid analgesia. The first post-operative bowel action occurred on a median of the second post-operative day (range 1-7 post-operative days). Pain scores at the time of the first bowel action were not related to the day on which this occurred ($p=0.15$), however there was a correlation between a later first bowel action and a greater need for oxycodone at this time ($p<0.04$). The patient who did not open his bowels until day 7 was the same patient who required admission to hospital for parenteral analgesia.

There was no correlation between specific patient factors and the amount of pain experienced after haemorrhoidectomy. In particular, there was no relationship between pain and patient age, sex, whether they were from a non-English speaking background or the number of haemorrhoidal complexes excised.

The mean nausea scores and the range of nausea scores recorded in the post-operative period are shown in Table 3.4.1.2. There was a wide range of nausea scores recorded, especially over the first three days. Most patients, however, experienced minimal nausea at any time in the post-operative period. This is reflected in the low mean nausea scores, which, with one exception, were all below 1.5.

The requirement for the anti-emetic metoclopramide during the post-operative period is shown in Table 3.4.1.3. Parenteral (intra-venous or intra-muscular) metoclopramide was given to 18 patients (19%) in the first four hours post-operatively. Four of these patients required further parenteral metoclopramide later on the day of surgery. These were the four patients who did not achieve same day discharge because of post-operative nausea and vomiting. There was no correlation between the use of post-operative fentanyl and the need for parenteral anti-emetic medication.

The use of oral metoclopramide at home was highest on the second post-operative day. There was a positive correlation between the requirement for oral metoclopramide and both higher pain scores ($p<0.002$) and oxycodone use ($p<0.03$). Fifty-seven of the 94 patients (61%) did not require metoclopramide at any time in the post-operative period.

The patients in this study were visited at home by a member of the Hospital at Home nursing staff a median of 4 times (range 1-9 times) over a median of 4 days (range 1-9 days).

The satisfaction ratings, recorded 30 days after surgery in conjunction with an independent assessor are shown in Table 3.4.1.4. Seventy-five of the 94 patients (80%) reported being either totally or very satisfied with their post-operative pain management. There was no correlation between the level of satisfaction with pain management and the pain score recorded after the first bowel action ($p>0.9$). Eighty-seven patients (93%) were either totally or very satisfied with the information provided to them during the peri-operative period and 89 patients (95%) were totally or very satisfied with their overall care. The 83 patients who were discharged on the day of surgery were asked "Did you like going home on the day of surgery?" Sixty-eight patients (81%) replied "Yes", 13 patients (17%) replied "No" and 2 patients (2%) replied "Not sure".

Discussion

This study provides a large body of data for discussion. The primary aim, to assess the safety and feasibility of day case haemorrhoidectomy, has been achieved. In addition, this study has provided a valuable prospective database for the study of post-haemorrhoidectomy pain and analgesia requirements. Interim analysis of this database at the end of 1997 led to findings that, in one instance, prompted a change in the post-operative medication regime and in another led to further research in the form of a prospective, randomised trial.

The place of ligation excision haemorrhoidectomy as the procedure of choice in the management of third and fourth degree

haemorrhoids, as well as for second degree haemorrhoids that have failed to respond to non-operative treatment, has been established in the introduction to this section. We have shown in this series that it is possible to perform the standard procedure as day surgery in a majority of selected patients (88% at this time). Although patients were excluded from this project for various reasons, they were not excluded because of the degree or severity of their haemorrhoids. Indeed, the majority of haemorrhoidectomies in this series were three complex procedures (67%) and 90% were performed on patients with third or fourth degree haemorrhoids. The high same day discharge rate thus cannot be attributed to the selection of patients requiring only minor procedures.

The control of post-operative pain was considered the greatest challenge to the successful performance of day case haemorrhoidectomy. The low mean pain scores throughout the post-operative period and the high level of patient satisfaction with pain control attest to the success of the multi-modal analgesic regime. The pain scores in this series are considerably lower than those published by authors who also used a Visual Analogue Scale for the recording of pain scores after haemorrhoidectomy (London et al 1987, Andrews et al 1993).

The wide range of pain scores confirms the subjective nature of pain and the variability of pain perception between individuals. This has also been reported after haemorrhoidectomy by other authors (Roe et al 1987, Pryn et al 1989, Seow-Choen et al 1992). Despite this variability, all but two patients were able to stay at home for post-operative analgesia. Given that these two patients did not take any of the regular indomethacin supplied in the post-

operative medication pack, it is probably unreasonable to place the entire responsibility for these failures on the analgesic regime.

The pain scores and analgesia requirements in the immediate post-operative period were particularly low and contributed significantly to the high rate of same day discharge. There is little available literature investigating pain in the immediate post-operative period after haemorrhoidectomy, with most papers only commencing pain scores at 24 hours post-operatively. Kilbride et al (1994) reported a mean pain score of 5.1 at 6 hours post-operatively. Mathai et al (1996) reported a median pain score of 4.0 at 4 hours post-operatively. The mean pain scores in this series of 2.2 at 30 minutes, 2.51 at 2 hours, and 2.44 at 4 hours post-operatively thus compare favourably to the published literature.

There are several possible causes of the low level of immediate post-operative pain, including the use of fentanyl at induction and the insertion of an indomethacin suppository at the completion of the procedure. These techniques have been widespread in the past and do not completely explain the situation. Firstly, fentanyl citrate has a short duration of action and, whilst the administration of this drug at induction of anaesthesia may influence the pain score 30 minutes after haemorrhoidectomy, it should not be considered an active component of the analgesic regime at 2 or 4 hours post-operatively. Secondly, indomethacin was taken throughout the post-operative period. The significant difference between pain on the second and third post-operative days and that recorded in the immediate post-operative period cannot therefore be attributed to the indomethacin suppository.

Interim analysis of this data was performed at the end of 1997. It was hypothesised at this time that the low pain scores in the first twenty-four hours, and in particular the first four hours after haemorrhoidectomy were due to the effect of the pre-emptive, local anaesthetic, ischio-rectal fossa block. At this time it was decided to test this hypothesis in a prospective, randomised, double-blind trial. This trial involved the randomisation of a small number of patients from the day case haemorrhoidectomy project to either receive or not receive the local anaesthetic block. All other aspects of peri-operative care were standardised according to the day case haemorrhoidectomy protocol. This trial was performed in 1998. The results of this trial are reported and discussed in the next section.

The increase in pain after the fifth post-operative day was unexpected. Because data was not collected between the fifth and tenth day, the exact details of this increase are not apparent. It was also noted that, at the 10-day outpatient appointment, several of the patients complaining of increasing pain had sloughy or discharging wounds. It was thus hypothesised that secondary infection may play a role in post-haemorrhoidectomy pain. Whilst this theory is based on anecdotal evidence, it is corroborated by an excellent study by Carapeti et al (1998) who showed, in a well-designed, randomised, placebo-controlled trial that metronidazole reduced pain on days 5 to 7 after haemorrhoidectomy.

On the basis of the above data, two further changes were made to the peri-operative protocol at the beginning of 1998. At the completion of haemorrhoidectomy, all patients in 1998 had a 1g metronidazole suppository inserted in addition to the indomethacin

suppository. Oral metronidazole 400mg twice a day was also added to the post-operative medication regime. It is difficult to assess the importance of these changes given that data was not recorded from day 5 to day 10. There did however appear to be fewer patients with sloughy or discharging wounds at the first outpatient review in 1998. The mean pain score on day 10 decreased from 3.01 in 1996/1997 to 2.81 in 1998 but this difference did not reach statistical significance.

It is the severe pain expected at the time of the first post-operative bowel action that has been the single greatest hurdle in achieving early discharge after haemorrhoidectomy. In the past, most patients have remained as inpatients until this time in order to receive parenteral opioid analgesia. In this study, although the first bowel action was the time of the highest pain score, 93 out of 94 patients (99%) were able to remain at home. Many commented that they were in fact better served in the comfort and privacy of their own home. The pain recorded at the first bowel action was highly variable, as was the analgesia requirement, with one in four patients needing no pain relief at this time.

This study provides mixed data regarding the importance of ensuring that the first bowel action is early in the post-operative period. There was no correlation between the day on which the first bowel action occurred and the amount of pain that it produced; however patients who waited longer for this bowel action required more oral opioid analgesia. The fact that the only patient requiring parenteral opioid analgesia did not open his bowels until day seven post-operatively provides strong, if somewhat anecdotal evidence, that an early bowel action after haemorrhoidectomy is desirable.

Opioid administration in the post-operative period may increase the incidence of post-operative nausea and vomiting. In the immediate post-operative period, nearly one in five patients required parenteral metoclopramide, but only four patients needed to be admitted because of nausea or vomiting. This is a considerably lower rate than that reported by Hirsch (1994). In the outpatient setting, the multimodal analgesic regime was able to minimise the need for oral opioid analgesia and, in combination with the availability of oral metoclopramide, kept the post-operative nausea scores to very low levels. In comparison, Kilbride et al (1994) reported nausea and vomiting in 10/17 patients (58%) who used transdermal fentanyl.

Many of the analgesic regimes designed to make haemorrhoidectomy more comfortable have a significant risk of causing acute urinary retention in the post-operative period. The high rate of this complication with spinal and caudal anaesthesia (up to 70%) is discussed in the introduction to this section. The subcutaneous morphine pump is also prone to this complication, with a reported urinary retention rate of 55% (Goldstein et al 1993). The exceptionally low rate of urinary retention in our study is considered to be due to the avoidance of the above analgesia delivery systems, the exclusion of patients with symptoms of bladder neck obstruction and the minimising of intra-venous fluids during the procedure. Other authors (Campbell 1972, Bailey and Ferguson 1976) have also reported the relationship between fluid restriction during anorectal surgery and a decrease in the urinary retention rate.

Community nursing support aids the performance of procedures such as haemorrhoidectomy as day surgery. In this study, a registered nurse visited the patient up to 9 times post-operatively. As the nurses were members of the hospital staff, the patients had often met their home nurses in the pre-admission clinic. This enabled the establishment of rapport and created a continuity of care into the post-operative period. The support of the home nursing team encouraged the appropriate use of medications and salt baths and allayed anxiety. We believe such support was vital to the success of this project.

Pre-operative education was an important component of the peri-operative protocol. Our focus was for our patients to achieve an understanding of the requirements of the study and, perhaps more importantly, to understand the available pain management strategies. An explanation was given regarding the pain management plan and common side effects of the medications. Emphasis was placed on the fact that not all post-operative pain would be eliminated, but that it would be tolerable with appropriate use of the medications. The importance of taking regular analgesia medication was also highlighted, as it has been shown that patients are often reluctant to take analgesia and believed that they would be healthier in the long term if it was avoided (Bostrum 1997, Fins 1997).

Education was provided at several times both before and after surgery. This began with the surgeon in the outpatient department and continued in the pre-admission clinic both verbally and with the provision of written information. The necessary information was reinforced after surgery but prior to discharge from hospital by

the nursing staff working on the convalescent ward. Finally, the provision of a 24-hour phone contact provided an important safety net for patients requiring advice after hours. The high levels of patient satisfaction with the information provided and the overall management confirms the success of the education strategies employed in this study.

Despite the considerable attempts to achieve a smooth transition to day case haemorrhoidectomy and the high satisfaction ratings achieved in this study, nearly 20% of the patients who achieved same day discharge were not entirely happy about going home on the night of their surgery. These patients expressed anxiety about caring for themselves immediately after such a procedure. Identification and further reassurance of these patients pre-operatively will be an on-going challenge for this project. Outside of the confines of a study such as this, it may be more appropriate to offer these patients 23-hour care, with overnight admission to the convalescent unit.

For the majority of selected patients, however, we have shown that the performance of ligation excision haemorrhoidectomy as day surgery is feasible, safe and it can engender a high level of patient satisfaction.

TABLE 3.4.1.1:

Pain scores recorded after haemorrhoidectomy.

Scores are recorded on a Visual Analogue Scale from 1 to 10 with 1 representing no pain and 10 representing the worst pain imaginable.

TABLE 3.4.1.1

Post-operative Time	Mean Pain Score	Pain Score Range
30 minutes	2.20	1-10
120 minutes	2.51	1-8
240 minutes	2.44	1-7
Day 1	2.61	1-8
Day 2	2.87	1-7
Day 3	2.87	1-8
Day 4	2.58	1-7
Day 5	2.35	1-8
Day 10	2.93	1-8

FIGURE 3.4.1.1:

Mean pain scores recorded after haemorrhoidectomy illustrated graphically to show trends. Pain scores recorded on Day 2 and Day 3 were significantly higher than in the first 4 hours post-operatively. Pain scores recorded on Day 10 were significantly higher than those recorded on Day 5.

FIGURE 3.4.1.1

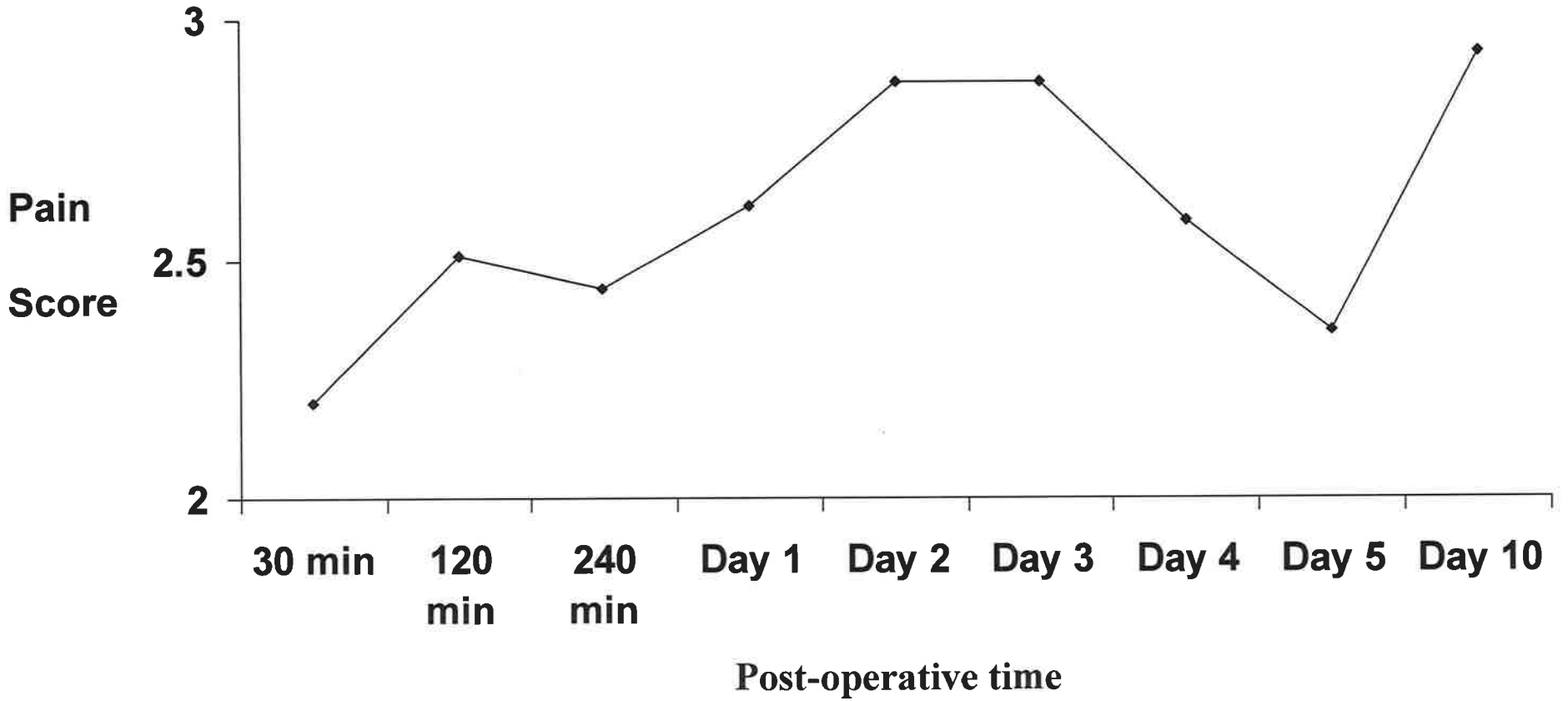

3
2.5
2
Pain
Score
30 min
120 min
240 min
Day 1
Day 2
Day 3
Day 4
Day 5
Day 10
Post-operative time

FIGURE 3.4.1.2:

Proportion of patients recording pain scores of 3 or greater (on VAS 1-10) after haemorrhoidectomy.

FIGURE 3.4.1.2

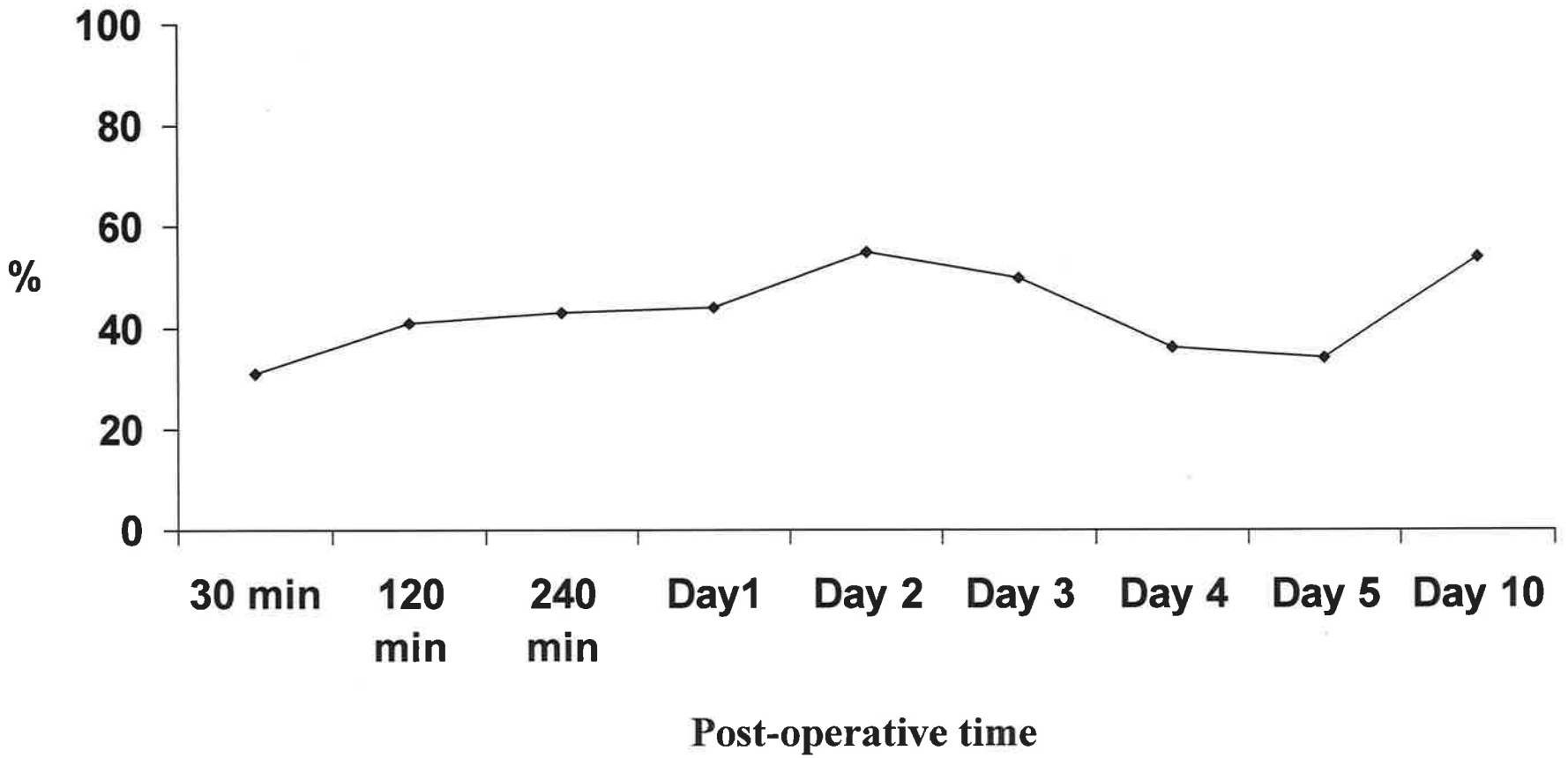

100
80
60
40
20
0
%
30 min
120 min
240 min
Day1
Day 2
Day 3
Day 4
Day 5
Day 10
Post-operative time

FIGURE 3.4.1.3:

Analgesic requirements after day case haemorrhoidectomy.

FIGURE 3.4.1.3

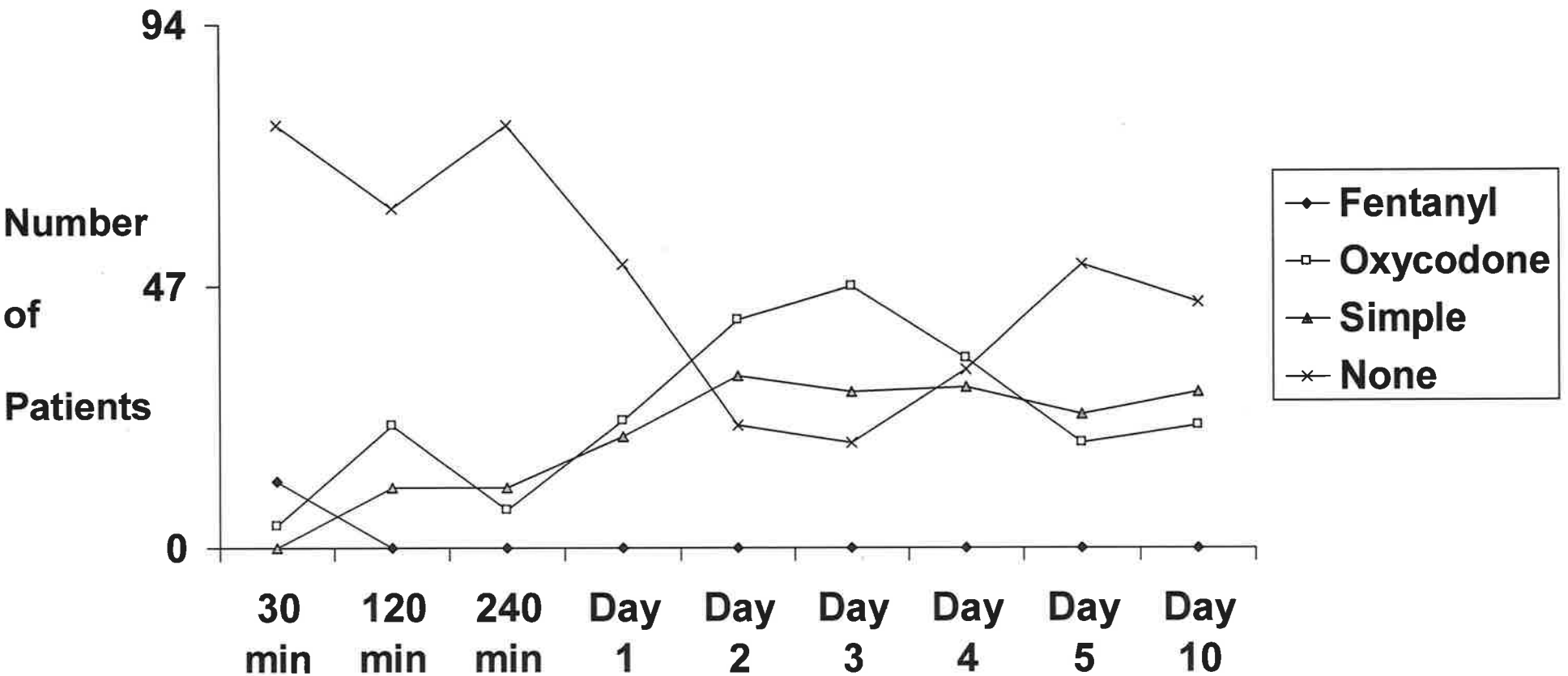

94
47
0
Number of Patients
30 min
120 min
240 min
Day 1
Day 2
Day 3
Day 4
Day 5
Day 10
Fentanyl
Oxycodone
Simple
None
Post-operative time

TABLE 3.4.1.2:

Nausea scores after haemorrhoidectomy.

Scores are recorded on a Visual Analogue Scale from 1 to 10 with 1 representing no nausea and 10 representing severe nausea or vomiting.

TABLE 3.4.1.2

Post-operative Time	Mean Nausea Score	Nausea Score Range
30 minutes	1.25	1-10
120 minutes	1.48	1-8
240 minutes	1.28	1-5
Day 1	1.39	1-8
Day 2	1.73	1-10
Day 3	1.45	1-8
Day 4	1.23	1-6
Day 5	1.10	1-4

TABLE 3.4.1.3:

Anti-emetic requirements in the post-operative period after haemorrhoidectomy.

TABLE 3.4.1.3

Post-operative Time	Parenteral Metoclopramide	Oral Metoclopramide	No Anti-emetic
30 minutes	6	0	88
120 minutes	10	2	82
240 minutes	2	3	89
Day 1	4	5	85
Day 2	0	21	73
Day 3	0	14	80
Day 4	0	9	86
Day 5	0	4	90

TABLE 3.4.1.4:

Satisfaction ratings recorded for the day case haemorrhoidectomy project as stated by patients 30 days after surgery in consultation with an independent assessor.

TABLE 3.4.1.4

	Pain Management	Information Provided	Overall Management
Totally Satisfied	41	49	51
Very Satisfied	34	38	38
Satisfied	14	6	2
Unsatisfied	2	0	2
Very Unsatisfied	3	0	0
Totally Unsatisfied	0	1	1

3.4.2 The effect of a pre-emptive, local anaesthetic, ischio-rectal fossa block on pain and analgesia requirements after haemorrhoidectomy.

A prospective, randomised, double-blind clinical trial

This trial was designed after analysis of the post-haemorrhoidectomy pain data produced by the day case haemorrhoidectomy project at the end of 1997. There was a statistically significant difference between the pain scores recorded in the first four hours post-operatively and those recorded on the second and third days post-operatively, with less pain in the immediate post-operative period. It was hypothesised that this difference was due to the effect of the local anaesthetic that had been injected into each ischio-rectal fossa prior to the commencement of surgery. The aim of this trial was to test this hypothesis.

Subjects

The patients involved in this trial had already been accepted into the day case haemorrhoidectomy project. The inclusion and exclusion criteria for the patients in this trial are therefore the same as has been documented in the previous section (Section 3.4.1).

Methods

As the patients were involved in the day case haemorrhoidectomy project, the pre-operative education and preparation, as well as all aspects of surgery, anaesthesia and post-operative care was standardised according to the protocol outlined in the previous section. The only difference between the two groups analysed in this trial was the method of local anaesthetic delivery prior to surgery.

After induction of anaesthesia and immediately prior to commencement of the procedure, the patients were randomised to one of two groups by the opening of a sealed, opaque envelope containing a card on which was written either "Anal block" (Group 1) or "Infiltration" (Group 2). For both groups, a solution containing 20ml 0.5% bupivacaine, 10ml 1% lignocaine and 10ml normal saline was prepared. For the patients in Group 1, with the patient in the lithotomy position, this solution was injected into the ischio-rectal fossae in the four and eight o'clock positions and fanned out from these injection points. This was supplemented by perianal infiltration of all haemorrhoidal complexes with the same solution. Patients in Group 2 received infiltration of the haemorrhoidal complexes alone. At the completion of the procedure, the wounds of all patients were infiltrated with the local anaesthetic solution.

Nursing staff assessed pain at 30 minutes, 2 hours, 4 hours and 24 hours post-operatively using a Visual Analogue Scale (VAS 1-10, where 1 represented no pain and 10 represented the worst pain imaginable). All analgesic requirements were recorded and

classified as parenteral opioid (fentanyl citrate), oral opioid (oxycodone) or simple analgesia (paracetamol or dextropropoxyphene/paracetamol).

Neither the patients nor the members of nursing staff recording the pain scores and analgesia requirements were aware of which local anaesthetic protocol had been used. Statistical analysis was performed on individual values using Student's t-test or the Mann Whitney rank sum test. The trend of pain scores over time was analysed using a repeated measures analysis of variance.

Results

Between February and June 1998, twenty patients were enrolled into the trial. Ten patients were randomised to Group 1 ("anal block") and 10 patients were randomised to Group 2 ("infiltration"). Table 3.4.2.1 shows the demographic details of the patients. The groups were equivalent with regards to age and sex. There was also no difference in the dose of fentanyl citrate given at induction.

The mean pain scores recorded at 30 minutes, 2 hours, 4 hours and 24 hours post-operatively are seen in Table 3.4.2.2. At all times, pain was less in the patients who had received the pre-emptive ischio-rectal fossa block. The differences seen reached statistical significance for the 4 and 24 hour post-operative pain scores. Analysis of all pain scores by a repeated measures analysis of variance, illustrated graphically in Figure 3.4.2.1, showed an even higher degree of significance ($p=0.0004$) with a difference in

favour of the anal block group.

Total analgesic requirements are tabled in Table 3.4.2.3. Parenteral fentanyl citrate was not required in the anal block group but was given to two patients (60 mcg and 40 mcg) who received perianal infiltration alone. Patients in group 1 used less oral opioid and less simple analgesic medication in the first 24 hours post-operatively than those in group 2. None of the differences between the groups in analgesic requirements reached statistical significance.

There were no post-operative complications in either group. No patient suffered post-operative urinary retention.

Three patients required overnight admission, 1 from the anal block group (due to post-operative nausea and vomiting) and 2 from the infiltration group (1 due to delayed post-operative voiding and 1 due to post-operative nausea and vomiting). The median stay for group 1 was 5 hours (range 3-25 hours) compared to 7.5 hours (range 4-24) for group 2 patients. This difference did not reach statistical significance.

Discussion

Control of pain immediately after haemorrhoidectomy is vital. Decreased pain during this period has been shown to result in a decreased rate of urinary retention and faecal impaction (Bleday et al 1992) and significantly improved patient satisfaction (Jamison et al 1997). It is clearly essential if same day discharge is planned.

Achieving adequate pain control in the immediate post-haemorrhoidectomy period is problematic, especially if one is to avoid complications that may preclude same day discharge. Spinal anaesthesia does provide excellent analgesia, but has an unacceptable rate of urinary retention for a day surgery project (Petros and Bradley 1990). The use of caudal anaesthesia has also been reported with excellent results in terms of analgesia, but with a high rate of urinary retention (Pybus et al 1983) as well as a failure rate of 5-10% (Pryn et al 1989). Pryn et al (1989) also reported leg weakness, or even an inability to walk for up to 11 hours after caudal anaesthesia. Finally, several authors have raised concerns regarding the theoretical risk of infection when spinal or caudal anaesthesia is used for haemorrhoidectomy (Rubin 1979, Chester et al 1990).

Other analgesic options are not without their complications. The subcutaneous morphine pump reported by Goldstein et al (1993) has a high rate of urinary retention. Transdermal fentanyl was described for pain management after haemorrhoidectomy by Kilbride et al (1994). This paper raised such serious concerns about the risk of respiratory depression that it prompted a letter to the editor from the Director of Anesthesia and Analgesia Research and the Vice President of Medical Affairs at the company that produces the medication. They stated that they "emphatically discourage the use of transdermal fentanyl in the management of all types of acute or post-operative pain" (Bernstein and Klausner 1994). The use of intra-sphincteric ketorolac has not prompted criticism to this extent, but there are concerns regarding the risk of renal failure. Its efficacy is unclear, with Richman (1993) reporting that 17% of their patients still required parenteral opioid anaesthesia. Intra-

sphincteric ketorolac has not as yet been shown to be superior to indomethacin suppositories in anorectal surgery.

Local anaesthesia maintains a good balance between effectiveness and lack of complications in the post-operative setting. The use of local anaesthesia to decrease pain in the immediate post-operative period after haemorrhoidectomy has been investigated in the past with poor results, as discussed in the introduction to this section. The technique described in this paper, and indeed used in all patients in the preceding section on day case haemorrhoidectomy, differs in several respects from the techniques employed by other authors.

Of primary importance is that the local anaesthetic is injected prior to the commencement of surgery. There is now evidence that such 'pre-emptive' analgesia is more effective and that analgesia in general is considerably less effective once pain is established (Goodman and Gilman 1990, Moote 1992)). The theoretical basis of pre-emptive analgesia using local anaesthesia prior to surgery is that it inhibits the peripheral nociceptive response and thereby alters the central processing that amplifies post-operative pain (Kissin 1996). The use of pre-emptive local anaesthesia for haemorrhoidectomy has not been previously published.

The use of both lignocaine and bupivacaine in the ischio-rectal fossa block provides the dual benefit of the rapid onset of the former and the long duration of action of the latter. The use of two local anaesthetic medications has also not been previously reported.

The final element to the success of this technique is the injection of the solution into the ischio-rectal fossae a short distance from the operative site. The local anaesthetic should interrupt the inferior rectal branch of the pudendal nerve and the perineal branch of the S4 nerve root on each side, leading to partial paralysis of the external anal sphincter and decreased sensation in the anal canal and perianal skin. Pre-emptive infiltration into the perianal area alone is less successful as these nerves are not interrupted and much of the medication is excised with the haemorrhoidal complexes.

The hypothesis that a significant reduction in post-haemorrhoidectomy pain and analgesic requirement is produced by the use of a pre-emptive, local anaesthetic, ischio-rectal fossa block has been upheld by this randomised, double blind trial. It is a simple technique that can be performed by the surgeon after induction of anaesthesia and prior to surgery. It has none of the real or potential side effects of other analgesic options. We believe this technique to be a significant advance in the management of the pain of operative haemorrhoidectomy.

TABLE 3.4.2.1:

Comparison of patient demographics and fentanyl dose at induction in the local anaesthesia for haemorrhoidectomy randomised trial.

Data are expressed as median (range).

P values are calculated using the Mann-Whitney rank sum test* or the Pearson Chi-square test of homogeneity^{+}.

TABLE 3.4.2.1

	Anal block group	Infiltration group	p value
Age	54 (33-70)	49.5 (30-75)	0.6494*
Sex	3M:7F	4M:6F	0.6392^{+}
Initial fentanyl dose	87.5 (50-100)	90 (50-100)	0.6865*

TABLE 3.4.2.2:

Comparison of pain scores in the first twenty-four hours after haemorrhoidectomy in the local anaesthesia for haemorrhoidectomy randomised trial.

Data are expressed as mean (standard error of the mean)

P values are calculated using the Mann-Whitney U test. P values <0.05 are considered significant*.

TABLE 3.4.2.2

Post-operative time	Anal block group	Infiltration group	p value
30 minutes	1.5 (0.31)	3.4 (0.72)	0.0613
2 hours	1.8 (0.32)	3.4 (0.80)	0.1752
4 hours	2.1 (0.34)	3.9 (0.57)	0.0204*
24 hours	2.5 (0.34)	5.1 (0.60)	0.0029*

FIGURE 3.4.2.1:

Trend of pain scores for the first twenty-four hours after haemorrhoidectomy, comparing patients randomised to receive the full ischio-rectal fossa block with those who had infiltration of the haemorrhoidal complexes only.

The difference between these lines was analysed using a repeated measures analysis of variance. The difference was highly significant ($p=0.0004$).

FIGURE 3.4.2.1

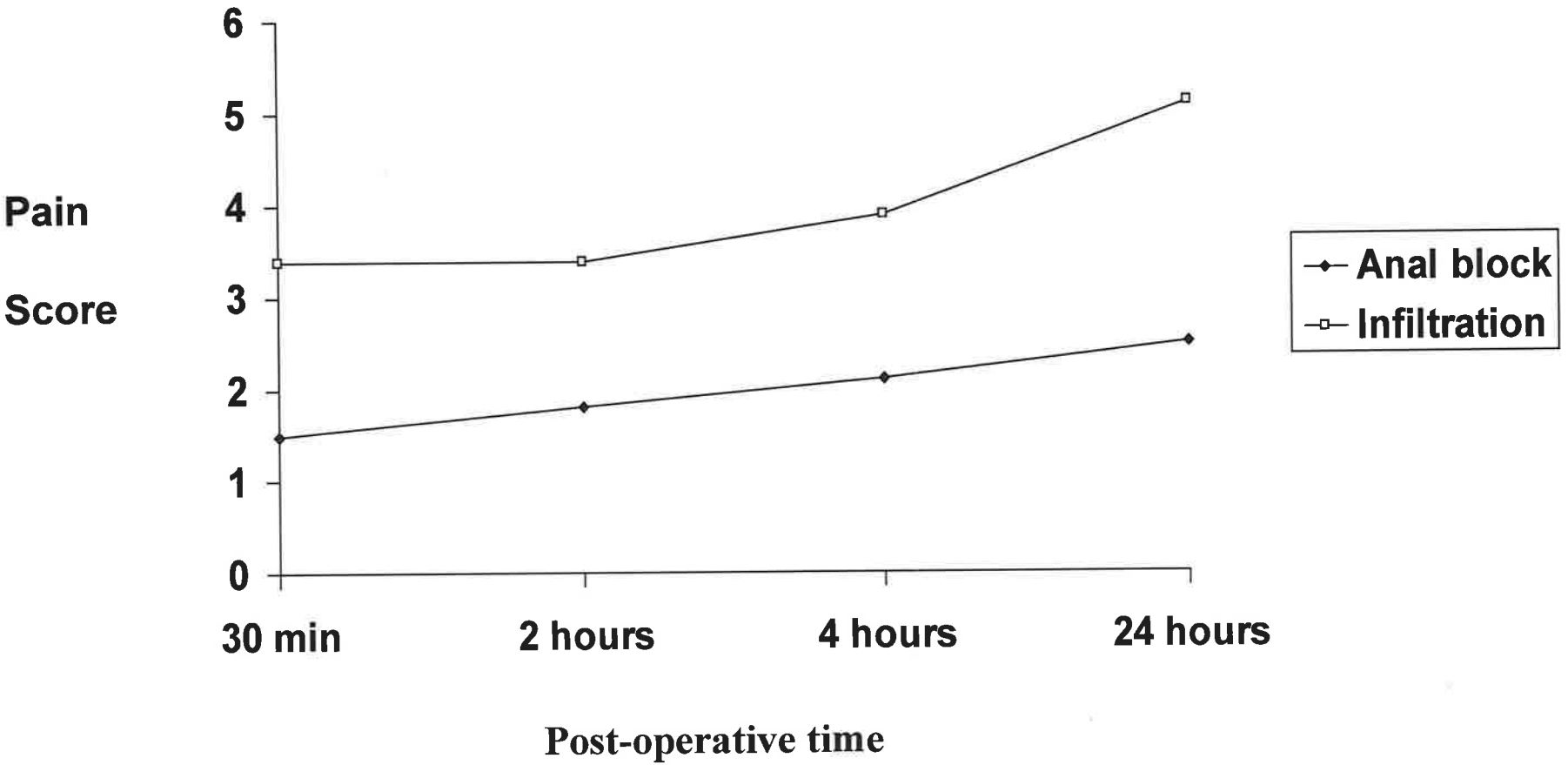

Pain
Score
6
5
4
3
2
1
0
30 min
2 hours
4 hours
24 hours
Anal block
Infiltration
Post-operative time

TABLE 3.4.2.3:

Comparison of analgesic requirements in the first twenty-four hours after haemorrhoidectomy in the local anaesthesia for haemorrhoidectomy randomised trial.

TABLE 3.4.2.3

Analgesia type	Anal block group	Infiltration group
Fentanyl	None	100 mcg
Oxycodone	45 mg	85 mg
Simple Analgesia	16 tablets	35 tablets

3.4.3 Topical glyceryl trinitrate paste *versus* lateral sphincterotomy in the treatment of chronic anal fissure.

A prospective, randomised clinical trial in progress.

The aim of this trial was to compare the merits of the most promising of the new pharmacological treatments for chronic anal fissure, glyceryl trinitrate (GTN) paste, with the gold standard surgical treatment, that being lateral subcutaneous internal sphincterotomy (LSIS). This trial was approved by the Ethics of Human Research Committee at The Queen Elizabeth Hospital. The trial will continue into 1999. The data presented in this thesis should thus be regarded as interim results and analysis. This interim data was analysed by a statistician from the University of Adelaide to determine the patient numbers that will be required for an appropriate final analysis.

Subjects

Patients were considered for enrolment in the trial if they had had the classic symptom of anal fissure, anal pain that is worse with defaecation, for longer than two weeks. A visible fissure was a preferred but not essential criterion for entry into the trial. If there was any doubt about the diagnosis, however, particularly in older patients with per rectal bleeding as well as the pain, further investigation was carried out before consideration of entry into the trial.

Patients were excluded from the trial if they could not safely be randomised to either treatment arm, or if they had complex perianal disease in association with a systemic condition. The specific exclusion criteria were as follows;

1. Anal fissure associated with inflammatory bowel disease or Acquired Immune Deficiency Syndrome.
2. Prior lateral internal sphincterotomy or anal stretch.
3. Concomitant medical conditions precluding general anaesthesia.
4. A history of faecal incontinence precluding sphincterotomy.
5. Cardiovascular or peripheral vascular disease requiring oral, sublingual or topical nitrates.

Methods

Enrolment of subjects

A letter describing the background, rationale and protocol of the trial was circulated to all general surgical consultants and registrars asking for patients suitable for enrolment. The letter was also sent to all general practitioners in the area served by The Queen Elizabeth Hospital. When a suitable patient was seen in the Outpatient or Emergency Departments of The Queen Elizabeth Hospital or in general practice, the consultant, registrar or general practitioner were asked to contact the trial organiser.

An appointment was made in the Day Surgery Unit consulting suite on either the day of referral or the following day. After explanation of the nature of anal fissure and the available

management options, the trial organiser explained the requirements of the study to the patient. The patient was supplied with a written information sheet and informed consent for the trial was obtained in writing. Once consent had been given the patient was randomised into either the glyceryl trinitrate paste group or the lateral sphincterotomy group by the drawing of a closed envelope from a central registry. At this time a thorough continence questionnaire was also completed and acted as a baseline for further continence assessment.

Lateral sphincterotomy group

Patients randomised to the sphincterotomy group had their surgery arranged on the next available elective operating list. The patients had a pre-operative anaesthetic assessment and were admitted on the day of surgery.

The operation was a left lateral internal sphincterotomy. The exact approach to sphincterotomy (open or closed) was at the discretion of the operating surgeon.

Patients were discharged on the day of surgery if pain, nausea and bleeding were controlled and they had voided urine. If these criteria were not met, the patient was admitted overnight to the convalescent ward for as long as required by standard discharge criteria.

Glyceryl trinitrate group

Patients randomised to the Glyceryl trinitrate group were given instructions as to how to apply the 0.2% paste. The patients were told to wear gloves when applying the paste to minimise systemic absorption and decrease the incidence of the major side effect of headache. Patients were instructed to apply enough paste to cover the pulp of the tip of the index finger to the skin of the perianal area. This application continued three times a day at 0800hrs, 1400hrs and 2000hrs for eight weeks.

The 12 hour gap between the night-time application and the next morning application was recommended because there is evidence from other studies of tachyphylaxis (tolerance) to GTN paste developing if the anal sphincters are constantly exposed to it (Watson et al 1996). This was less likely to be problematic than a break during the day because the resting anal tone is approximately 40mmHg lower overnight than during the day (Auwerda and Schouten 1994).

Patients were asked to record their level of pain on a Visual Analogue Scale (VAS). The VAS was based on a scale from one to ten with one representing no pain and ten representing the worst pain imaginable. The initial pain score was recorded immediately prior to the first application of the paste, followed by a second pain score 30 minutes later. Patients were then asked to record their worst pain score of the day every day from the initial consultation for the first two weeks and subsequently three times per week until the final visit at eight weeks. In addition, patients were asked to record their worst headache of the day on a similar scale, their

requirements for oral analgesia, whether or not they had opened their bowels and whether or not there were any problems.

The patients taking the GTN protocol were told that if they were suffering intolerable anal pain at any time during the treatment period that a request to undergo lateral sphincterotomy before the end of the 8-week course of GTN would be granted.

Both groups

Other aspects of care were standardised. Both groups of patients were asked to take one teaspoonful of the stool softener Metamucil™ (Proctor & Gamble, Parramatta, N.S.W.) dissolved in water each morning from the time of the initial visit until the final review at eight weeks. Patients were encouraged to take warm salt baths twice a day. All patients were provided with the analgesic medications paracetamol and dextropropoxyphene/paracetamol.

Patients were provided with a telephone contact number for advice. All patients were reviewed at two-weekly intervals until they were pain free and their fissure had healed.

Results

At the time this section was written, that is at the end of November 1998, 49 patients with chronic anal fissure had been enrolled in the trial and randomised to initial treatment by either lateral sphincterotomy (LS) or glyceryl trinitrate (GTN) paste. There were 28 patients in the GTN group and 21 patients in the LS

group. Four patients in the GTN group are yet to complete their eight-week course of treatment. Three patients randomised to lateral sphincterotomy are either waiting for their procedure or have not yet reached the minimum post-operative follow up of 2 weeks. The data for these 7 patients are therefore incomplete and have been excluded from the interim analysis.

A further 2 patients were excluded from the trial after randomisation had taken place. A 54-year-old woman, randomised to the lateral sphincterotomy group, had lax sphincters and no evidence of an anal fissure at examination under anaesthesia. It was not considered appropriate to perform the sphincterotomy because of the lack of pathology and the risk of causing incontinence. A 66-year-old man was randomised to the GTN group after telephone contact between a surgical registrar and the study organiser. The patient had severe chronic airways limitation requiring home oxygen therapy that would have precluded general anaesthetic. As he would have been excluded from the trial had he been randomised to lateral sphincterotomy, it was considered inappropriate to include his data in the trial analysis. He was treated with GTN paste. His fissure healed with the standard 8-week course.

The data from 40 patients is available for interim analysis. Twenty-three of these patients were randomised to receive GTN paste and 17 had lateral sphincterotomy. The glyceryl trinitrate group consisted of 5 men and 18 women with an average age of 36 years (range 17-86 years). In the lateral sphincterotomy group, there were 7 men and 10 women with an average age of 38 years (range 21-60 years).

Lateral sphincterotomy group

The details and outcomes for those patients randomised to undergo lateral sphincterotomy are shown in Table 3.4.3.1. Lateral sphincterotomy resulted in healing of the fissure in all 17 patients. Fifteen of the 17 patients (88%) were free of pain and had healed fissures at the first follow up appointment 2 weeks after surgery. The remaining patients still had fissures present at this time. One of the patients had a healed fissure 4 weeks post-operatively, the other required six weeks for her fissure to heal. One patient required overnight admission for analgesia after lateral sphincterotomy. All other patients had the procedure performed as day surgery.

The patients in the lateral sphincterotomy group waited a median of 13.5 days (range 1-40 days) between the day of randomisation and the day of surgery. The four patients who presented with severe, constant pain due to their fissure all underwent lateral sphincterotomy within 48 hours of first presentation. There were no short-term complications from lateral sphincterotomy in this group. No patient has reported any incontinence for flatus or faeces after this procedure.

Glyceryl trinitrate paste group

The details and outcomes for the patients randomised to treatment with glyceryl trinitrate paste are shown in Table 3.4.3.2. The primary endpoint of a healed fissure at the end of eight weeks of treatment was achieved in 16 of the 23 patients (70%). Another patient was pain free at this time but required a further 4 weeks of treatment with glyceryl trinitrate before the fissure healed. Thus the

primary healing rate with GTN paste was 17/23 patients (74%). This was significantly less than the 100% primary healing rate achieved with lateral sphincterotomy (p=0.0112). Several patients had healed fissures earlier than 8 weeks after starting GTN paste, with healing seen at 2 weeks in 2 patients (9%), at 4 weeks in 6 patients (26%) and at 6 weeks in 9 patients (39%).

The remaining six patients (26%) failed to achieve primary fissure healing with glyceryl trinitrate paste. In one patient the paste was stopped because of headaches; the other five patients had non-healing fissures despite the appropriate GTN regime. These patients all requested lateral sphincterotomy between 4 and 8 weeks after commencing treatment with GTN paste. The procedure was performed as day surgery in all patients. All 6 patients had healing of their anal fissure within two weeks of surgery. There was one complication of this surgery, with a 36-year-old woman presenting 6 weeks after surgery with widespread left buttock cellulitis. This responded to oral antibiotic treatment.

Two of the 17 patients (12%) who achieved primary fissure healing suffered a recurrence of the condition. Both patients re-presented with recurrence of pain 4 weeks after stopping the GTN paste application. Both patients were prescribed a further 4 weeks of GTN paste. In one patient, this produced healing of the fissure. There has been no further recurrence, however the second follow up period is only 4 weeks at this time. The other patient's fissure did not heal with the second course of GTN paste. She underwent lateral sphincterotomy, with a good result including healing of her fissure within two weeks of surgery.

Pain scores

Complete data sheets were returned by 15 of the 23 patients in the GTN group, including 11/17 patients who had primary fissure healing (but neither of those who had a recurrence) and 4/6 patients who did not have primary fissure healing. A comparison of the pain scores between those who did and those who did not achieve primary fissure healing is shown in Figure 3.4.3.1. The patients numbers used to generate this graph are too small to subject to statistical analysis at this time. Nevertheless, there are trends apparent on this graph, which may reach significance if they are sustained when the patient numbers are greater.

The mean pain scores for all patients were similar for the first two days. After this time, the patients whose fissure subsequently healed had a decrease in mean pain score over days 3 and 4, from a mean of between 4 and 5 to a mean of below 2. This low mean pain score was then sustained throughout the treatment period. In the patients who did not have primary fissure healing, a decrease in mean pain scores was seen, but it was seen later, occurring on days 6 to 9. It was also less pronounced, with the lowest mean score being 2.7 on days 10 to 14 and it was not sustained, with increasing mean pain scores recorded over the subsequent weeks. By week 6, all of the patients who recorded data and did not have healing of their fissures had stopped using the paste pending lateral sphincterotomy. There is thus no data for comparison for weeks 7 and 8 of the GTN course.

The range of pain scores recorded was wide for both groups. Even at the time when the mean scores were the most widely

separated, on day 4 and during week 4, there was overlap of the ranges. On day 4, the range of pain scores was 1 to 5 for the healed group and 2 to 7 for the non-healed group. During week 4, the range of pain scores was 1 to 5 for the healed group and 2 to 8 for the non-healed group.

Eight patients recorded the immediate effect of glyceryl trinitrate paste on their anal pain. Four patients recorded no difference in their pain score 30 minutes after application of the paste. The other four patients recorded a decrease in pain by one digit, for example from 7 to 6.

Headache scores

Two of the 23 patients (9%) who were treated with glyceryl trinitrate stopped the paste because they were unable to tolerate the side effect of headache. Neither of these patients recorded data on the data sheets. The mean headache scores for the 15 patients who did record this data are shown in Figure 3.4.3.2. Headaches on day 1, even for those patients who were able to tolerate them, were considerable, with a mean score recorded of 4.4 (range 1-8). The mean score decreased to 3.3 (range 1-6) on day 2, and continued to decrease throughout the treatment course.

Discussion

The recent publication of a number of series investigating the use of topical nitrates for anal fissure has clearly established two facts. Firstly, topical nitrates applied to the perianal skin produces

a reduction in resting anal tone. Lund et al (1996) report a decrease from 118.7 cmH_2O to 70.3 cmH_2O 20 minutes after application ($p<0.001$). Schouten et al (1996) reported a decrease from 111 mmHg to 86 mmHg ($p<0.001$). Secondly, the use of topical nitrates in this way will produce healing of the fissure in a significant number of patients, as detailed in the introduction to this section.

The existing literature is however deficient in two major respects. Of primary importance is the apparent assumption that a non-surgical treatment is better for the patient than a surgical treatment, with no data to support such an assumption. In addition, the nitrate regimes prescribed in published papers vary widely in terms of dosage, timing of application, length of course and the exact nature of the nitric oxide carrying medication. Bacher et al (1997) used 0.2% glyceryl trinitrate three times a day. This group did not specify the length of the treatment course. Gorfine (1995) used 0.5% glyceryl trinitrate, as often as the patient thought it was required, for eight weeks. Lund et al (1996) used 0.2% glyceryl trinitrate twice a day for eight weeks. Schouten et al (1996) used isosorbide dinitrate every three hours for between six and twelve weeks. Watson et al (1996) varied the concentration of the glyceryl trinitrate paste on a case by case basis, using the concentration required to produce a 25% reduction in resting anal pressure in each individual patient. Their treatment lasted for six weeks. It is thus difficult to define the exact merits of this new treatment, and even more difficult for individual practitioners to establish appropriate treatment protocols for the management of anal fissure.

The trial presented in this thesis varies in several respects from those that have been published to date. There is a direct and

randomised comparison between the management of chronic anal fissure with glyceryl trinitrate paste and with the established surgical gold standard of lateral sphincterotomy. The forty patient interim analysis presented in this thesis is larger than any other such trial currently available. In addition, this trial attempts to provide a more practical and clinical appraisal of the role of nitrates in the management of chronic anal fissure. This was achieved firstly by choosing a nitrate regime that could be easily followed by our patients and, in the future, by clinicians reading the published data; secondly by quantifying the anal pain and headaches that the patients using glyceryl trinitrate paste were experiencing over the course of treatment; and thirdly by allowing patients who were not responding to request surgery if they were not satisfied with their progress.

The major endpoint in the assessment of different treatment regimes for chronic anal fissure is healing of the fissure. In this trial, 100% of the patients who had a lateral sphincterotomy (17/17 in the LS group and 7/7 of those who required LS after failure of GTN) had healing of the fissure. This is in comparison to a 74% (17/23) primary healing rate for GTN paste with a 12% (2/17) recurrence rate. Based solely on this criterion, lateral sphincterotomy is a superior treatment than topical nitrate therapy.

GTN paste also is considerably more labour intensive for both patient and doctor than lateral sphincterotomy. Patients must apply the paste several times a day to the perianal area. They must also be seen at least at two weekly intervals for at least two months to ensure that progress is being made. The not inconsiderable recurrence risk infers that long term follow up is also required.

This is in comparison to the procedure of lateral sphincterotomy, which, in this series, was day surgery in all but one patient and allowed patient discharge with a healed fissure after 2 weeks in all but two patients.

Assessment of the relative merits of these management regimes for anal fissure is however, a far less simple matter than comparing the fissure healing rate or the number of outpatient follow up appointments. Lateral sphincterotomy is a surgical procedure that in most cases requires a general anaesthetic. The attendant risks of the anaesthetic as well as bleeding or infection are small, but must be taken into account. Temporary or even permanent faecal soiling or incontinence, whilst not seen in this series, has also been reported with lateral sphincterotomy. It has also become apparent during this trial that the patients, in possession of all of the known facts regarding the treatment of anal fissure, would in general prefer a medical treatment to a surgical one as first line management. For these reasons and perhaps most importantly the latter, the assessment of treatments such as GTN paste must continue.

In this trial, patients waited up to six weeks from the time of their outpatient review before surgery could be performed, with a median waiting period of nearly two weeks. Outside of the confines of a clinical trial the wait may be longer. Patients treated surgically for anal fissure must therefore remain in pain for some considerable time before definitive treatment. This waiting period provides a window of opportunity for a medical treatment such as topical nitrate application, which can commence immediately. It is perhaps in this context that the data provided by the GTN patients in this

trial should be evaluated.

The patient compliance with data collection in this study was poor, particularly in comparison to that achieved in the day case haemorrhoidectomy study. This can be attributed to two factors. Firstly, the patients in this trial continued to work and were not at home recovering from surgery. They were therefore less likely to remember to record the pain scores. Secondly, data collection in the day case haemorrhoidectomy study was performed at home by the patient in conjunction with a registered nurse, whereas in this trial the patients had to remember to record the data themselves.

Gorfine (1995), using the stronger 0.5% GTN paste, reported that all patients reported dramatic relief of anal pain within 3 to 4 minutes of paste application that lasted between 2 and 6 hours. Quantitative data are not provided. This is contrary to the data presented in this trial, with patients reporting either no change or only a small decrease in pain 30 minutes after the first application of the paste. In fact, the patients in this trial waited until day 3 before there was a demonstrable decrease in the pain of anal fissure. This decrease was then sustained in those patients who achieved primary fissure healing with GTN paste.

The apparent difference in pain score trend between the GTN patients with primary fissure healing and those without primary fissure healing is of interest. The patient numbers are thus far too small to establish whether or not one may predict the likelihood of fissure healing on the basis of pain scores after a certain length of treatment with GTN. The range of pain scores in both groups suggests that such a prediction may never be possible on an

individual patient basis. This possibility is nevertheless intriguing and one that warrants further assessment when the final data set is available.

The definitive conclusions that will be drawn from this trial must await the formal assessment of all data once patient accrual and treatment is complete. A practical and clinically useful protocol for the active management of chronic anal fissures will be included in these conclusions. This interim analysis does however provide enough data for the important aspects of such a protocol to be presented. They are as follows;

1. Patients diagnosed with chronic anal fissure should be placed on the waiting list for lateral sphincterotomy, to reduce the waiting time if glyceryl trinitrate paste is unsuccessful.

2. Patients diagnosed with chronic anal fissure should be commenced on a glyceryl trinitrate paste regime whilst awaiting surgery.

3. Patients should be reviewed, or at least contacted by phone, weekly to assess progress and plan the appropriate timing of surgical intervention if this is indicated.

4. Patients responding to glyceryl trinitrate paste should be removed from the surgical waiting list but followed closely for the entire course of treatment. They should also have contact numbers available should their fissure recur at a later date.

5. Patients with severe constant pain due to anal fissure should probably be offered lateral sphincterotomy as an urgent or semi-urgent procedure, given that the pain relief afforded by GTN paste does not commence until day 3 of treatment.

In an invited commentary in The Lancet, Simons and Beart (1996) stated "thus far, treatment with nitric oxide donors seems to be a safe and simple alternative for potentially treating anal fissures. In experienced hands however, lateral internal sphincterotomy is an extremely effective and proven method, and it is likely that both forms of treatment will continue to play an important role in the management of anal fissures." This final statement holds the key to the production of an ideal management protocol. The data provided by the randomised trial reported in this thesis will go a considerable way towards placing the appropriate perspective on the role of each of these important treatments in the management of chronic anal fissure.

TABLE 3.4.3.1:

Patient details and outcomes for patients with chronic anal fissure randomised to primary treatment by lateral sphincterotomy.

TABLE 3.4.3.1

Age/Sex	Date of Randomisation	Date of Surgery	Waiting Time (days)	Outcome
56F	5/1/98	14/1/98	9	Healed at 2 weeks
30M	27/1/98	29/1/98	2	Overnight admission. Healed at 2 weeks
21M	19/2/98	23/2/98	4	Healed at 2 weeks
42F	1/3/98	13/3/98	12	Healed at 2 weeks
52M	30/3/98	12/4/98	15	Healed at 2 weeks
48F	16/4/98	17/4/98	1	Healed at 2 weeks
60F	20/4/98	27/4/98	7	Healed at 2 weeks
54F	23/4/98	15/5/98	22	Excluded from trial
37F	30/4/98	3/6/98	34	Healed at 2 weeks
42M	4/6/98	18/6/98	14	Healed at 2 weeks
30M	8/6/98	18/7/98	40	Healed at 2 weeks
44F	18/6/98	21/7/98	33	Fissure present at 2 and 4 weeks. Healed at 6 weeks
41F	30/7/98	31/7/98	1	Healed at 2 weeks
21F	30/7/98	9/9/98	40	Fissure at 2 weeks Healed at 4 weeks
42F	1/8/98	9/8/98	8	Healed at 2 weeks
20M	17/9/98	13/10/98	26	Healed at 2 weeks
37F	1/10/98	13/10/98	12	Healed at 2 weeks
39M	1/10/98	20/10/98	19	Healed at 2 weeks
30M	15/10/98	17/11/98	31	Incomplete.
37M	5/11/98	24/11/98	19	Incomplete.
31F	5/11/98	6/11/98	1	Incomplete.

TABLE 3.4.3.2:

Patient details and outcomes for patients with chronic anal fissure randomised to primary treatment with glyceryl trinitrate paste.

Legend: GTN = glyceryl trinitrate paste
LS = lateral sphincterotomy

TABLE 3.4.3.2

Age/Sex	Date of Randomisation	Outcome
30F	5/1/98	Failed. Requested LS after 4 weeks. LS performed on 18/2/98. Healed at 2 weeks post LS.
36F	5/1/98	Failed. Requested LS after 6 weeks. LS performed on 2/3/98. Healed at 2 weeks post LS. Buttock cellulitis at 6 weeks post LS requiring antibiotics.
39M	18/1/98	Healed at 8 weeks. No recurrence.
41F	22/1/98	Failed. Requested LS after 8 weeks. LS performed on 24/4/98. Healed at 2 weeks post LS.
29F	30/1/98	Healed at 4 weeks. No recurrence.
40M	12/2/98	Healed at 8 weeks. No recurrence.
28F	28/2/98	Healed at 2 weeks. No recurrence.
30M	28/2/98	Pain-free but not healed at 8 weeks. Healed at 12 weeks after further 4 weeks of GTN paste. No recurrence.
27F	13/3/98	Healed at 4 weeks. No recurrence.
45F	17/3/98	Stopped GTN after 8 days due to headaches. Fissure healed at 2 week follow up. No recurrence.
47F	26/3/98	Healed at 8 weeks. Recurrence 4 weeks later that did not respond to 4 weeks GTN paste. LS performed on 13/7/98. Healed at 2 weeks post LS.

TABLE 3.4.3.2 (continued)

Age/Sex	Date of Randomisation	Outcome
43F	9/4/98	Failed. Requested LS after 6 weeks. LS performed on 23/6/98. Healed at 2 weeks post LS.
36M	26/4/98	Healed at 8 weeks. No recurrence.
35F	26/4/98	Stopped GTN after 14 days due to headaches. Requested LS. LS performed on 25/5/98. Healed at 2 weeks post LS.
22F	30/4/98	Failed. Requested LS after 6 weeks. LS performed on 1/7/98. Healed at 2 weeks post LS.
33F	18/6/98	Healed at 8 weeks. No recurrence.
30F	18/6/98	Healed at 8 weeks. No recurrence.
33F	25/6/98	Healed at 4 weeks. No recurrence.
55F	25/6/98	Healed at 8 weeks. Recurrence 4 weeks later. Healed with a further 4 weeks of GTN paste.
29F	30/7/98	Healed at 4 weeks. Stopped GTN paste at this time as due to have embryos implanted. No recurrence.
33M	30/8/98	Healed at 6 weeks. No recurrence.
20F	1/9/98	Healed at 6 weeks. No recurrence.
21F	1/10/98	Healed at 6 weeks. No recurrence.
86F	22/10/98	Incomplete.
48M	22/10/98	Incomplete.
17M	5/11/98	Incomplete.
31F	13/11/98	Incomplete.

FIGURE 3.4.3.1:

Comparison of pain scores between the glyceryl trinitrate patients who had healing of their fissure by 8 weeks with those whose fissures did not heal.

Pain scores are measured on a Visual Analogue Scale (VAS 1-10, where 1 represents no pain and 10 represents the most severe pain imaginable).

FIGURE 3.4.3.1

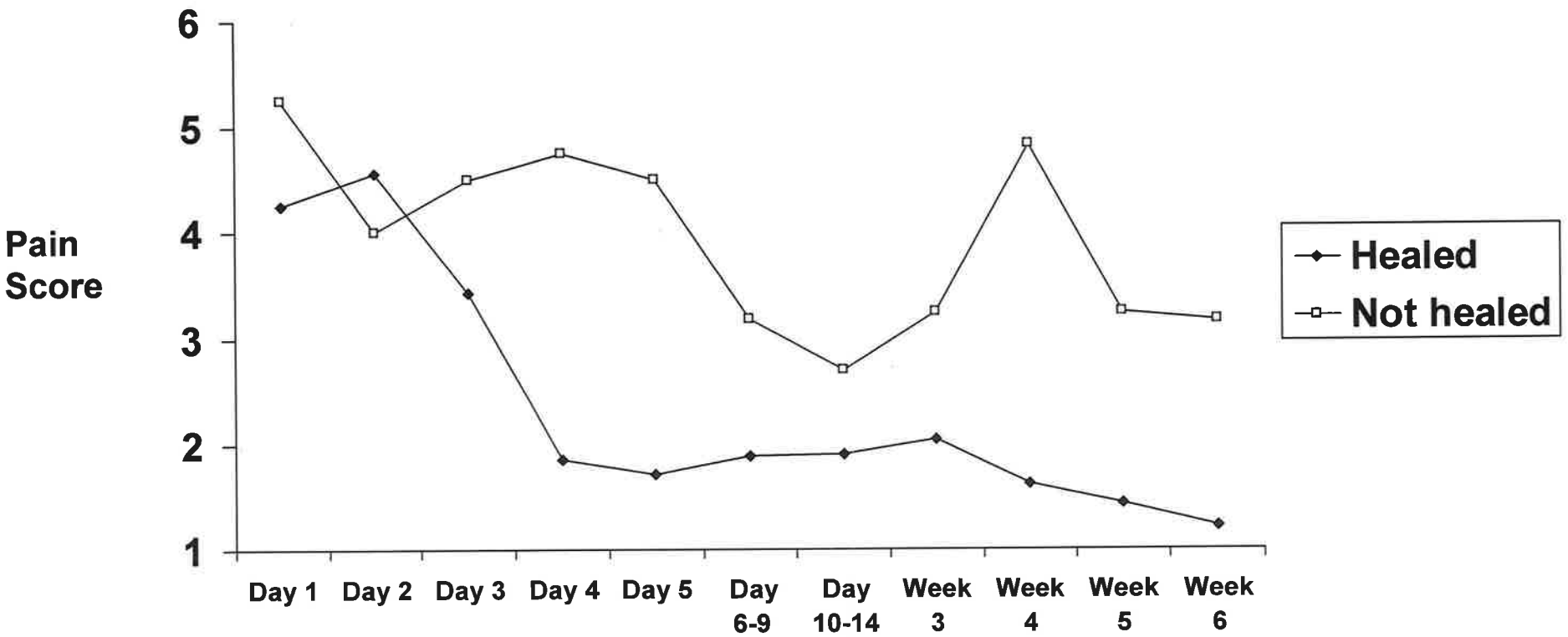
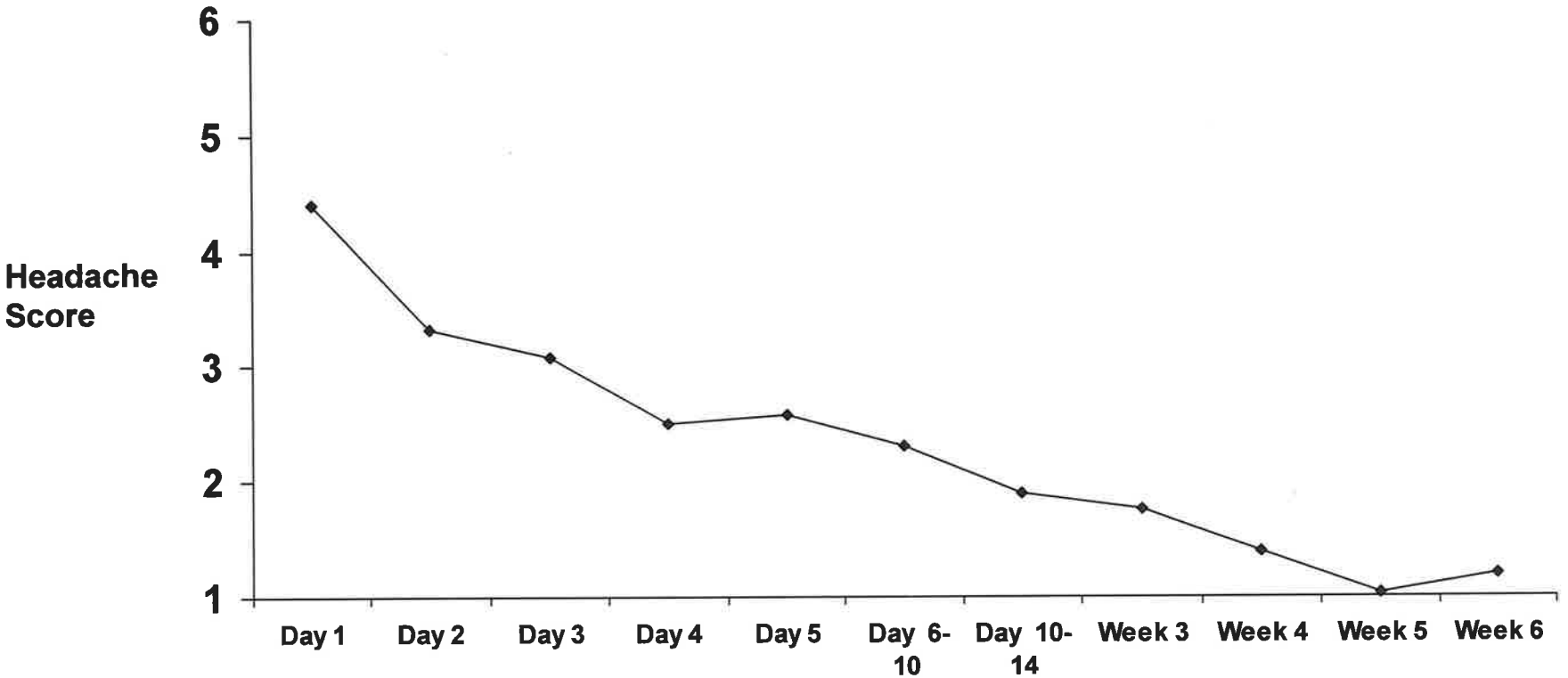

Pain Score
6
5
4
3
2
1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6-9
Day 10-14
Week 3
Week 4
Week 5
Week 6
Healed
Not healed

FIGURE 3.4.3.2:

Headache scores recorded by patients using gylceryl trinitrate paste.

Headache scores are measured on a Visual Analogue Scale (VAS 1-10, where 1 represents no headache and 10 represents the most severe headache imaginable).

FIGURE 3.4.3.2


Headache Score
6
5
4
3
2
1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6-10
Day 10-14
Week 3
Week 4
Week 5
Week 6

3.5 PATIENT INFORMATION BY VIDEO

3.5.1 The impact of video information on pre-colonoscopy anxiety and knowledge levels.

A prospective, randomised clinical trial

A video aimed at providing information to patients prior to colonoscopy and produced by the Australian Gastroenterology Institute in conjunction with Lederle Laboratories was acquired by the Colorectal Surgical Unit in August 1997. A trial designed to analyse the effect of this video on the anxiety and knowledge of patients scheduled to undergo colonoscopy was performed. This trial was approved by the Ethics of Human Research Committee at The Queen Elizabeth Hospital.

Subjects

Patients scheduled for colonoscopy in the Day Surgery Unit of The Queen Elizabeth Hospital were considered for enrolment into this trial. Patients were excluded if, under normal circumstances, they would require a third party to complete the consent process, namely patients under 16 years of age, patients who did not adequately understand English and those with mental impairment.

Methods

The patients were approached to consider enrolment in the trial at the time of the pre-operative anaesthetic assessment, after both the clinic nurse and the anaesthetist had assessed them. This appointment was approximately 7 days prior to colonoscopy. The trial did not interfere with the standard information and consent process as the patient had seen both colonoscopist and anaesthetist prior to enrolment in the trial.

The purpose and requirements of the trial were then explained to the patient and informed consent for the trial was obtained in writing. Details of patient age, sex, education, previous experience of colonoscopy and the indication for this colonoscopy were recorded. All patients were given a written information sheet regarding the trial and a separate information sheet about colonoscopy.

Each patient then completed the Spielberger State-anxiety self-evaluation questionnaire (State-Trait Anxiety Inventory [STAI Form Y-1]; Spielberger et al 1970). This questionnaire is designed to evaluate an individual's momentary or situational anxiety. It consists of 20 statements with four answers, producing a score between 20 and 80 inclusive. A higher score reflects a higher level of anxiety. This score was called the "first anxiety score". An example of this questionnaire is included in the Appendix.

Randomisation into 'video' and 'no video' groups was then performed by the opening of a sealed, opaque envelope. Patients in the 'video' group were taken to a separate room to watch a 10-

minute videotape. A well-known Australian actor narrates the video in layman's language. The narrator discusses the procedure with the colonoscopist and with the patient, who has had a previous colonoscopy. The narrator is then present whilst the procedure is in progress.

On arrival at the Day Surgery Unit on the day of their colonoscopy, all patients were asked to complete the same anxiety questionnaire as that which had been answered one week previously. This anxiety score was called the "second anxiety score".

A knowledge questionnaire was then completed. The questionnaire consisted of three sections to test the patients' knowledge of the purpose (maximum 4 points), procedural details (maximum 5 points) and the potential complications (maximum 3 points) of colonoscopy. A copy of the knowledge questionnaire and an explanation of the scoring system are included in the Appendix.

After completion of the trial questionnaires, the patient changed into a hospital gown and proceeded to colonoscopy. No post-procedural data were collected.

Statistical analysis was performed using a linear regression model and the Pearson Chi-square test of homogeneity [BMDP Statistical Software (Program 5V)].

Results

Between January and August 1998, 198 patients were asked to consider enrolment into the trial. Forty-eight patients were excluded from the trial, 9 because they spoke inadequate English to understand the video, 7 patients could not comprehend the purpose of the trial and 1 patient could not read the self-evaluation questionnaire because of poor eyesight. Thirty-one patients were not interested in participating in the trial.

The remaining 150 patients consented to enrolment into the trial. Seventy-two patients were randomised to the 'video' group and 78 patients to the 'no video' group. The patient demographics are shown in Table 3.5.1.1. The groups were well matched in terms of age, sex, education, experience of a previous colonoscopy, indication for the current colonoscopy and first anxiety score.

The effect of each of the above patient variables on the first anxiety score was calculated using linear regression analysis. The patient's age ($p=0.4048$) and education ($p=0.1173$) did not influence initial anxiety level; nor did the indication for colonoscopy (as defined in Table 3.5.1.1).

First anxiety scores did however vary widely depending on sex and prior experience of colonoscopy. Female patients were significantly more anxious than male patients one week prior to colonoscopy ($p=0.0008$). Patients who had not had a previous colonoscopy had significantly greater anxiety than those who had experienced the procedure before ($p=0.0008$). The effect of patient gender and prior experience of colonoscopy on first anxiety scores

was so profound that separate estimates, calculated by linear regression analysis, for the first anxiety score can be made based on these variables. These are shown in Table 3.5.1.2.

The significant factors in the level of anxiety immediately prior to the colonoscopy (second anxiety score) were the first anxiety score and whether or not the patient had watched the video. All other factors did not reach significance because of the strength of the effect of a patient's initial anxiety on subsequent, pre-colonoscopy anxiety levels.

First anxiety score and whether or not the video was viewed affected the second anxiety score via an interaction that is seen in the graph in Figure 3.5.1.1. At all times the pre-colonoscopy anxiety is less for patients who had been randomised to view the video. As the graph has a steeper slope in the 'no video' group, the difference is greater for patients who reported a higher first anxiety score. Even for patients with low initial anxiety, however, those who watched the video had significantly lower second anxiety scores than those who did not watch the video.

The results of the knowledge questionnaire are shown in Table 3.5.1.3. Patients randomised to the video group scored significantly higher marks with regard to the purpose of the colonoscopy, the details of the procedure and the potential complications of colonoscopy than those who did not watch the video. None of the other patient variables, including education, were significant determinants of knowledge levels.

The marked calming effect of the video on patients with a high level of initial anxiety has been noted above and is tabulated in Table 3.5.1.4, which shows the results for all patients with a first anxiety score of greater than 50. This group of patients also showed the greatest variation in knowledge levels. Those with severe initial anxiety in the 'video' group had the highest mean scores, whereas the patients with severe anxiety who did not watch the video had the poorest results.

Discussion

The results of this trial have provided data for discussion on two aspects of pre-operative preparation for colonoscopy. Firstly, we have identified which patient variables are associated with higher levels of pre-colonoscopy anxiety. Secondly, the effect of patient information by video on the anxiety and knowledge levels of patients immediately prior to colonoscopy has been further elucidated.

The finding that female patients have higher levels of pre-operative anxiety has been previously reported. Male et al (1981) found that male gender was associated with a low anxiety score in day surgery patients. Male patients have also been shown to express less fear about anaesthesia (van Wijk and Smalhout 1990, Shevde and Panagopoulos 1991). Although it could be postulated that these findings may represent a reluctance on the part of male patients to admit to being anxious, it is likely that there is indeed a real difference in pre-operative anxiety levels between the sexes.

Patients with previous experience of colonoscopy were found in this trial to have lower levels of anxiety one week prior to the procedure. This finding has also been previously reported. Mackenzie (1989) found that previous experience of an anaesthetic to be associated with lower anxiety levels prior to a subsequent procedure.

The detrimental effect of pre-operative anxiety on outcome has been discussed in the introduction to this section. It is likely therefore, that it is female patients and/or those who have not had a previous colonoscopy that are the patients who will suffer the consequences of a high pre-operative anxiety state unless a suitable anxiety-reduction strategy is available.

The provision of information by video to the patients in this trial produced a significant reduction in the second anxiety score (immediately prior to the colonoscopy), in comparison to patients who had been randomised to the 'no video' group. This effect was most evident in patients with high first anxiety scores, but was still present at the low anxiety end of the scale. This data confirms statistically anecdotal evidence given to the study organisers by many patients after they had viewed the video. A large number of patients, particularly those with high levels of anxiety initially, appeared considerably more relaxed after watching the video. Several patients commented that it was the video that was directly responsible for their change in anxiety level.

The ability of a video to reduce the anxiety levels of pre-operative patients has been previously reported. Mahler et al (1993) reported in a simulated experiment with college students that

subjects randomly assigned to view a video prior to preparing for coronary artery bypass surgery had less anxiety than those who did not watch the video. In the clinical setting, Herrmann and Kreuzer (1989) showed a significant reduction in anxiety in patients about to undergo coronary angiography who were randomised to watch a video about the procedure. The group of patients who did not watch the video had no significant reduction in anxiety score.

Shipley et al (1978) took this concept one step further. As well as showing that watching a video produced less anxiety in patients scheduled for endoscopy than not watching the video, this group also showed that watching the video three times caused a further reduction in anxiety in comparison to watching it once. Whilst this is a most interesting finding, in clinical practice this approach is likely to be impractical.

In addition to reducing the level of anxiety, the information video has been shown in this randomised trial to significantly increase the short-term knowledge of patients preparing for colonoscopy regarding the purpose, procedural details and potential complications of the procedure. As discussed in the introduction to this section, there is ample literature to corroborate these findings.

The provision of information by video is less successful in increasing long term knowledge retention. Moldofsky et al (1979) compared learning between two groups with asthma. The group receiving video information learned more, but 16 months after intervention, the patients' knowledge scores had fallen to those of the control group. Stalonas et al (1979) compared video, live lecture and written information in instructing alcoholics on the

problems of alcoholism. Video instruction proved more effective in increasing knowledge than the other methods, but the knowledge of the video group returned to baseline after one month. The apparent inability of video information to increase knowledge level in the long-term is not of concern in the current situation, however, as the information is only required in the immediate pre-colonoscopy period.

The setting in which video information is watched and the technique that the video uses to impart the information are considered important in increasing short-term recall of the information and in decreasing patient anxiety. Kleemeier and Hazzard (1984) showed videos on parenting tips to two randomised groups of parents. One group saw the video in a structured setting in a separate room, the other group in a general waiting room. The first group of parents learned much more. This was taken into consideration in our trial, with all patients watching the video in a separate room without the distraction of staff members or other patients.

The video used for this trial contained a combination of lecture style information and role modelling. It has been shown in other studies that the addition of role modelling can allow the patient to identify more successfully with the video and that this is associated with a reduction in anxiety. Melamed et al (1975) compared the effect of a peer-modelling information video with a lecture information video and found that the modelling video group reported less anxiety and showed less sympathetic arousal than the lecture video group. Both groups, however, did better than a control group that saw an unrelated video. Gatchel (1986) reported

decreased anxiety in dental patients who watched a modelling video.

The combination of lecture information and modelling has also been shown to potentiate learning as well as allay anxiety. In an elegant study, Uzark et al (1985) showed the parents of newborns with congenital heart defects either a lecture video explaining cardiac defects or a modelling video using the parents of babies with heart defects to convey the same information. The modelling group scored higher marks on knowledge tests than the group who saw the lecture video.

The use of an excellent video which utilises both lecture information and role modelling, in combination with the fact that it was watched in a structured and undisturbed setting and that the effect was only required in the short-term has allowed the benefits of video information for colonoscopy to be maximised in this trial. The dual benefit of the video in the improvement of knowledge and the reduction of anxiety is best illustrated by the effect on patients who had high initial anxiety scores. The reduction of anxiety produced by the video was at its greatest at this end of the scale. In addition, anxious patients who viewed the video showed the best results of all patients in the knowledge questionnaire. It is unclear whether it is the decrease in anxiety level that allows increased knowledge acquisition or whether the knowledge gained by watching the video results in the reduction of anxiety.

There are several other issues that must be discussed before any conclusion or recommendations can be made on the basis of the results of this trial. Firstly, randomisation into 'video' and 'no

video' groups was made after the standard information and consent process provided by colonoscopist and anaesthetist had been completed. The video acted as an adjunct to this process in this trial and should only be used in such a role in clinical practice. It should add to rather than replace the information provided by the clinician. The use of a video does however, as stated by Gagliano (1988) "assure a consistent core of information not subject to the varying abilities or opinions of different educators".

Secondly, the issue of choice needs to be addressed. A large number of patients (31) did not agree to enrolment in this trial. Some of these patients refused to be a part of the trial because they were unable to make the choice as to whether to watch the video or not. Other patients, many of them apparently extremely anxious, wanted to know nothing about the procedure. A further group of patients were excluded because of an inability to understand the trial or eyesight that was too poor to read the trial paperwork. It is possible that many of these patients would have been prepared to watch the video out of the confines of a trial. The benefits of the video seen in the 'video' group in this trial may be more widespread in general clinical practice than we have been able to show in a randomised trial.

Thirdly, the anxiety provoked by colonoscopy is not entirely brought about by concern for the procedure per se. As it is a diagnostic procedure, some patient anxiety is caused by worry regarding the findings, in particular the diagnosis of colorectal cancer. This component of the overall anxiety level cannot be alleviated by video information about the procedure itself. In theory, therefore, given the impressive reduction in anxiety

produced by video for colonoscopy, it is possible that providing information by video for therapeutic procedures may be even more valuable. This claim, however, is not substantiated by available data at this time, as most research workers have used diagnostic procedures such as coronary angiography or endoscopy to assess the value of information videos.

Many of the questions regarding the use of video information as a component of pre-operative preparation cannot be answered by the results of this trial. We can however conclude that watching a well designed video produced a significant reduction in the level of anxiety and an improvement in the knowledge levels of patients scheduled to undergo colonscopy. The use of video in this setting is highly recommended for all such patients and is particularly valuable in patients with severe anxiety about the procedure, which in this trial were female patients and those who have not had a previous colonoscopy. If further studies show that this medium is of similar or greater value in preparing patients for therapeutic medical or surgical procedures, provision of patient information by video should become an important component of pre-operative preparation.

TABLE 3.5.1.1:

Details of patients in the information video randomised trial.

*Age data are expressed as median (range).

[+]First anxiety scores are expressed as mean (standard error of the mean).

TABLE 3.5.1.1

	VIDEO GROUP	NO VIDEO GROUP
NO. PATIENTS	72	78
AGE*	59.5 (20-82)	62 (22-88)
SEX: Males	38	39
Females	34	39
EDUCATION: Primary	18	19
Secondary	45	51
Tertiary	9	7
PRIOR COLONOSCOPY:		
Yes	35	37
No	37	41
INDICATION:		
PR bleeding	20	21
Abdominal pain	12	12
Cancer surveillance	24	25
Family history	7	6
Abnormal Ba enema	3	3
Other	6	11
FIRST ANXIETY SCORE^{+}	36.89 (4.51)	37.62 (4.12)

TABLE 3.5.1.2:

Estimated first anxiety score (by Spielberger State Anxiety self evaluation questionnaire) depending on sex and previous experience of colonoscopy.

*Data are calculated by linear regression analysis and expressed as estimate (asymptotic standard error).

TABLE 3.5.1.2

SEX/PREVIOUS COLONOSCOPY COMBINATION	ESTIMATED FIRST ANXIETY SCORE
Male/Previous colonoscopy	29.5 (1.9)
Male/No previous colonoscopy	36.4 (1.9)
Female/Previous colonoscopy	37.7 (2.1)
Female/No previous colonoscopy	44.5 (1.8)

FIGURE 3.5.1.1:

Interaction between first anxiety score (7 days prior to colonoscopy) and second anxiety score (immediately prior to colonoscopy) depending on whether or not the patient watched the information video.

*Data are calculated using linear regression analysis. Second anxiety score (ANX2) can be estimated from first anxiety score (ANX1) as follows;

Video group: $ANX2 = 13.05 + (0.476 \times ANX1)$

No video group: $ANX2 = 13.05 + (0.774 \times ANX1)$

FIGURE 3.5.1.1

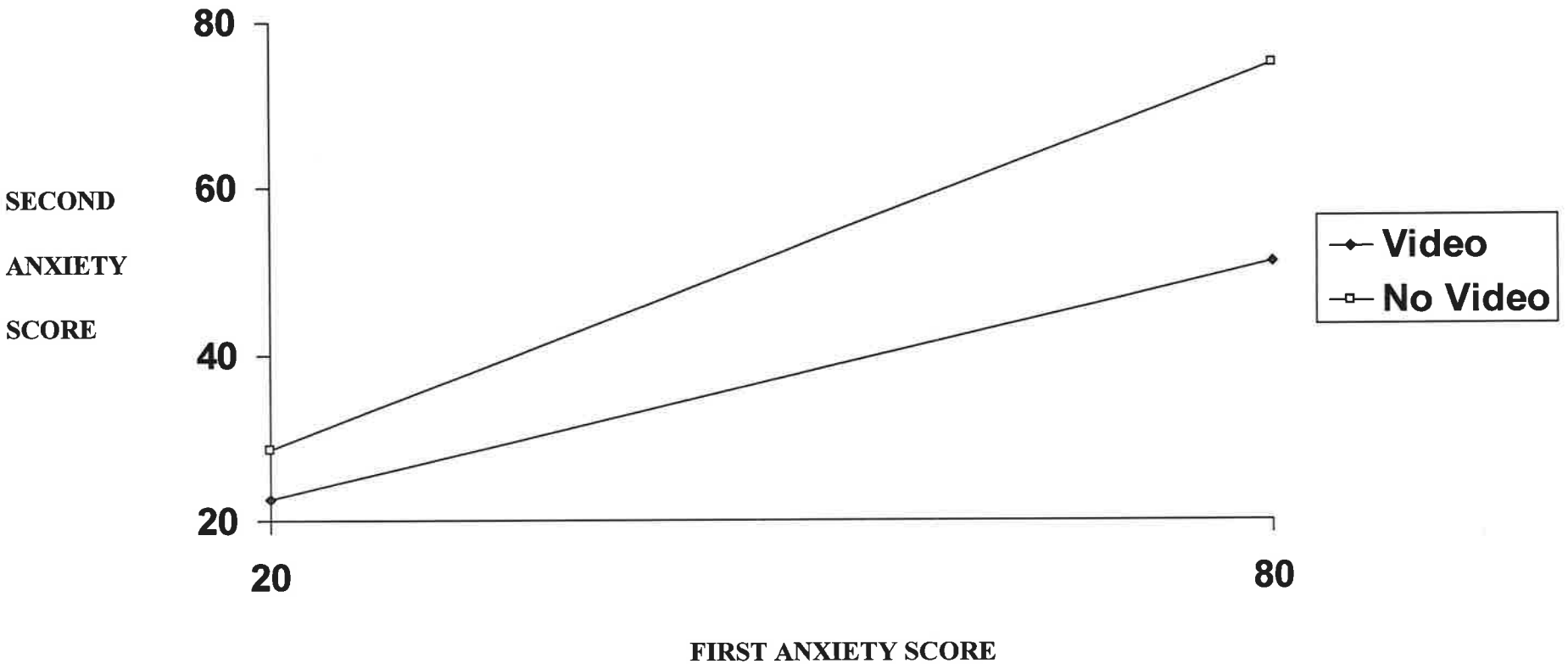

SECOND
ANXIETY
SCORE
80
60
40
20
20
80
Video
No Video
FIRST ANXIETY SCORE

TABLE 3.5.1.3:

Results of pre-colonoscopy knowledge questionnaire.

*Data are calculated by linear regression analysis and expressed as estimate (asymptotic standard error).

p values have been calculated using the Pearson chi-square test of homogeneity.

TABLE 3.5.1.3

TOPIC	VIDEO GROUP	NO VIDEO GROUP	P VALUE
Purpose of colonoscopy (Maximum 4)	3.24 (0.10)	2.68 (0.10)	0.0001
Procedural details (Maximum 5)	4.15 (0.12)	3.67 (0.12)	0.0048
Potential complications (Maximum 3)	2.49 (0.13)	1.94 (0.13)	0.0027
TOTAL (Maximum 12)	9.88 (0.35)	8.31 (0.35)	0.0001

TABLE 3.5.1.4:

Effect of the information video on the knowledge and anxiety levels of patients with high first anxiety scores (Spielberger State Anxiety >50).

*Data are expressed as mean (standard error of the mean).

TABLE 3.5.1.4

	VIDEO GROUP (n=16)	**NO VIDEO GROUP** (n=14)
First anxiety score (1)	61.2 (2.1)	61.4 (2.4)
Second anxiety score (2)	41.6 (4.5)	60.8 (4.2)
Change in anxiety (2-1)	-19.6 (4.9)	-0.6 (2.8)
Knowledge - Purpose (/4)	3.50 (0.25)	2.50 (0.23)
Knowledge - Details (/5)	4.25 (0.34)	3.36 (0.32)
Knowledge - Complications (/3)	2.69 (0.26)	1.50 (0.35)
Knowledge - TOTAL (/12)	10.44 (0.7)	7.36 (0.8)

SECTION IV

SUMMARY AND CONCLUSIONS

Advances in technology have had a considerable impact on colorectal surgery in the recent past and are likely to continue to do so in the future. In this thesis, the impact and application of several aspects of new technology to colorectal surgery have been examined.

4.2 Intra-operative ultrasound

Intra-operative ultrasound is likely to have an increasing role during colorectal resection for neoplastic disease. The study reported in Section 3.1.1 confirmed the findings of other workers that intra-operative ultrasound of the liver is more accurate than pre-operative computed tomography or intra-operative inspection and palpation in the detection of hepatic colorectal metastases. Several considerations must be taken into account, however, before the role of this technique in liver assessment at the time of primary colorectal resection can be defined.

The superiority of intra-operative ultrasound is not as marked as has been previously reported, because a lesion-by-lesion analysis inflates the statistical differences between techniques, but does not reflect the clinical situation. In addition, improvements in computed tomography technology have meant that this investigation is able to detect almost as many lesions as intra-operative

ultrasound in 1998. Whilst computed tomography can detect the presence of the majority of abnormalities, it is considerably inferior to intra-operative ultrasound in the diagnosis of the nature of the lesions, particularly in the differentiation between liver cysts and metastatic deposits.

The ideal protocol for liver assessment at the time of primary colorectal cancer resection should commence with pre-operative computed tomography. If abnormalities are found, they should be carefully investigated by intra-operative ultrasound. The exception to this rule is the patient with multiple widespread metastatic deposits on computed tomography that are clearly unresectable. Intra-operative ultrasound will not add useful clinical information in this situation.

There is no evidence from the study reported in this thesis that intra-operative ultrasound of the liver is of value if pre-operative computed tomography is normal. As this contradicts the findings of many other studies, it is prudent to recommend further investigation rather than to suggest that intra-operative ultrasound is abandoned in this situation. It is also important to note that negative peri-operative liver investigations do not imply that the liver will be free of metastatic disease for life, as evidenced by one patient in the current study. As there has only been a short follow up period, it is possible that other patients will also develop liver metastases that were not detectable in the peri-operative period.

The role of intra-operative ultrasound of the liver in laparoscopic colectomy for cancer is less well defined. It is an evolving technique with a long learning curve and there is little

available data regarding its accuracy. Analysis of the small cohort of patients who had laparoscopic liver ultrasound in this study adds little to the available data, but does confirm the difficulty of both the technique and the ability to ensure that the entire hepatic parenchyma has been visualised. Ultrasound of the liver during laparoscopic colectomy for cancer should be performed in all cases, preferably under clinical trial conditions. This will enable laparoscopic surgeons to become adept at the technique and assess its value in comparison to pre-operative screening techniques.

Intra-operative ultrasound of the colon may also be of value during surgery for colorectal neoplastic disease. The benchtop ultrasound study reported in Section 3.1.2 showed that this technique could produce excellent images of both normal colon and colonic neoplasia. If the lumen is filled with normal saline, the technique is at its most accurate, with superb images allowing localisation of all impalpable lesions. In two cases benchtop ultrasound was able to localise the remnants of malignant polyps that could not be found with confidence using intra-operative colonoscopy. The images were of such clarity that intra-operative locoregional staging might be possible. It is unlikely, however, that this information will be of value in colorectal malignancy, as surgical decision making will not be affected.

Intra-operative ultrasound of the colon was successfully used in the in vivo setting to localise an impalpable colonic polyp requiring resection. The technique has several theoretical advantages over other methods of intra-operative localisation of impalpable lesions and would provide a most convenient localisation tool if the images produced on the benchtop can be

matched in the intra-operative setting. Further intra-operative investigation is continuing.

4.2 Laparoscopic colorectal surgery

Laparoscopic techniques have revolutionised many abdominal operations, leading to post-operative patient benefits including decreased pain, decreased hospital inpatient stay and improved cosmesis. These benefits are possibly more subtle in colorectal surgery than with other abdominal procedures, and are best seen in elective, non-resectional colorectal surgical procedures.

Laparoscopic reversal of Hartmann's procedure is essentially the same procedure as the open operation, except that it obviates the need for a long midline incision. The series reported in Section 3.2.1 confirms the feasibility of the procedure, that it is safe to perform, but that it is a prolonged procedure requiring considerable laparoscopic expertise. The post-operative recovery of the patients in this series was excellent, with the post-operative hospital stay being a median of 4 days and the longest stay being 8 days. Whilst one must be cautious when comparing such data to that available in the literature, the profound shortening of hospital stay from that reported with the open procedure is most encouraging, as is the rapid return of bowel function and low short-term complication rate seen in this series. It is possible that laparoscopic reversal of Hartmann's will become an acceptable alternative, if not a preferred alternative, to the open procedure in the future.

Laparoscopic-assisted colonoscopic polypectomy is an evolving technique with considerable potential. It has, thus far, only been reported in sporadic case reports. The small series reported in Section 3.2.2 has confirmed that selected colonic polyps, considered unsuitable for conventional polypectomy, can safely be excised by colonoscopic snare excision if the serosal surface of the colon is observed laparoscopically to ensure that there is no breach of the colonic wall or full-thickness thermal damage. Laparoscopic manipulation or mobilisation of the bowel can enable colonoscopic access to polyps that would otherwise be inaccessible. This series reported successful polypectomy in all cases, with discharge the following day and early return to full activity. This procedure is a useful addition to the options available for the management of large colonic adenomata and may, in time, become the procedure of choice. A paper reporting this series has recently been accepted for publication in *Surgical Endoscopy* and, when published, will be the largest series in the international literature.

The advent of laparoscopic surgery has encouraged considerable research into the physiological changes that are produced by surgery and anaesthesia, and the differences in these parameters between open and laparoscopic surgery. In Section 3.2.3, the core temperature changes caused by colorectal surgery were investigated. Two types of statistical analysis were used in this study, with somewhat conflicting results. As important conclusions can be drawn from each analysis, two sets of conclusions must be presented.

Analysis of the minimum temperature recorded for each patient during surgery was initially performed. There was no difference in the incidence of hypothermia between laparoscopic and open colorectal surgery, either in the overall analysis or in subgroup analysis controlling for the use of the forced-air warming device. The patient numbers were too small to confirm previously published data that the forced-air warming device decreases the incidence of hypothermia during open surgery. This study did, however, show that the use of the forced-air warming device was associated with a significant reduction in the incidence of hypothermia during prolonged laparoscopic surgery, a finding that has not been previously reported. Because the study was case-controlled, this finding requires confirmation in a randomised trial.

Linear regression analysis of the trend of temperature change over time was expected to produce similar results to the minimum temperature data, with the addition of investigating for any patient demographics that may impact on the temperature response to surgery. This analysis identified a patient's gender as influencing the degree of hypothermia produced by different operative conditions. Female patients having laparoscopic surgery had less hypothermia than those having open surgery. Female patients who had the forced-air warming device applied during surgery had less hypothermia than those who did not. Neither of these differences was seen in male patients. This is an important finding because, if corroborated by other data, it implies that the forced-air warming device should be used for female patients having either open or laparoscopic surgery, but is not required for male patients. Whilst this finding has not been previously reported, there is minimal published data regarding the impact of a patient's gender on the

core temperature response to the hypothermic stimulus of surgery.

The analysis of this series has posed more questions than it has answered, having produced data and conclusions that require further investigation. A prospective randomised trial, which will specifically aim to confirm the value of the forced-air warming device in prolonged laparoscopic surgery and to elucidate the impact of gender on peri-operative hypothermia, has recently commenced.

4.3 Advanced prognostic techniques in colorectal cancer

Adjuvant treatment with chemotherapy or chemoradiotherapy has been shown to decrease the recurrence rate and prolong survival in patients with Dukes' C colorectal cancer. It is possible that adjuvant therapy may have similar impact on some patients with Dukes' B disease. This hypothesis has led to a search for clinical, pathological and molecular biological indicators that can identify those patients with early stage, but poor prognosis colorectal cancer.

In Section 3.3.1, the relative merits of three techniques for the detection of small numbers of colorectal cancer cells in the peritoneal cavity at the time of surgery were assessed. It is well recognised that large numbers of such cells implies a poorer prognosis, but the prognostic value of detecting small numbers of cells is unknown.

Conventional cytology, using a Papanicolaou stain, was unable to detect malignant cells in any of the specimens provided. This corroborates previous data that conventional cytology of peritoneal fluid from patients with colorectal cancer has a poor sensitivity. Immunocytochemistry, using the best-known markers Ber-EP4 and AUA1, was also unable to detect colorectal cancer cells in the peritoneal cavity in this study.

The technique of immunobead reverse transcriptase-polymerase chain reaction (RT-PCR) has previously been shown to detect colorectal cancer cells in the peripheral blood during the peri-operative period, and that these results have prognostic significance. Immunobead RT-PCR of wound protector specimens was unsuccessful in this study, but there were several positive results reported with immunobead RT-PCR of the peritoneal washings collected from the pelvis and the tumour bed, both before and after resection of the cancer.

Positive results to markers of epithelial cells cannot be considered evidence of free intra-peritoneal malignant cells because non-neoplastic epithelial cells are likely to contaminate the specimens. Multiple positive results to mucin 2 in patients with mucinous adenocarcinoma of the colon, as seen in two patients in this study, may be the exception to this rule. The progress of these patients will be closely followed.

There is early evidence from this study that the positive results to markers of colorectal malignancy detected by immunobead RT-PCR of peritoneal washing specimens may have prognostic significance. Two patients with Dukes' B colorectal

cancer had positive results to the malignant markers in this study and both have developed locoregional recurrence of disease within 9 months of surgery. None of the other Dukes' B patients have recurrent disease.

The final assessment of the place of immunobead RT-PCR of peritoneal washings in the assessment of prognosis in colorectal cancer is not yet possible. Long term follow up is required, as is the case-by-case comparison of immunobead RT-PCR of normal and malignant solid colon specimens with peritoneal washings that is currently taking place. Nevertheless, the preliminary results are most encouraging, and clearly justify further investigation.

4.4 Ambulatory anal surgery

The increasing emphasis on ambulatory surgery and its impact on the practice of anal surgery were examined in Section 3.4 of the thesis. The results of a day surgery haemorrhoidectomy project were presented, followed by the interim results of a randomised trial comparing glyceryl trinitrate paste with lateral sphincterotomy in the management of chronic anal fissure.

It is now over sixty years since Milligan and Morgan first described ligation excision haemorrhoidectomy. This procedure is still the operation of choice of most surgeons for the treatment of third and fourth degree haemorrhoids and second degree haemorrhoids that have failed to respond to less invasive treatment. The reputation of this procedure as one that causes severe post-operative pain has often precluded early hospital discharge and has

certainly kept such patients away from day surgery suites in the past. The key concepts that were addressed in an attempt to introduce day case haemorrhoidectomy were the provision of adequate peri-operative analgesia, appropriate pre-operative education and close home nursing support.

The project reported in this thesis shows that the performance of ligation excision haemorrhoidectomy as day surgery is feasible and safe, with an 88% same day discharge rate and all patients being discharged within 28 hours of surgery. There was a low readmission rate and a low short-term complication rate. Six-month follow up is currently being undertaken in order to ascertain the long-term complication rate.

This project also provided a prospective database for the study of the pain levels experienced by patients after haemorrhoidectomy and their analgesia requirements. A wide range of pain levels was recorded at all times in the post-operative period. This finding has also been reported by other authors, and is not surprising, given the subjective nature of the symptom of pain. Pain levels in this series were in general well controlled by the combination of a pre-emptive, local anaesthetic, ischio-rectal fossa block and a multimodal analgesic regime consisting of opioids, non-steroidal anti-inflammatory medication and simple analgesia. Mean pain scores were between 2 and 3 out of 10 at all times in the post-operative period and high levels of patient satisfaction with the pain management protocol were recorded.

Interim analysis of the pain score data at the end of 1997 identified two significant trends. The first trend was that the pain

scores recorded on the second and third post-operative days were significantly higher than those recorded in the first four hours after surgery. It was hypothesised that this was due to the effect of the pre-emptive local anaesthetic ischio-rectal fossa block on pain in the immediate post-operative period. In 1998, this hypothesis was tested in a prospective, randomised, double blind clinical trial. This trial confirmed the hypothesis, with the patients randomised to receive the block recording significantly lower pain scores in the first 24 hours after surgery than those who had local anaesthetic infiltration of the haemorrhoidal complexes only. The ischio-rectal fossa block group also required less analgesia in the first 24 hours post-operatively. The ischio-rectal fossa block is simple to perform, and the impressive results of this randomised trial would suggest that it is a valuable adjunct to systemic analgesic medication in the control of pain during the immediate post-operative period after haemorrhoidectomy.

The other trend in the pain scores that was identified by the interim analysis at the end of 1997 was an increase in pain after the fifth post-operative day, with pain scores at the day 10 outpatient visit being significantly higher than those recorded on day 5. Because pain score data was not recorded between day 5 and day 10, the exact nature of this increase is not apparent. Several of the patients complaining of increased pain had sloughy and offensive wounds on day 10. It was hypothesised that secondary infection may play a role in post-haemorrhoidectomy pain and because of this metronidazole was added to the protocol for 1998. The effects of this change are difficult to gauge because of the lack of data on day 6 to 9, but there was a slight decrease in the mean day 10 pain score in 1998 as well as less complaints of sloughy and offensive wounds.

Pain scores at the time of the first bowel action after haemorrhoidectomy were significantly higher than at any other time in the post-operative period. All but one patient, however, were able to manage at home at this time, with many commenting that they were better served in the comfort and privacy provided by their own home. The data from this trial regarding the importance of the first bowel action early in the post-operative period shows mixed results. There was no correlation between pain scores and the day on which the first bowel action occurred, but those who waited longer required more oral opioid analgesia.

The support that was provided to patients in the day case haemorrhoidectomy project by having a nurse visit each day was essential to its success. Patient satisfaction with day surgery haemorrhoidectomy without close home nursing follow up is likely to be considerably less than that recorded in this project, and such an approach may lead to higher readmission rates.

Considerable emphasis was placed on the role of pre-operative patient education in this project. The high levels of patient satisfaction with the information supplied and with overall care suggest that this emphasis was appropriate and that pre-operative education is an important component of a new management regime.

Despite the excellent patient satisfaction ratings and low pain scores recorded after day case haemorrhoidectomy, there were a group of patients (approximately 1 in 5) who were either unhappy or unsure about going home on the night of surgery. These patients stated that they were anxious about being at home so soon after

such a procedure. It is important for the future of the day case haemorrhoidectomy project that these patients be identified and, if possible, reassured prior to surgery. If reassurance is unsuccessful in allaying anxiety, overnight admission should be offered.

It has been shown in the introduction that surgery is the treatment of choice for prolapsing haemorrhoids. The emphasis of this thesis, therefore, was in minimising those factors that have precluded ambulatory haemorrhoidectomy in the past. In the case of chronic anal fissure, however, there is increasing evidence that surgery may no longer be required for treatment. The study presented in Section 3.4.3 had a different emphasis therefore, being a comparative analysis of the most appropriate first line treatment. This was achieved by means of a randomised trial comparing the most promising of the pharmacological treatments, glyceryl trinitrate paste, with the established surgical gold standard, lateral sphincterotomy.

This trial confirmed the findings of other workers that glyceryl trinitrate paste applied topically to the perianal skin can produce healing of a chronic anal fissure in approximately two thirds of patients over an eight-week period. There was a small (approximately 10%) recurrence rate and one of these patients responded to further glyceryl trinitrate treatment.

The healing rate for glyceryl trinitrate in this trial was significantly less than that achieved by lateral sphincterotomy, which produced early healing of the fissure in all patients. If this was the only criterion by which the treatments are to be judged, then lateral sphincterotomy is a superior treatment. Glyceryl

trinitrate treatment is also considerably more labour intensive for both patient and doctor than the surgical procedure.

The waiting time for lateral sphincterotomy and the fact that treatment with glyceryl trinitrate can commence immediately opens a window of opportunity for the medical treatment. The fact that most patients appeared to prefer a medical treatment as first line management will also encourage further assessment of glyceryl trinitrate.

The pain scores recorded by patients using glyceryl trinitrate in this trial suggested that there might be a difference early in the treatment period between those patients who will achieve healing of their fissures and those who will not. The patient numbers are thus far too small to confirm this finding. This concept is of interest in that, if this difference in pain scores can be confirmed, a protocol involving initial treatment with glyceryl trinitrate with early patient review could be designed. Those patients with low pain scores at review would continue with the glyceryl trinitrate treatment, whereas those who had not responded would be offered lateral sphincterotomy.

Such a protocol, combining the best aspects of both treatment regimes, may in time prove to be the optimum management for chronic anal fissure. It is too early at this time; however, to formally propose such a protocol based on the small patient numbers that have been accrued thus far. The trial reported in this thesis will continue into 1999.

4.5 Patient information by video

High levels of anxiety experienced by a patient prior to a medical or surgical procedure can negatively influence their post-operative progress. There is increasing evidence that knowledge about and understanding of the procedure may decrease rather than increase pre-operative anxiety. The ideal medium with which to impart information has not been defined. The impact of an information video on the anxiety and knowledge levels of patients booked for colonoscopy was analysed in Section 3.5.1 in the form of a prospective, randomised trial.

The pre-randomisation anxiety scores recorded in this trial allowed analysis of the patient demographic details that may influence anxiety prior to colonoscopy. Female patients were significantly more anxious than male patients. Patients with no prior experience of colonoscopy were more anxious than those who had undergone the procedure previously. The level of anxiety was not influenced by a patient's age, level of education or the indication for the colonoscopy.

Patients randomised to watch a video that was designed to impart information about colonoscopy were significantly less anxious immediately prior to the procedure than those patients who had been randomised to the 'no video' group. The difference between the groups was most marked in those patients who had the highest levels of initial anxiety. Even at the low anxiety end of the scale, however, there was a significant difference, in terms of decreased pre-procedural anxiety, in favour of the group of patients who had watched the video.

The patients who were randomised to watch the information video also had a better understanding of colonoscopy. This group scored higher marks in a questionnaire designed to test knowledge regarding the purpose of colonoscopy, the procedural details of colonoscopy and the potential complications of colonoscopy. There was a significant difference between the groups in each of these sections of the questionnaire, as well as the overall marks. The greatest difference was recorded between the patients with severe initial anxiety that watched the video, who scored the highest marks of any subgroup, and those with severe initial anxiety that did not watch the video, who scored the lowest marks.

This trial has clearly demonstrated an interaction between anxiety and knowledge in patients preparing for colonoscopy, with higher levels of knowledge corresponding to decreased anxiety. The exact nature of this interaction is less clear. Whilst it is possible that the acquisition of knowledge caused a decrease in anxiety, it is equally possible that a lower anxiety level enabled the information to be absorbed and understood.

It is also apparent that, whatever the exact nature of the interaction between the anxiety and knowledge levels, the information video had a positive influence on both of these parameters. Patients with the highest levels of initial anxiety, which in this trial were female patients with no previous experience of colonoscopy, gained the most benefit. There was evidence, however, that all patient groups gained some benefit from watching the video.

The aims of this trial are too narrow to allow the drawing of wide ranging conclusions. It is certainly not possible to claim that the provision of patient information by video should be provided for all patients preparing for all medical or surgical procedures. The use of a well-designed video in a structured setting was of value to this group of patients preparing for colonoscopy and its use can be recommended. If further research shows that video information is similarly valuable for other procedures, this medium may become a standard component of the pre-operative preparation for medical and surgical procedures.

The studies reported in this thesis have covered several broad areas of colorectal surgery and the influence and application of new technology to these areas. It is difficult to gauge the importance of the findings at this time. The results of all of the studies presented in this thesis have the potential to improve the surgical care of our patients in the future, from the improved prognostic techniques of intra-operative ultrasound of the liver and immunobead RT-PCR to the post-operative benefits of laparoscopic surgery and day case haemorrhoidectomy. From the point of view of our patients, however, it may be that the video paper, investigating techniques to improve patient knowledge and decrease anxiety, is the most significant. As technology becomes increasingly important in the provision of surgical care, it may become more and more difficult for the patient to understand the details of the treatment. It is essential then that new technology be used not only to improve the patient parameters that are measured by doctors, but also to improve those parameters that are of importance to our patients.

APPENDIX I

SELF EVALUATION QUESTIONNAIRE **STAI Form Y-1**

Please provide the following information:

Name_____ **Date**_____ **S**___

Age_____ **Gender (Circle) M F** **T**___

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment.* There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your feelings best.

1= not at all 2= somewhat 3= moderately so 4= very much so

1.	I feel calm.....	1	2	3	4
2.	I feel secure.....	1	2	3	4
3.	I am tense.....	1	2	3	4
4.	I feel strained.....	1	2	3	4
5.	I feel at ease.....	1	2	3	4
6.	I feel upset.....	1	2	3	4
7.	I am worrying over possible misfortunes.....	1	2	3	4
8.	I feel satisfied.....	1	2	3	4
9.	I feel frightened.....	1	2	3	4
10.	I feel comfortable.....	1	2	3	4
11.	I feel self-confident.....	1	2	3	4
12.	I feel nervous.....	1	2	3	4
13.	I am jittery.....	1	2	3	4
14.	I feel indecisive.....	1	2	3	4
15.	I am relaxed.....	1	2	3	4
16.	I feel content.....	1	2	3	4
17.	I am worried.....	1	2	3	4
18.	I feel confused.....	1	2	3	4
19.	I feel steady.....	1	2	3	4
20.	I feel pleasant.....	1	2	3	4

APPENDIX II

KNOWLEDGE QUESTIONNAIRE FOR VIDEO TRIAL

A. PURPOSE OF COLONOSCOPY

1. What is a colonoscopy?

a) A procedure that enables the doctor to see the inside lining of you bowel.
b) A procedure that enables the doctor to see the inside lining of your stomach.
c) A procedure that enables the doctor to remove cancers from your bowel.
d) All of the above.
e) Unsure.

2. What is the purpose of colonoscopy?

a) To treat haemorrhoids (piles).
b) To cure stomach pain.
c) To diagnose problems inside the bowel.
d) All of the above.
e) Unsure.

3. It is possible to treat the following problems during the colonoscopy.

a) Polyps Yes / No / Unsure
b) Cancer Yes / No / Unsure

B. PROCEDURAL DETAILS

1. You need a bowel cleaning process because

a) The doctor needs to see the lining clearly.
b) Infection is less likely.
c) It is healthier.
d) All of the above.
e) Unsure.

2. You will be given medication to make you sleepy during the procedure.

True / False

3. The colonoscopy will take approximately

a) 5 to 10 minutes.
b) 20 to 40 minutes.
c) 45 to 60 minutes.
d) 1 to 2 hours.
e) Unsure.

4. How long do you need to stay in the hospital after the procedure?

a) 30 minutes.
b) 3 to 4 hours.
c) 8 to 12 hours.
d) One day.
e) Unsure.

5. The effects of the medication can last for

a) Up to 2 hours.
b) Up to 8 hours.
c) Up to 24 hours.
d) Up to one week.
e) Unsure.

C. POTENTIAL COMPLICATIONS OF COLONOSCOPY

1. Possible complications of a colonoscopy are

a) Bleeding from the bowel.
b) A hole in the bowel.
c) Infection.
d) All of the above.
e) Unsure.

SCORING SYSTEM FOR KNOWLEDGE QUESTIONNAIRE

A. PURPOSE OF COLONOSCOPY

1. Correct answer is a). One point for correct answer.
2. Correct answer is c). One point for correct answer.
3. Correct answers are a) Yes and b) No. One point for each correct answer.

MAXIMUM SCORE = 4 points.

B. PROCEDURAL DETAILS

1. Correct answer is a). One point for correct answer.
2. Correct answer is True. One point for correct answer.
3. Correct answer is b). One point for correct answer.
4. Correct answer is b). One point for correct answer.
5. Correct answer is c). One point for correct answer.

MAXIMUM SCORE = 5 points

C. POTENTIAL COMPLICATIONS OF COLONOSCOPY

1. Correct answer is d). Three points for correct answer. One point for each answer a), b) and/or c) circled. No points for e).

MAXIMUM SCORE = 3 points

TOTAL MAXIMUM SCORE = 12 points

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