New Treatment Modalities in Rectal Cancer

Fazl Q. Parray
Nisar Ahmad Chowdri
Editors

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Foreword

I feel extremely delighted and honored to write a foreword for the book which is edited by my dearest postgraduate student, Dr. Fazl Q. Parray, who later on became my departmental colleague and is already a professor by now in the same department where I rendered my services for more than two decades. This book is focused on rectal cancer, and the beauty lies in wonderful selection of chapters which do not only address the recent modalities of surgical treatment but also the immunological and pathological aspects of the disease. The chapters on TME, pouches, laparoscopy, NOTES, and ERAS have added a special flavor to this unique book. The support from evidence and beautiful illustrations has glorified its quality. Prof. Nisar Ahmad Chowdri who is the coeditor must have contributed in a significant way to add to its quality. I wish this book a huge readership and great success, and I am sure that this duo of editors will continue to publish in the future also about more challenging topics in colorectal surgery.

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Foreword

There are many books and other publications which address rectal surgery. There are fewer such works which delve into certain facets of colorectal surgery such as functional disorders, neoplasia, inflammatory conditions, or technology. Professor Parray has managed to deftly blend a variety of themes across the gamut of rectal surgery which shares the common thread of being new and/or controversial. There are many books and other publications in the field of colorectal surgery. There is a dearth of these works devoted exclusively to rectal cancer. An even smaller subset deals with technology often in the form of atlases. Professor Parray has deftly blended all of the new, exciting, and sometimes controversial techniques in one armamentarium against colorectal cancer. He is to be congratulated for having teased out the essence of each of these facets including total mesorectal excision, autonomic nerve preservation, restorative resection, minimally invasive surgery, and non-operative management. In addition to being well written and easy to read, the book has numerous outstanding and easy-to-follow illustrations. Dr. Parray has thus managed to give the reader an opportunity to peruse both a textbook and an atlas. In addition, he offers the complete tour of all of the new and controversial themes within the realm of surgical management of colorectal cancer. I congratulate him upon his work and thank him for the honor of allowing me to author this foreword.

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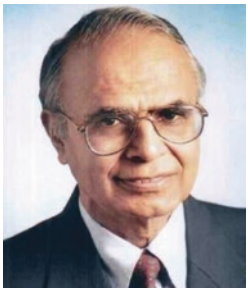
Foreword



Dr. Fazl Q. Parray, professor of Surgery, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, is a young upcoming surgeon with a vision for the future to promote new technique with basic learning in surgical training dealing with all types of problems in colorectal procedures.

This book enlightens the new procedures with technical details and importance of anatomy and pathophysiology of rectal area and its disorders. He has wisely given the importance to newer techniques in minimal invasive surgery, maintaining tissue planes and saving tissue for faster recovery. The role of robotic surgery is also defined with caution, emphasizing its importance in the future.

This is a comprehensive book to learn and develop techniques to master procedures in colorectal disorders. It will be of great use to all practicing colorectal surgeons, laparoscopic surgeons, and all general surgeons who deal with a good volume of rectal cancer.

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Preface

Colorectal surgery in my days of residency was more about hemorrhoidectomies, fissurectomies, fistulectomies, and abdominoperineal resections with a permanent stoma. In the last two decades, the subject emerged as a sub-specialty because of better understanding of the pathogenesis, molecular genetics, and so many technical advances made in the field for managing colorectal diseases. Besides, sphincter-saving surgeries, natural orifice access, laparoscopes, robots, and staplers are the new concepts and new weapons to deal with a spectrum of colorectal diseases in a more effective way. Also, the role of neoadjuvant therapy has been commendable to downstage, to salvage sphincters, and to convert many inoperable into operable cancers. Adjuvant treatment by now has a very well-established role to improve the overall survival. The multimodality concept is the present preferred and accepted management for this dreadful malignancy to provide better QOL. The boom of technology introduced so many new concepts to deal with rectal cancers that ideally a surgeon feels confused to decide and know about the new techniques and to deal in an appropriate way with a particular cancer in the rectum. This book is written with a concept that all practicing surgeons and physicians dealing with rectal cancer possibly may benefit from this book by reading about all new modalities of treatment and choose the best possible modality for their patient.

This book exclusively deals with newer concepts especially in the field of surgery which have evolved in the last one to two decades, and a deliberate attempt has been made not to discuss etiology, anatomy, physiology, and age-old surgeries for rectal cancer like abdominoperineal resection, anterior resection (anterior approach), and Kraske's and Bevan Masson procedure (posterior approach). The golden textbooks have already described these procedures elaborately and extensively. Also, to make this book more interesting, readable, and of benefit to all practicing surgeons, we have tried to make it a concise book. We have also added many quality operative pictures from our collection and very few from the Internet for better understanding of the reader. We are sure that reading this book is definitely going to prove beneficial for all those interested to know more about new surgical modalities for rectal cancer with better understanding. My coauthor, Prof. Nisar Ahmad Chowdri, worked quite hard to suggest important additions and deletions in this book to make it more concise and presentable.

It gives me immense pleasure to write the preface of this book, *New Treatment Modalities in Rectal Cancer*. Technology is progressing fast, and every surgeon should keep pace with the advances in this field. Rectal cancer is one of the commonest cancers in the world and was associated with significant mortality and morbidity before the invention of new techniques and advances in technology. Writing a book on this subject was the need of the day. All the efforts have been made to write each and every topic up to date and interesting for the readers. The experienced colorectal surgeons of national and international fame have worked hard to prepare various chapters for the book.

I pray and hope that this book will be useful not only for the colorectal surgeons but also for residents, postgraduate students, and surgeons in general.

Srinagar, India — Fazl Q. Parray
Srinagar, India — Nisar Ahmad Chowdri

Acknowledgment

We would like to thank our great teachers, namely, Prof. Mehmooda Khan, Prof. Nazir A. Wani, Prof. M. Afzal Wani, Prof. M. Ashraf Darzi, Prof. G. Q. Peer, Prof Khursheed Alam, Prof. Omer J. Shah, and Prof. Muneer Khan, for their guidance, support, and encouragement at different stages of life, and our colleagues, namely, Prof. Sameer H. Naqash, Prof. Ajaz A. Malik, Dr. Ajaz A. Rather, Dr. Rauf A. Wani, Dr. Shamsul Bari, Dr. Mubashir A. Shah, Dr. Munir A. Wani, Dr. Natasha Thakur, Dr. Asif Mehraj, Dr. Mudassir Khan, Dr. Mushtaq Laway, and Dr. Arshad Baba, for their love and affection at all stages of my career.

Dr. Parray would also like to thank his lovable parents, wife (Nighat), kids (Shaheem and Liqa), brothers and sisters, and very dear friends who stood by him in long hours of toil with all possible moral and psychological support.

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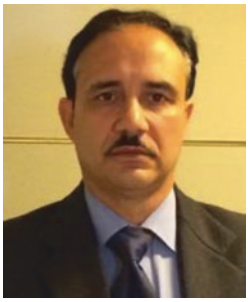
About the Editors

Fazl Q. Parray has graduated from the Government Medical College, Srinagar. He obtained his master's degree in Surgery from Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India, where he is currently professor in the Department of General and Minimal Invasive Surgery. He then pursued multiple international fellowships in minimal access surgery. He has many research publications in various international and national journals and has authored two books. He specializes in management of colorectal cancer and advanced laparoscopic procedures like laparoscopic low and ultralow resections, total proctocolectomies, pouches, and natural orifice endoscopic endoluminal surgeries.



Nisar Ahmad Chowdri has graduated from the Government Medical College, Srinagar. He obtained his postgraduation from Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India, where he is presently working as professor and head of the Department of General and Minimal Invasive Surgery. He then pursued several national and international fellowships in minimal access surgery. He has many research publications in various national and international journals and has contributed to several books. He recently published a book titled *Benign Anorectal Disorders: A Guide to Diagnosis and Management*.

Technological Advances in Management of Colorectal Cancer

1

Asif Mehraj and Fazl Q. Parray

Abbreviations

3D-EUS	Three-dimensional endoultrasound
ADR	Adenoma detection rate
APC	Adenomatous polyposis coli
APR	Abdomino perineal resection
CAP	Cap assisted colonoscopy
CE-EUS	Contrast-enhanced endoultrasound
CIT	Caecal intubation time
CRC	Colorectal cancer
CT	Computerised tomography
DNA	Deoxy ribose nucleic acid
EC	Endocuff
EMR	Endoscopic mucosal resection
ER	Endorings
EUS	Endoultrasound
FDA	Food and Drug Administration
FICE	Fujinon intelligent chromoendoscopy
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
FUSE	Full spectrum endoscopy
gFOBT	Guaiac faecal occult blood test
HD	High definition
ICG	Indocyanine green
INIF	Intraoperative near-infrared fluorescence
M2-PK	M2 pyruvate kinase

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miRNA	Micro ribose nucleic acid
NBI	Narrow band imaging
NIR	Near infrared fluorescence
NOTES	Natural orifice transluminal endoscopic surgery
PEG	Polyethylene glycol
SD	Standard definition
sDNA	Stool deoxy ribose nucleic acid
SLN	Sentinel lymph node
Ta TME	Transanal total mesorectal excision
TAMIS	Transanal minimal invasive surgery
TEMS	Transanal endoscopic microscopic surgery
TER	Third eye resectoscope
TME	Total mesorectal excision
WAC	Water-assisted colonoscopy
WE	Water exchange

1.1 Colorectal Cancer (CRC)

Colorectal cancer (CRC) continues to be one of the commonest malignancies of gastrointestinal tract, with significant variation in its incidence rates across different parts of the world. The global burden of CRC is expected to markedly increase by 60% with detection of more than 2.2 million new cases and 1.1 million cancer deaths by 2030. However, in most of the developed countries, there has been a decline in the overall incidence as well as mortality of CRC (Ferlay et al. 2013). The recent innovations in science and technology are believed to play an important role in it. Improvements in scientific technology have helped patients suffering from colorectal cancer at every stage, be it early screening, diagnosis, treatment or even rehabilitation. In this chapter, we will highlight various latest innovations in the management of colorectal cancer.

1.2 Advances in Screening

Screening is a process used to identify the possible presence of a yet to diagnosed disease in an individual who has no signs or symptoms, and hence it is performed on normal healthy population. Screening is done to identify disease in a community early, thus enabling earlier intervention and management in the hope to reduce morbidity and mortality from the disease. CRC begins with a precursor lesion (adenoma) and over a period of time progresses to frank carcinoma and hence screening

will help to pick the disease in its early/intermediate stage and thereby reduce the morbidity and mortality.

1.2.1 Faecal Screening Tests

There is a wide range of faecal tests available for colorectal cancer screening.

1.2.1.1 guaiac Faecal Occult Blood Test (gFOBT)

The guaiac faecal occult blood test (gFOBT) was one of the first faecal tests used in colorectal cancer screening. FOBT works by indirectly identifying haemoglobin through a peroxidase reaction. Annual gFOBT has reduced CRCs mortality by picking up early lesions which are amenable to curative resections; however, there are certain limitations of gFOBT which include:

- Low sensitivity after a single round which indicates the need for annual testing to improve its sensitivity
- Low sensitivity for advanced adenomas
- Need for dietary and medication restrictions
- Requirement for the collection of three consecutive stool samples for testing

These limitations have led to the development of the faecal immunochemical test (FIT).

1.2.1.2 Faecal Immunochemical Tests (FITs)

Faecal immunochemical tests (FITs) detect human globin by means of an antibody-based assay. FITs provide both qualitative and quantitative result in terms of faecal Hb concentration per gram faeces.

Its advantages include:

- Improved sensitivity in comparison to gFOBT
- Need for only a single sample
- No dietary or medication restrictions

FIT has limitations, which include:

- Decrease in sample reliability with prolongation of time from collection to analysis
- Poor sensitivity for advanced adenomas
- Unclear optimal threshold for haemoglobin detection

Differences between gFOBT and FIT screening in average-risk individuals

gFOBT	FIT
Repeat sampling from multiple bowel movements	Single sampling from one bowel movement
Dietary restrictions	No dietary restrictions
Qualitative result	Quantitative or qualitative result
Semi-automated analysis	Automated analysis
Sensitivity CRC 31–63%[a]	Sensitivity CRC 69–100%[b]
Specificity CRC 92–96%[a]	Specificity CRC 92–96%[b]

[a]gFOBT has a sensitivity and specificity of detecting CRC in 31–63% and 92–96% respectively
[b]FIT has a sensitivity and specificity for detecting CRC in 69–100% and 92–96% respectively

1.2.1.3 DNA-Based Stool Tests

DNA-based stool tests have emerged as a big tool for screening CRC in clinical practice. Mutations in various genes like APC, P53, K RAS, and others are involved in development of CRC. Colonocytes containing DNA with these mutated genes are continuously shed with stool which has led to the development of stool DNA (sDNA) as a screening test for CRC. In 2014, US FDA approved multi-target stool DNA test for screening of CRC. These multi-target stool DNA tests are more expensive than the FOBTs and come with a relatively low specificity. Furthermore, adherence rates have not been evaluated. Therefore, a sensitive single biomarker or panel of biomarker (stool) tests at affordable cost is much awaited.

1.2.1.4 Micro RNAs (miRNAs)

Micro RNAs (miRNAs) are short, endogenous, non-coding RNAs that regulate gene expression, thereby affecting various processes in carcinogenesis. Expressions of various miRNAs have been tried for detection of CRC of which miR21 is the most studied oncogenic miRNA besides others like miR92.

1.2.1.5 Stool-Based Proteins

Faecal calprotectin and M2 pyruvate kinase (M2-PK) are the two most studied faecal protein markers for CRC screening.

Though calprotectin has lower sensitivity and specificity for both CRC and adenoma, M2PK has a good potential as a screening test.

1.2.2 Plasma-Based DNA Markers

Plasma-based DNA markers can be detected once they are released into the bloodstream via vascular invasion in carcinogenesis which likely happens at a later stage as compared to exfoliation upon which stool-based tests are based resulting in low specificity and sensitivity as compared to sDNA (Dickinson et al. 2015). This observation may also explain lower sensitivity of plasma-based tests for detection of advanced adenomas as compared to CRC as vascular invasion occurs at a later stage in tumorigenesis. One such marker that has been studied is SEPT9 gene, which has been evaluated as potential screening target for CRC and advanced adenomas. However, the place of mSEPT9 in the CRC screening is still uncertain at this time.

Identification of gut microbiota can open new avenues in both screening and diagnosing CRC. Expansion of molecular biomarker screening tests may become imaginable in the future (Schreuders et al. 2016).

1.2.3 Colonoscopy

Colonoscopy remains the gold-standard investigation for screening CRC and identifying adenomas. It helps in establishing diagnosis by taking direct tissue biopsies from the lesion. Besides, it can be used for therapeutic interventions as well. However, there is considerable variation in detecting some lesions especially flat polyps, lesion below the haustra and also due to technical difficulties of withdrawal.

Over the last few years, innovations in colonoscopy have led to improved detection rate of polyps and better management of other colorectal lesions.

1.2.3.1 Preparation for Colonoscopy

A proper bowel cleansing is crucial for the efficacy of colonoscopy. Caecal intubation rate and adenoma detection rate (ADR) which are considered to be key quality indicators are higher in patients with adequate bowel preparation (Froehlich et al. 2005). Furthermore, adequate bowel preparation leads to improved rate of detection of flat lesions within the proximal colon (Parra-Blanco et al. 2006).

Earlier regimens of bowel preparation included large volumes of hypertonic saline solutions which were cumbersome for the patient, but over the recent years these have been replaced by osmotically balanced solutions containing polyethylene glycol (PEG) and electrolytes. Introduction of split-dose bowel preparation regimens, where half the dose is given the day before the test and half on the day of the test, has significantly enhanced the ability to achieve high-quality cleansing with adequate preparation achieved in 85% compared with 63% in single-dose preparations (Cohen 2010) and also resulted in improved ADRs and detection of flat lesions (CDC 2013). The quality of bowel preparation also depends on time interval between the last dose of bowel preparation and colonoscopy, and ideally should be less than 4 h (Siddiqui et al. 2009).

1.2.3.2 Advances in Mechanical Designs

Cap Assisted Colonoscopy

In Cap Assisted Colonoscopy (CAC), a transparent cap is attached to the tip of a standard colonoscope. It was initially designed to assist in endoscopic mucosal dissection. The advantages of CAC include:

- Better polyp detection rate because of its inherent ability to flatten haustral folds upon withdrawal
- Improved mucosal visualisation by providing a barrier between mucosa and endoscope lens, thereby preventing its adherence

One of the limitations in the use of CAC is the accumulation of faecal matter, which may hamper proper visualisation, especially in patients with poor bowel preparation.

Balloon Assisted Colonoscopy

The Navi Aid G-EYE (SMART Medical Systems Ltd, Ra'anana, Israel) is a novel balloon colonoscope consisting of a standard adult colonoscope combined with an inflatable balloon located 1–2 cm proximally to the distal tip of the colonoscope which can be inflated up to 60 mm diameter with unremarkable alteration in scope's outer calibre. During withdrawal, colonic folds and flexures are mechanically straightened by the inflated balloon, thus revealing potential suspicious lesions located in their proximal aspect (Gralnek et al. 2014).

Endocuff

Endocuff (EC) (Arc Medical Leeds, UK) is a soft plastic cap with rows of finger-like projections attached onto the tip of the colonoscope. The advanced version endocuff (Endocuff Vision) consists of a single row of finger-like projections which are 3 mm longer, which help to grip the colon mechanically. These projections help in gripping during shortening manoeuvres, during insertion, and thus preventing slippage when removing loops. During withdrawal, they flatten the mucosa allowing visualisation of the proximal aspect of colonic folds. The EC also assists in stabilising the colonoscope during polypectomy (Fig. 1.1).

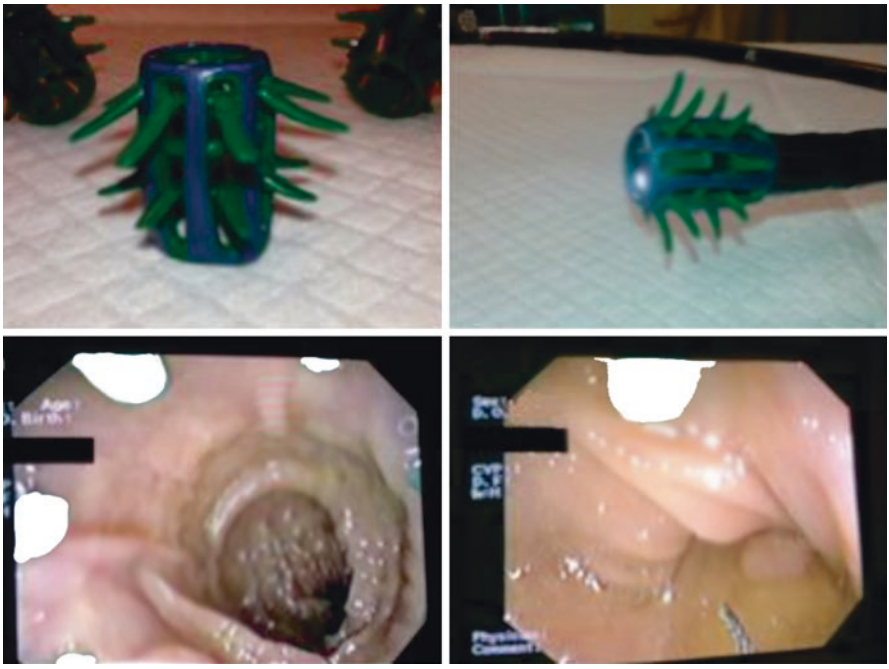

Fig. 1.1 Endocuff with finger-like projections; colonoscopic view with an endocuff in colon

Endorings

Endorings™ (ER; Endoaid Ltd. Caesarea, Israel) are soft and flexible, circular silicone rings that can be attached to the tip of the colonoscope. Visualisation of potentially hidden polyps is made possible because they flatten colonic folds on withdrawal. Besides, these rings also improve scope stability.

1.2.3.3 Advances in Optical Designs

High Definition Colonoscopy

High Definition (HD) colonoscopies differ from Standard Definition (SD) colonoscopies in having more pixels. New HD endoscopes can generate up to 1080 lines of vertical screen resolution, whereas SD systems generate 480–576 lines, thus improving image quality which in turn improves detection of lesions. As a result of better visualisation of small, flat and right sided colonic polyps, HD colonoscopy has shown a little benefit in adenoma yield.

1.2.3.4 In Visual Enhancement

Chromoendoscopy Uses Application of Dye

Chromoendoscopy uses application of dye (methylene blue and indigo carmine) which enhances mucosal inspection (Fig. 1.2). It may also increase adenoma detection rate in routine colonoscopy. Though there is an increase in detection of diminutive lesions but it comes at a cost of increased procedure time.

Virtual chromoendoscopy utilises electronic image processing without physical dye application. Systems such as narrow band imaging (Olympus), i-scan (Pentax), and FICE (Fujinon) have made such technology widely available. These techniques are particularly useful for lesion classification but have not consistently been shown to improve adenoma detection. Differentiating hyperplastic lesions from neoplastic lesions and identifying higher grades of dysplasia can be done using NICE system and Kudo's pit pattern. This can help in deciding whether a lesion is resectable endoscopically or may require a surgical approach (Ishaq et al. 2017).

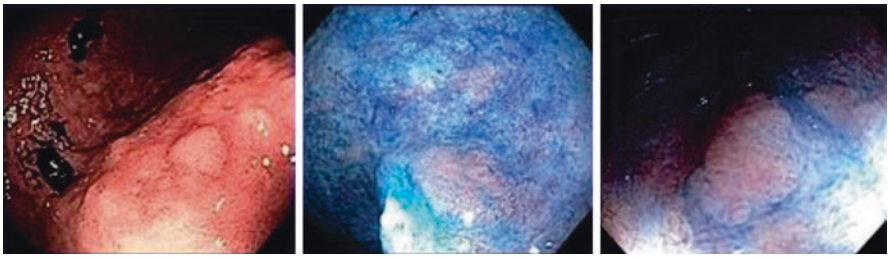

Fig. 1.2 Chromoendoscopic view of colon

Full Spectrum Endoscopy (FUSE)
Increasing the optical field of view may increase the detection rate of adenomas that are located behind mucosal folds, at flexures, or low in the rectum. Full spectrum endoscope (FUSE; Endo Choice, GA, USA) has two additional optical lenses, located on either side of the tip which gives a 330° field of view. In comparison, a standard colonoscope has a limited 170° field of view. However, it is too early to comment on its definite advantage over standard colonoscopy in terms of adenoma detection rate or adenoma miss rate.

Third Eye Retroscope (TER)
The TER (Avantis Medical Systems, Inc., Sunnyvale, CA) is a disposable auxiliary imaging device. It is inserted through a standard colonoscope's working channel and after reaching the caecum it is advanced 42 mm beyond the tip and bent 180° to form a J configuration. The cap contains a locking mechanism which secures it in its viewing position. A polarising filter prevents the colonoscopies light from blinding the retroscope's image.

TER appears to increase polyp detection, but there are certain limitations to its routine use which include:

- Technically difficult to perform
- Inferior image quality
- Reduced suction capacity
- Requirement for its removal in order to pass other accessories through the channel
- The disposable nature of the device which increases procedure expenditure

1.2.4 Water-Assisted Colonoscopy

Water-assisted colonoscopy (WAC) involves water infusion during scope insertion, instead of traditional air or CO_2 insufflations. It was first reported by Falchuk and colleagues in 1984, who showed that water infusion facilitates scope insertion in patients with diverticulosis (Falchuk and Griffin 1984).

There are two variations of WAC:

1. *Water immersion (WI)* technique, during which water is infused to inflate the lumen during scope insertion and then aspirated during withdrawal
2. *Water exchange (WE)* technique, where removal of infused water occurs predominantly during insertion (Leung 2013)

The advantages of WAC include:

- Improved patient comfort with less sedation
- Completion of difficult or previously incomplete procedures (due to angulations or redundant colons)
- Increased adenoma detection rate

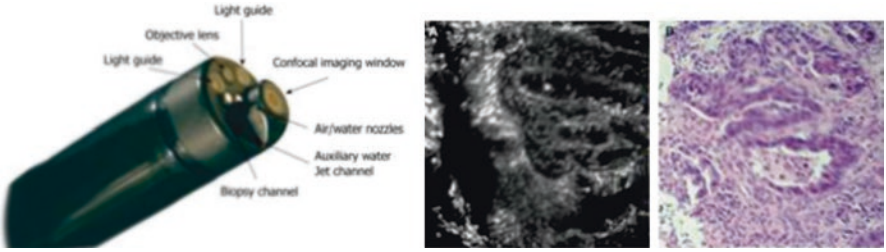

Fig. 1.3 Confocal microscopic view with in vivo histological view

- Does not interfere with patients' fluid and electrolyte status
- Can be used therapeutically for endoscopic resolution of sigmoid volvulus in patients with high surgical risks, as well as polypectomy (Sugimoto and Mizukami 2015)

Underwater endoscopic mucosal resection (EMR) has recently been proposed as an option in the excision of challenging lesions, such as in cases of failed conventional EMR and recurrent polyps, with promising outcomes in terms of recurrence and complication rates (Wernli et al. 2016; Binmoeller et al. 2012).

The main limitation of WAC includes prolongation of caecal intubation time (CIT); however, there are conflicting reports in literature whether this really holds true (Rex 2014; Cadoni et al. 2015).

1.2.5 Confocal Microscopy

Confocal microscopy enables subsurface imaging of living tissue during colonoscopy and may offer an instant and reliable diagnostic tool for in vivo histology. Since histopathological examination of tissue biopsy obtained by colonoscopy remains the gold standard for final diagnosis of colorectal lesions. However, this process is time consuming and may limit the ability of the endoscopist to immediately determine the necessity for resection during ongoing colonoscopy, resulting in the need for repeat colonoscopies. Furthermore, overtreatment (resection of benign lesions) or undertreatment (biopsy instead of resection for neoplastic tissue) can lead to unnecessary risks for the patients. Recently, a confocal laser endomicroscope has been developed that is integrated in the distal tip of a standard video colonoscope (Fig. 1.3).

1.3 Endoultrasound (EUS)

EUS is an established imaging technique used for diagnosing and staging of rectal cancer patients. It plays an important role in diagnosing early cancers and thereby aids in selecting patients for local excision instead of major resection procedures. EUS can also be used to perform image-guided aspiration from suspicious lesions in the perirectal area and thus help in establishing the diagnosis of local recurrence.

Proximal lesions in the colon can also be staged using the advanced versions of forward-viewing radial echo endoscope. This latest form of EUS has an accuracy of 81% for T staging and 52.4% for N staging. Overall, EUS has been found to be more accurate as compared to CT (81.0% vs 68.4%) and it is believed that these results can be further improved in future (Kongkam et al. 2014). With the use of this new echo endoscope, it is possible to both diagnose and stage a rectal tumour during the same procedure during the preoperative evaluation of CRC patients.

1.3.1 Contrast-Enhanced EUS (CE-EUS)

Ultrasound with injection of intravenous contrast agent can be used for better characterisation of lesions based on their vascular enhancement. Colorectal tumour angiogenesis can be determined based on time-intensity curve (TIC) analysis using CE-EUS. Area under the curve (AUC) which is one of the parameters can be used as an indirect indicator of blood volume, and it has been shown to be significantly higher in adenocarcinomas compared to adenomas (Zhuang et al. 2012). However, for dynamic measurements of tumour angiogenesis in CRC, definitive role of CE-EUS is yet to be validated and needs further research.

1.3.2 EUS Elastography

EUS elastography displays the differences between tissues hardness by adding a colour overlay coding for different elasticity values to the conventional grey-scale images. Tissue strain is measured based on an integrated software application that analyses backscattered ultrasound signals and thus it is possible to evaluate elastic properties of tissues, a feature that can better characterise and differentiate benign from malignant tumours (Fusaroli et al. 2011). In colorectal tumours, benign tumours can be differentiated from malignant ones using EUS elastography (Fig. 1.4).

1.3.3 Three-Dimensional EUS

Three-dimensional (3D) EUS increases imaging resolution by displaying multiplanar rectal and perirectal tissues. This has led to improved accuracy for staging rectal cancer as compared to conventional EUS and CT, both in terms of T and N staging (Kim et al. 2006; Kolev et al. 2014). 3D-EUS can overcome some of the limitations experienced with conventional USG and hence its role in managing rectal cancer needs further evaluation.

1.3.4 EUS-Guided Insertion of Fiducial Markers

Fiducial marker placement uses imaging guidance to place small metal objects in or near a tumour for localising the target lesion and guide radiotherapy for more precision and less toxicity. EUS-guided fiducial marker insertion is considered to be safe

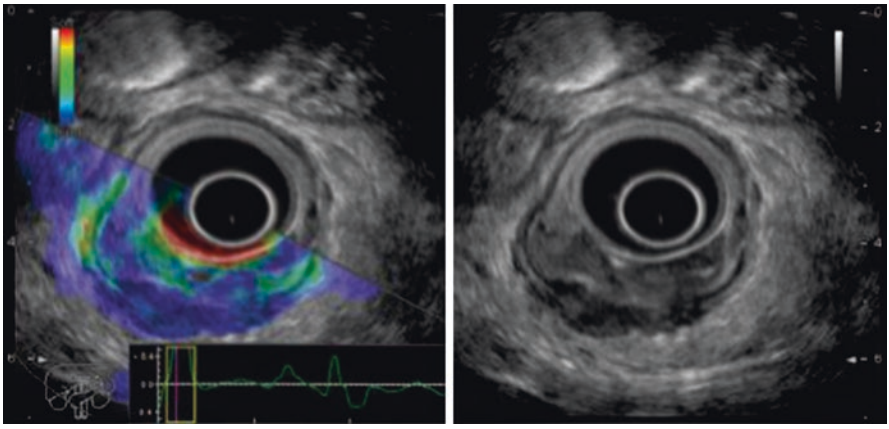

Fig. 1.4 Endoscopic ultrasonography elastography image of a rectal adenocarcinoma with a predominantly blue pattern indicating a low strain mass (left side real-time sono-elastography mode, right side B mode; (World J Gastroenterol. Feb 7, 2016; 22(5): 1756–1766)).

and with high technical success rates. Since radiation therapy plays a pivotal role in management of rectal cancers, so further research in this area is needed.

1.4 Intraoperative Near-Infrared Fluorescence (INIF) Imaging System

Localization of the rectal tumours during surgery is essential and this becomes challenging during laparoscopic and robotic surgery, especially when the tumour is small and in early stage. Colonoscopy is not an ideal investigative tool for assessment of localization in colorectal cancer because of the flexible nature of colonoscope. Recently, near-infrared (NIR) fluorescence imaging has been introduced for real-time intraoperative localisation of tumours, besides identifying vital structures like ureters and for detection of sentinel lymph nodes (SLNs) (Vahrmeijer et al. 2013). Indocyanine green (ICG) is currently being used for the purpose. ICG absorbs light in the NIR range between 790 and 805 nm, and re-emits electromagnetic energy at 835 nm, which can be visualised by its fluorescence in the vasculature by NIR irradiation. ICG is a more suitable dye for tattooing because of relatively long absorption time and potentially increased detection using NIR fluorescence imaging compared to macroscopic colour perception. Also ICG has very few side effects (Watanabe et al. 2009).

There is an ongoing trend of using ICG-enhanced fluorescence for assessment of blood perfusion status of the cut ends of colon and thereby improving the outcome of laparoscopic anastomotic colorectal surgery. The commonly used laparoscopes today are capable of showing only one light modus at a time; however, there are camera systems that can depict white light and NIR channels at the same time, and for better orientation of anatomical structures can produce white light-NIR overlay video.

1.5 Artificial Sphincter

For very low rectal and anal cancers, abdomino perineal resection (APR) is still being performed. The resultant permanent stoma leads to a significant psychological trauma to the patient. Various autologous tissues like gracilis muscle have been used to form a pseudo continent perineal colostomy. However, the faecal continence rates are not satisfactory. To overcome high rates of incontinence, artificial sphincters (AS) have been employed to help achieve better continence rates (Fig. 1.5).

It consists of a soft anal band ring which is placed inside the surgically created circular pocket around the distal colon near artificial anal opening. There is also a valve that is activated by simply pressing on the skin above it. Once activated, liquid flows from the band back to the activator allowing the artificial sphincter to open. Applying pressure (with the palm) on the skin above the activator causes liquid to flow into the band. This closes the artificial sphincter, leaving the patient continent. If a bump is visible under the skin, the sphincter is open. If the skin is lying flat, the sphincter is closed. A puncture port is used for patient-specific adjustment of the liquid volume in the system.

In comparison to neosphincter reconstruction using autologous tissues, implantation of an artificial sphincter is simpler to perform; however, it is associated with many complications, common among them being infection and erosion of the implant besides others.

Many other technological innovations in magnetic resonance imaging of pelvis have led to improved preoperative staging of rectal tumours, and thus better management, which has been discussed elsewhere in this book. Similarly, newer surgical platforms have been invented like Transanal Endoscopic Microscopic Surgery (TEMS) and Transanal Minimal Invasive Surgery (TAMIS) {discussed in other chapters}, which have revolutionised the natural orifice transluminal endoscopic surgery (NOTES) and along with the concept of Transanal Total Mesorectal Excision (Ta TME) may well be the gold standard in the management of rectal cancers.

Fig. 1.5 AMI anal band

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Magnetic Resonance Imaging (MRI) in Rectal Cancers

2

Feroze A. Shaheen, Naseer Choh, and Nowsheen Makhdoomi

Colorectal cancer is the third most common malignancy worldwide (Jemal et al. 2005), and rectal cancer accounts for about a third of all colorectal cancers. The age-adjusted incidence rate for colorectal cancers in India is among the lowest in the world as per the Indian cancer registries (Curado et al. 2007). However, the incidence is showing a rising trend (Yeole 2008), especially in our part of the world, with colorectal cancer being the fourth most common cancer following cancers of esophagus, lung, and stomach as registered at our Regional Cancer Centre (RCC) (Rasool et al. 2012). Improvements in the oncosurgical and medical oncological management of the disease brought in during the last few years have reduced the incidence of invasive cancers, reduced local failure, and have resulted in improved survival rates (Herald et al. 1998). This has also been attributed to colorectal screening programs, which allow earlier detection and early intervention. Adenocarcinomas account for the vast majority (98%) of rectal cancers. Other rectal tumors are relatively rare and include carcinoid tumors, lymphoma, and gastrointestinal stromal tumors.

The main post treatment problems to be addressed by the operating surgeon are local recurrence and impairment of anorectal and genitourinary functioning, which may occur secondary to the involvement of internal and external anal sphincter,

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and the pelvic autonomic plexus either by the disease or by the surgical procedure used. However, the occurrence of these outcomes in patients who received properly planned treatment has been reported to be very low (MacFarlane et al. 1993).

Various treatment modalities that have led to improved survival and overall prognosis of rectal cancer patients include surgical technique like total mesorectal excision (TME) and preoperative radiation and chemotherapy. TME is considered to be an optimal surgical technique for curing early-stage localized rectal cancers (Wibe et al. 2002). In total mesorectal excision (TME), the mesorectal fascia forms the plane of dissection and therefore the potential circumferential resection margin (CRM). Presence of tumor within 1 mm of the potential CRM is a risk factor for local recurrence and therefore indicates poor prognosis. Moreover, randomized controlled studies have shown that adjuvant preoperative radiation therapy/chemoradiotherapy has an effective role in reducing local recurrence and prolonging survival in patients with rectal cancers, especially those with locally advanced or node-positive disease (Colorectal Cancer Collaborative Group 2001). Thus, preoperative radiation therapy is becoming standard treatment for advanced rectal cancer. However, radiation therapy may be complicated by toxicity and therefore should be tailored as per the disease status. The optimal management of rectal cancer therefore demands detailed preoperative evaluation that includes assessment of the relation of tumor to the mesorectal fascia (Burton et al. 2006).

Several modalities exist at present for staging of rectal cancer. These include endorectal ultrasonography (EUS), with rigid or flexible probes; computed tomography (CT); magnetic resonance imaging (MRI) with traditional body coil, endorectal coil, or phased array coil; and positron emission tomography (PET) with or without CT fusion.

Endorectal ultrasonography (EUS) is an established modality for evaluating the integrity of the layers of rectal wall (Rifkin et al. 1989). Although very accurate for staging for superficial cancers, EUS is not very useful for assessing advanced rectal cancers due to limited depth of acoustic penetration with inadequate delineation of the mesorectal excision plane, substantial interobserver variability, and suboptimal staging of stenotic lesions (Garcia-Aguilar et al. 2002).

Computed tomography (CT) has an advantage that it allows visualization of entire abdomen and pelvis. In theory, the new generation multidetector row spiral CT scanners are expected to perform better than conventional CT scanners (Chiesura-Corona et al. 2001). CT would have the advantage that a single investigation can be used to combine local, regional, and distal staging. With that capability and the addition of fast acquisition time and relatively low cost, staging with CT would be beneficial for both the patient and the health care system. However, its role in rectal cancer staging is yet to be completely explored.

It is well known that magnetic resonance imaging (MRI) is the modality with highest soft tissue contrast. With the introduction of endoluminal coil, improved image resolution and detailed evaluation of rectal wall layers became feasible (Vogl et al. 1998). However, there were certainly some problems that have made endorectal MR imaging go out of practice. Limited availability, high cost, a limited field of view as a result of sudden signal drop-off at a short distance, with resultant difficult visualization of mesorectal fascia and surrounding pelvic structures makes

endorectal MRI unsuitable for local staging (Brandva et al. 2013). The positioning of an endorectal device is another issue in cases with high and/or stenosing growths.

The dedicated external coils like phased array coils that possess the ability of high spatial resolution allow an enhanced imaging field (Hadfield et al. 1997). The advantages of high spatial resolution with a large field of view make phased array MR imaging suitable for staging of both superficial and advanced rectal tumors. The experience with a 3 T system in the high-resolution protocol is still limited, but it is likely that there are few or no benefits with this system for the staging of rectal cancer (Maas et al. 2012).

2.1 Normal Anatomy

The rectum is that part of the gastrointestinal tract which extends from the upper end of the anal canal to the recto sigmoid junction and is approximately 15 cm in length. Anatomically, it can be divided into three segments, i.e., the low, mid, and high rectum. These segments correspond to the first 7–10 cm, the next 4–5 cm, and last 4–5 cm, measuring from the anal verge (Iafrate et al. 2006).

The proximal part of the anal canal is characterized by insertion of the levator ani muscle into the fibers that form the puborectalis sling.

The rectal wall, as seen in cross section, consists of mucosal layer, muscularis mucosa, submucosa, and muscularis propria. Most of the rectum is below the peritoneal reflection; so only upper third is invested by serosa or peritoneum. On MR imaging, the mucosal layer of the bowel wall is visible as a fine, low signal intensity layer. The submucosa is seen as thicker, higher signal intensity layer external to the mucosal layer. The muscularis propria is seen as two distinct layers, the inner circular and outer longitudinal layer. The mesorectum is the perirectal fatty tissue, seen on axial MR imaging as a high signal intensity structure that surrounds the rectum and contains lymph nodes, lymphatics, and vessels. It is surrounded by the mesorectal fascia, seen as thin hypointense linear structure, which represents the CRM when TME is performed. It is optimally visualized on high-resolution, thin-section MR imaging (Fig. 2.1).

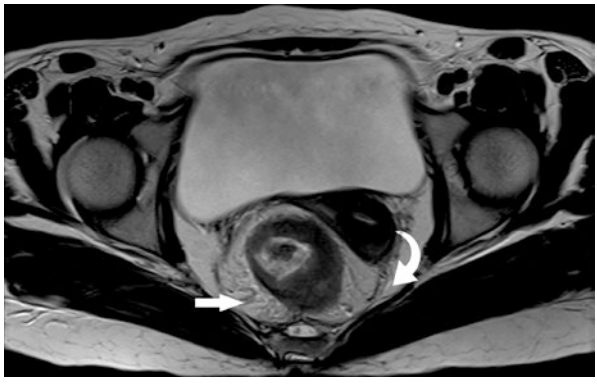

Fig. 2.1 Axial T2-weighted MR image showing mesorectal fat (arrow) and mesorectal fascia (curved arrow)

Benign nodes within mesorectum are seen as uniform signal intensity ovoid structures with smooth margins and homogenous signal.

The parietal fascia fuses with the sacral periosteum at the level of sacral promontory overlies the muscles of pelvic wall. Anteriorly, it is attached to body of pubis and cannot be distinguished from the underlying muscles. The retrorectal space is a potential space situated between presacral parietal fascia and the mesorectal fascia and forms the plane of dissection in TME surgery. Rectosacral fascia is a pelvic floor fascial structure of variable thickness, which is seen on sagittal MR imaging as an oblique low signal intensity band extending from the junction of the S3 and S4 vertebrae to the posterior wall of the rectum, adjacent to the anal sphincter complex. The peritoneal reflection is easily seen on sagittal MR imaging as a low signal intensity thin linear structure that extends over surface of bladder posterior to its point of attachment onto the rectum (Fig. 2.2).

Denonvilliers fascia is a well-developed fascia that derives from the urogenital septum during embryonal development. It forms the anterior surface of mesorectum on its lower part and is seen as low signal intensity layer adjacent to prostate in men and as the rectovaginal septum behind the posterior vaginal wall in women.

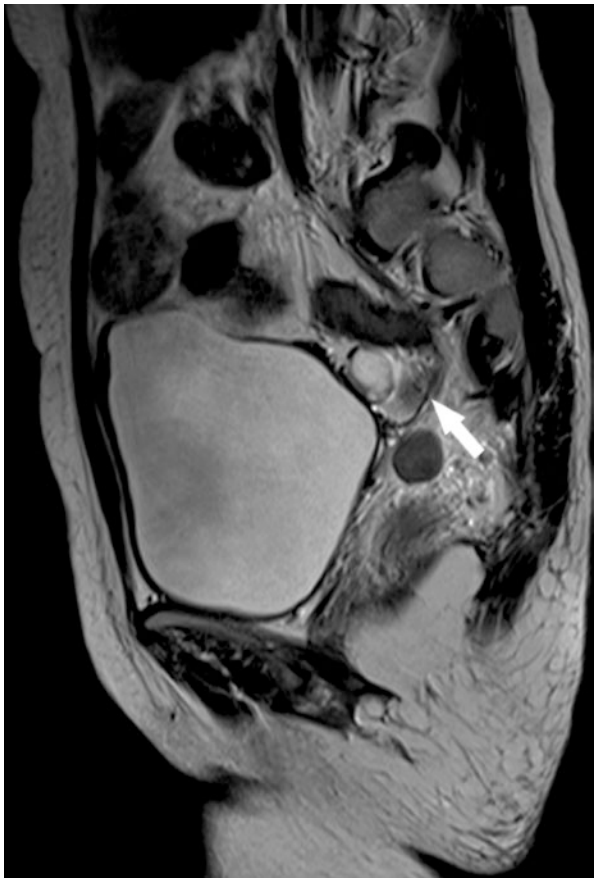

Fig. 2.2 Sagittal T2-weighted MR image showing peritoneal reflection

2.2 Imaging Technique

The introduction of phased array coil system has improved staging of rectal cancer which along with fast spin echo T2-weighted sequences enables high-resolution imaging. A 1.5 T system along with phased array coils is sufficient for staging, allowing optimum field of view. Patients are positioned in supine, head first position within the scanner. No bowel preparation, air insufflation, or intravenous antispasmodic agents are necessary. The flexible multi element phased array body coil is placed firmly over pelvis to ensure good compression and coverage and to minimize possibility of motion.

2.2.1 Imaging Protocol

- Axial T1-weighted conventional spin echo images of the pelvis using 24 cm FOV, 4 mm section thickness, and 0.5 mm intersection gap and 540/16 TR/TE.
- Axial and sagittal T2-weighted spin echo acquisition of the anatomic pelvis using 24 cm FOV, 5 mm contiguous sections, 4000/85 TR/TE.
- These T1- and T2-weighted images are used to plan T2-weighted thin-section axial images with 16 cm FOV, 3 mm section thickness, no intersection gap, 4000/85 TR/TE; perpendicular to long axis of tumor and through the adjacent perirectal tissues or in a plane perpendicular to rectal curve.
- Fat-saturated T1 and contrast-enhanced sequences using 0.1 mmole per kg of gadolinium diamide (Omniscan) in orthogonal planes (optional).

2.2.2 Interpretation of MR Images

Staging is done according to the criteria laid down by AJCC (American joint committee on Cancer) as T staging, T substaging, and N staging through careful interpretation of thin-section, high-resolution. and small FOV T2-weighted images obtained perpendicular to the rectal wall.

2.2.2.1 T Staging

The tumor could be described by morphology as polypoid, ulcerating, circumferential, or semi-circumferential. On T2-weighted images, non-mucinous tumors are seen as intermediate signal and mucinous tumors as high signal intensity. In addition, the distance of the tumor from anal verge and the approximate length of the tumor are to be assessed.

- T1 tumors show invasion of submucosa with partial preservation of high signal intensity submucosa beneath the intermediate signal intensity of the tumor (Fig. 2.3).
- T2 tumors show partial or complete thickness involvement of muscularis propria without extension into mesorectal fat (Fig. 2.4).

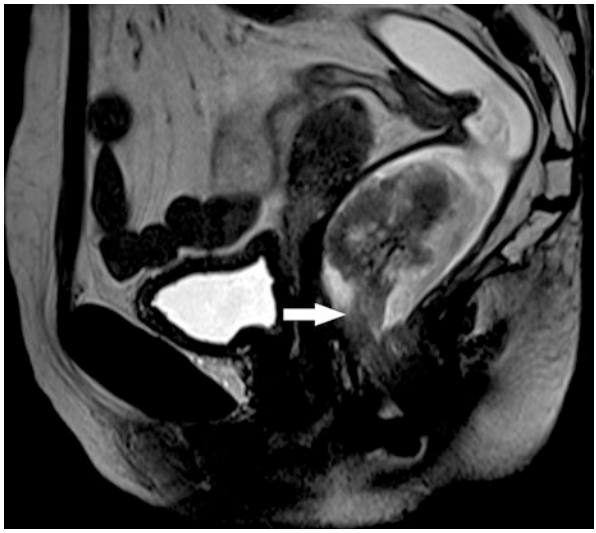

Fig. 2.3 Sagittal T2-weighted image of the patient showing origin of the lesion in lower rectum with stalk T1 lesion (arrow)

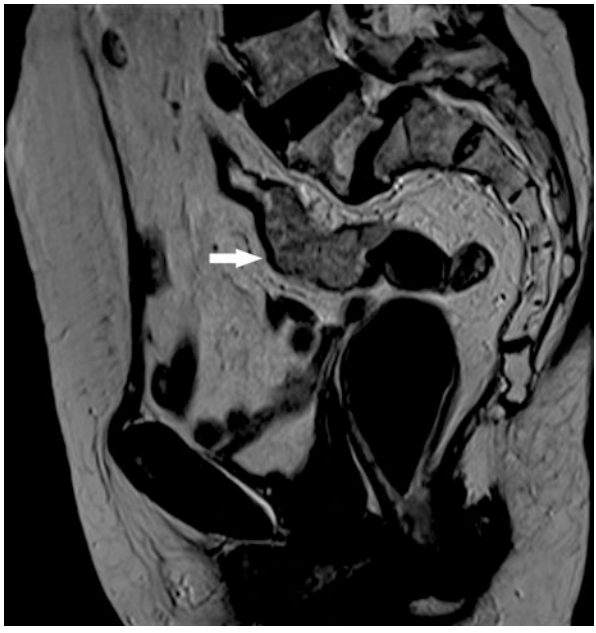

Fig. 2.4 Axial T2-weighted MR image showing eccentric wall thickening confined to bowel wall, i.e., T2 lesion (white arrow)

- T3 tumors show extramural invasion, either bulge or nodular projection of intermediate signal tumor into mesorectal fat (Fig. 2.5).

Depending upon the depth of the extramural spread of the tumor from outermost edge of muscularis propria, T3 tumors are substaged into

- T3a—<1 mm beyond muscularis propria
- T3b—1–5 mm beyond muscularis propria

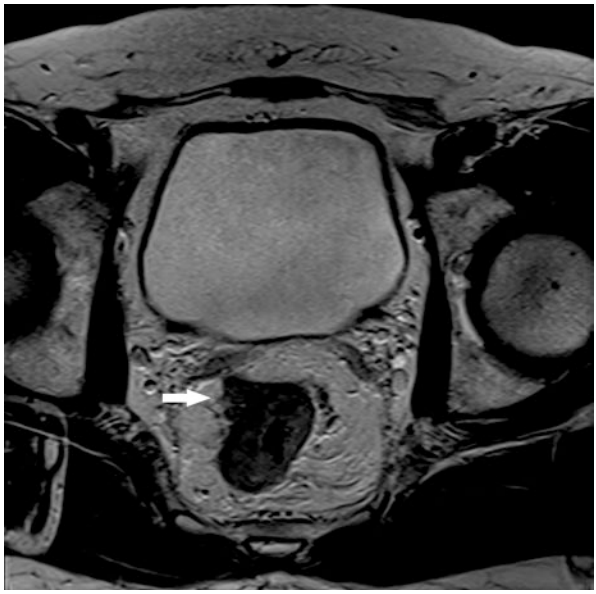

Fig. 2.5 Axial T2-weighted MR image showing T3 lesion, extending into perirectal fat (arrow) with mesorectal fascia at risk of involvement

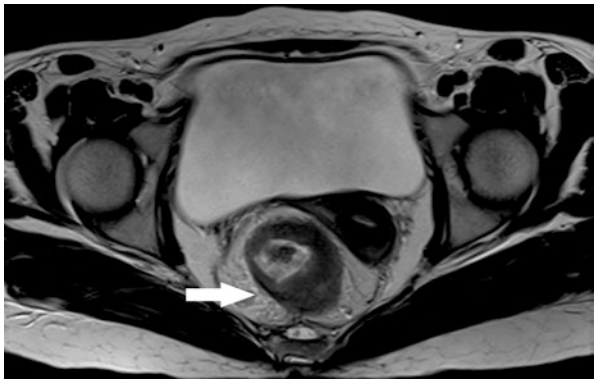

Fig. 2.6 Axial T2-weighted MR image showing T3 lesion with mesorectal fat stranding (arrow)

- T3c—5–15 mm beyond muscularis propria
- T3d—>15 mm beyond muscularis propria (Taylor et al. 2008)

The T substage has the prognostic implications as exemplified by the fact that T3a tumor has identical prognosis to T2 tumor (Fig. 2.6).

T4 tumor suggests adjacent organ/viscus invasion and includes two groups—T4a that shows invasion of adjacent organs or structures and T4ab that has perforated peritoneal reflection (Fig. 2.7). Mid and upper rectal tumors may involve uterus, bladder, or seminal vesicles as well as peritoneum and may have lateral and posterior extension into pelvic side walls and sacrum.

The low rectal tumors need special consideration as far as staging is concerned. The conventional TNM staging is insufficient due to the fact that mesorectal envelope tapers at or above this level. Many authors (Taylor et al. 2008; Shihab et al.

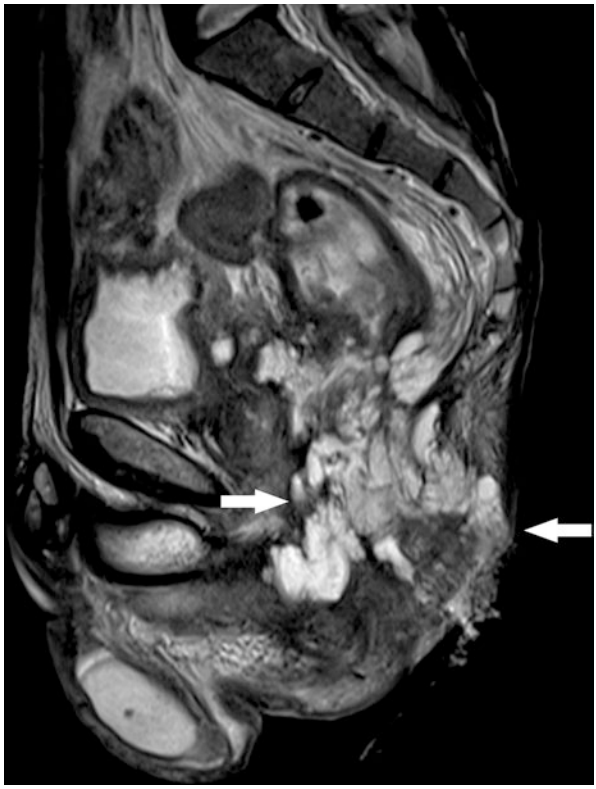

Fig. 2.7 Sagittal T2-weighted MR image showing T4 lesion with extensive invasion in adjacent perirectal soft tissue, levator, and subcutaneous tissue (arrows)

2009a, b) have proposed a new staging system that takes into account the relevant local anatomy.

MR Staging of Low Rectal Tumors

Stage 1: tumor confined to bowel wall but does not extend through full thickness; intact outer muscle coat.

Stage 2: tumor replaces muscle coat but does not extend into intersphincteric plane.

Stage 3: tumor invades intersphincteric plane or lies within 1 mm of levator muscle.

Stage4: tumor invades external anal sphincter and lies within 1 mm and beyond levator with or without invading adjacent organs.

The impact of this staging has been that margin positivity rate for low rectal resection has markedly decreased for abdominoperineal resection (Fig. 2.8).

For assessment of potential CRM involvement, the distance of the outermost radial border of the tumor from mesorectal fascia is measured. The distance is similarly measured for any tumor deposit within the mesorectal fat or any extramural vein showing luminal invasion. Tumor or any deposit within 1 mm of the mesorectal fascia strongly suggests positive potential margin and subsequent poor prognosis

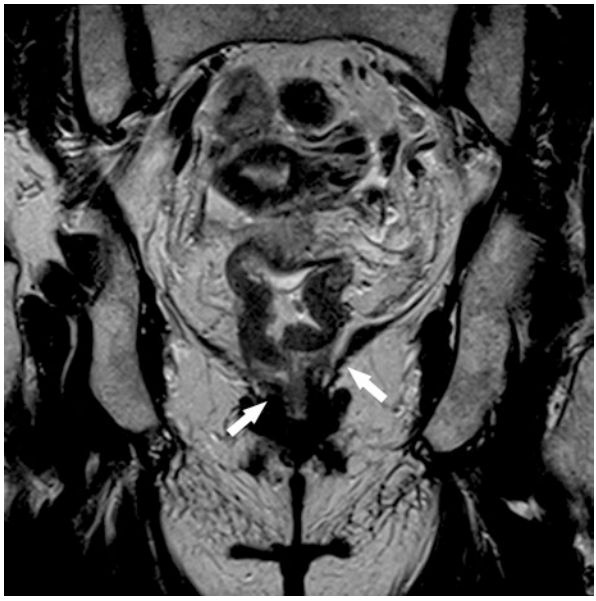

Fig. 2.8 Coronal T2 image showing the relation of the growth to anal sphincter complex and levator muscle (arrows)

(Mercury Study Group 2006). Same holds true for tumor affected lymph nodes or any form of extramural venous invasion (EMVI).

This measurement is therefore important for the prevention of local recurrence after TME (Patel et al. 2011; Hall et al. 1998).

Extramural venous invasion deserves special mention as it is an independent prognostic feature and that can be readily identified on MR imaging. It is defined by presence of tumor within signal flow void tubular structures on T2-weighted sequences lying perpendicular to rectal wall.

2.2.2.2 N Staging

Lymph node size has unfortunately proven to be unreliable criteria for tumor involvement; instead, the presence of irregular borders and/or mixed signal intensity correlates strongly with tumor positivity. Presence of 1–3 nodes is considered N1 and more than 4 nodes N2 disease.

Presence of enlarged pelvic side wall lymph nodes is associated with worse 5 year overall survival (OS) and disease-free survival (DFS) for patients undergoing primary surgery, without preoperative therapy (Mercury Study Group 2011). Therefore, this group of patients qualifies for neoadjuvant treatment in form of radiotherapy to achieve disease control within the pelvic nodes and to improve overall survival (Fig. 2.9).

Post Treatment Evaluation

In patients with advanced cancer, long course neoadjuvant chemoradiotherapy (CRT) followed by TME surgery have reduced local recurrence and improved rate of curative resection (Kapiteijn et al. 2001; Theodoropolus et al. 2002).

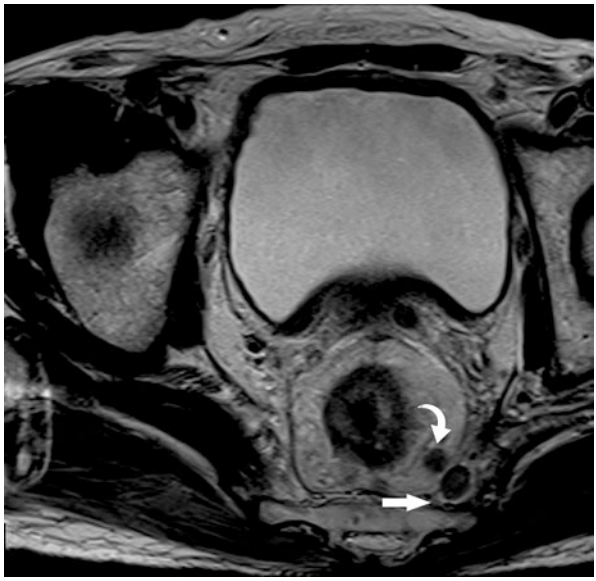

Fig. 2.9 Axial T2-weighted MR image showing mesorectal (bent arrow) and extramesorectal nodes (arrow)

The MRI technique for assessment of post treatment changes is same as that of pretreatment evaluation. For accurate evaluation of post treatment changes, the imaging axis should angled along same planes as pretreatment scans.

MR interpretation: Successful tumor response is represented on MRI either as hypointense foci on T2W high-resolution images representing fibrosis or in some cases as hyperintense fluid signal due to colloid response. Tumor tissue appears as intermediate signal foci.

Factors affecting local recurrence are

- distance to mesorectal fascia <1 mm
- low tumor extending to intersphincteric plane or beyond
- peritoneal involvement

Factors predicting distant failure are

- Extramural tumor spread >5 mm.
- Extramural venous invasion.
- Poor tumor regression grade (TRG)

Histopathologically, tumor regression grade is assessed as

Grade 1: Absence of residual tumor with fibrosis extending along rectal wall.
Grade 2: Presence of rare residual tumor cells scattered throughout fibrosis.
Grade 3: Increased number of tumor cells, however, with predominant fibrosis.
Grade 4: Residual tumor outgrowing fibrosis.
Grade 5: Absence of any tumor regression.

MRI TRG analysis is based on similar principles. The tumor is assessed to determine whether fibrosis or tumor signal intensity predominates (Mandard et al. 1994; Patel et al. 2012).

The MR evaluation after CRT should describe:

- Morphological appearance of tumor
- Height of treated tumor from anal verge compared with baseline pretreatment images
- MR imaging T stage and T substage, taking into account the depth of extramural spread
- MR imaging TRG
- Distance to potential CRM and whether this appears potentially involved or clear
- Presence of extramural venous invasion
- Mesorectal and pelvic sidewall nodal status (Patel et al. 2011)

While applying RECIST (response evaluation criteria in solid tumors) criteria to rectal cancers, one has to remember that there may be intra- and interobserver variability in measuring geometrically irregular tumors like rectal cancer, which therefore cannot be reproduced easily. Complete response (CR) is defined as complete disappearance of tumor, whereas partial response is defined as >30% reduction in tumor length and progression as at least 20% increase in tumor length. Stable disease is defined as neither sufficient increase nor sufficient shrinkage of disease.

It is known that post-CRT restaging using MRI is less accurate than baseline staging, with regard to T0 disease in particular, largely due to the difficulty in distinguishing fibrosis, edema, and normal mucosa from foci of residual tumor. To achieve the goal of accurate evaluation of tumor response, multi-parametric MRI which includes morphologic, volumetric, and functional imaging techniques is currently an active area of research. Functional MRI techniques, particularly diffusion-weighted MRI (DWI) and perfusion-weighted imaging like dynamic contrast-enhanced-MRI (DCE-MRI), provide added information about tumor biology. DWI has a high specificity and high negative-predictive value for the detection of complete response and is particularly useful for detecting residual tumor in cases with incomplete response (Blazic et al. 2017). However, the limited positive-predictive value limits the utility of DWI in complete responders. DCE-MRI remains an active area of ongoing research.

From a practical point of view, depth of tumor outside the muscularis propria has immense prognostic value. In T1, T2, and favorable early-stage T3a/T3b tumors, use of radiotherapy produces little survival benefit. However, it has an important role in more advanced stage T3c/T3d tumors, in which risk of local and distant treatment failure is high.

MERCURY study group has shown a close relation between MRI-derived and histopathologically derived maximal extramural depth of the tumor, so that MRI and histopathological assessments of tumor spread were considered equivalent (Mercury Study Group 2007).

Several studies have shown that MR imaging is a consistent and reproducible technique with high specificity for predicting negative CRM (Beets-Tan et al. 2001). A tumor-free margin of at least 1 mm on MR imaging can predict a histological-free margin with high degree of certainty. Evaluation of local depth of spread, presence or absence of EMVI, and CRM status using MR imaging have been shown to be more important and more easily reproducible than MR imaging assessment of nodal status.

Identification of metastatic lymph nodes remains a challenge for MRI staging of rectal cancer. The assessment of nodal disease generally relies on morphologic criteria. However, going by morphology alone, one may over-stage enlarged benign reactive nodes while one may under-stage small nodes with micro-metastases, which as a matter of fact occur with high frequency in rectal cancer. It has been recently reported that nodal margins and internal nodal characteristics are the most reliable indicators of malignancy and therefore might help in characterization of the nodes (Brown et al. 2003). Moreover, a new promising approach to identify metastatic lymph nodes is by combining MR imaging with a contrast medium in form of ultra-small superparamagnetic iron oxide particles (USPIO) for systemic MR lymphography (Koh et al. 2004). Further studies are however needed to assess the real diagnostic value of lymph node-specific agents.

The situation in case of low rectal cancers is different. Use of TME dissection in such tumors can result in perforation of tumors around level of puborectalis sling. The tumors are always more locally advanced than similar height tumors undergoing anterior resection and have had worse outcome as measured by margin involvement and perforation rate (Nagtegaal et al. 2005).

Therefore, the surgeon needs to be fully apprised about the radial extent of the tumor to the mesorectal fascial plane and intersphincteric plane by careful assessment of the sagittal, axial, and coronal images so that an enhanced surgical procedure such as extra-levator abdominoperineal resection or anteriorly enhanced abdominoperineal resection is chosen for these low rectal tumors instead of conventional TME resection.

2.3 Conclusion

MRI due to its inherent contrast resolution has distinguished itself as the best imaging modality for staging rectal cancer. High-resolution T2 sequence details the T stage of rectal cancer with close correlation with histopathological staging. T staging of rectal cancer determines the circumferential resection margin positivity and help decide treatment strategies like neoadjuvant CRT or surgery or both. This has helped reduce recurrence rate and improved overall survival. A special reference is made to low rectal cancers where MR staging to determine involvement of intersphincteric plane will result in opting for extra-levator approach with better results in achieving clear margins.

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Staplers in Colorectal Surgery

3

Ajaz Ahmad Malik and Shams-ul Bari

Abbreviations

GIA	Gastrointestinal anastomosis
MRI	Magnetic resonance imaging
PPH	Procedure for prolapse and hemorrhoids
USSC	United States Surgical Corporation
USSR	United States of Soviet Russia

Advances in surgery have led to many technological improvements in surgical procedures like by using surgical stapling devices with an attempt to achieve better patient outcome. However, one should be aware about the pitfalls and risks associated with stapling. These devices have also evolved over many decades like our surgeries with an attempt to get the most surgeon friendly and patient beneficial devices available in the market. Surgical staples are specialized staples which are used instead of sutures to close skin wound or remove and anastomose parts of the bowels or lungs. Stapling is considered to be much faster than suturing by hand, and also believed to be more accurate and consistent (Baker et al. 2004). Stapling is primarily used in bowel and lung surgery; since staple lines are more consistent, they have less chances of leakage of blood, air, or bowel contents (Cajozzo et al. 1990).

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Anastomosing a bowel segment has been a significant concern for the surgeons from so many decades. Leaks from the anastomosed segments cause significant morbidity and mortality even in present-day world. The introduction of surgical staplers has been an attempt to address this significant concern by standardizing the procedures and avoiding any individualized techniques of suturing. Even though the concern of leaks still persists but definitely it has given a consistency to these procedures besides making the anastomosis faster, accessible in inaccessible areas and providing hemostasis of the cut edges by virtue of compression for some time after firing the staplers (Brundage et al. 2001).

Humer Hultl is known as a father of surgical stapling as he was first to introduce surgical stapling devices in 1908 (Hardy 1990). However, use of these stapling devices has increased only after new and reliable disposable instruments became available during the past 30 years. The Hultl's prototype stapler had a weight of 8 lb (3.6 kg). Several hours were spent to assemble the instrument and for achieving a consistent staple line and a reliable and dependable patent anastomosis. Later in 1950s, various modifications were done in USSR and finally a first commercially viable reusable stapling device was developed for creation of bowel and vascular anastomoses (Choy et al. 2008; Fingerhut et al. 1995). It was Mark M. Ravitch, from United States of America who attended a conference in Soviet Union where a stapling device was introduced (Ravitch 1959). He got a sample of stapling device and introduced this stapling device to Leon C. Hirsch, a well-known entrepreneur in United States of America who established the United States Surgical Corporation (USSC) in 1964. The company started to manufacture surgical staplers under its Auto Suture brand. USSC was the only company manufacturing these surgical staplers till late 1970s (Gritsman 1966). It was in 1977 that Johnson & Johnson's Ethicon also introduced their own stapler into the market and nowadays staplers from both the companies are widely used along with many other competitors. In 1998, USSC was bought by Tyco Healthcare, which later on became Covidien on June 29, 2007. Lately in 2002, Waston Medical Appliance company Ltd. was founded. Waston is located in Wujin Hi-Tech Industry Zone in Changzhou, a city only 160 km east of Shanghai and is one of the most advanced manufacturing centers in China. As a young but vital company, Waston devotes itself to designing, manufacturing, and distributing of surgical staplers, including circular stapler, linear stapler, PPH stapler, linear cutter, and other kinds of staplers.

The staplers which were available in the initial phase were made of stainless steel with titanium staples loaded into reloadable staple cartridges (Chekan et al. 2013). The surgical staplers which are used nowadays are either disposable and made of plastic, or they may be reusable and made of stainless steel and in both types generally disposable cartridges are used. The staple line may be straight, circular, or curved. Although most surgical staples are made of titanium, some skin staples and clips made from stainless steel are also being used. Advantages of titanium are that it produces less reaction with the immune system and, being non-ferrous, titanium does not interfere significantly with MRI scanners, although some imaging artifacts may result (Detry et al. 1995). However, titanium staples are never purely titanium,

they all have some amount of nickel content. Patients who are allergic to nickel, and develop a rash or earring break-outs, oozing, or itching on wearing cheap jewelry, should discuss nickel allergies with their surgeon. Synthetic absorbable staples based on polyglycolic acid as with many synthetic absorbable sutures are now available and are being widely used (Damesha et al. 2008). Several designs of surgical staplers are available in the market and are used for placement of different types of staples. Some surgeons prefer to use disposable staplers, which are fitted with disposable cartridges and are used on a single patient. Other surgeons use reusable staplers made from stainless steel. In these reusable staplers a disposable cartridge is used, and the stapler is sterilized after the procedure so that it can be reused. Although reusable staplers decrease the cost of procedure and produce less surgical waste, energy is required to sterilize them, so the net environmental impact when compared to a disposable product is not very different.

3.1 Applications of Stapler

Circular staplers are usually used for end-to-end anastomosis after resection of the bowel and sometimes in esophagogastric surgery, although their use in esophagogastric surgery is still controversial (Lawson 1977). Staplers are also used in certain bariatric surgical procedures such as vertical banded gastroplasty ("stomach stapling") (Latimer 1975; Roberts et al. 2019). Staplers are also used to close both internal and external wounds and are used both in open and laparoscopic surgery. But the instruments used in open surgery are quite different from those used in laparoscopic surgery. Laparoscopic staplers are long, thinner, and are designed in such a way that good access is achieved through a 10 or 12 mm trocar ports. Some staplers are incorporated with a knife, to carry out both the excision and anastomosis in a single firing.

Use of staplers have also been attempted in vascular surgery but despite lot of research it has not been widely accepted as yet and hand suturing is still widely used in contrast to GI surgeries where staplers are routinely used for circular end-to-end anastomosis of digestive tract (Nazari 1990).

Very wide range of stapling devices are available in the market and are commonly used in the modern gastrointestinal surgery. Various staplers available in the market are enumerated below.

3.1.1 PPH Stapler

The PPH (procedure for prolapse and hemorrhoids) stapler is uniquely designed and developed to treat the rectal prolapse and hemorrhoidal disease. With this instrument the hemorrhoidal cushions are repositioned to their original location without excising them. Both the disposable PPH stapler and a reusable PPH stapler are available in the market.

3.1.1.1 Disposable PPH Stapler (Figs. 3.1 and 3.2)

Since it is a disposable instrument, it avoids the possibility of cross-infection. The instrument can accommodate a large cartridge and can excise even an extensive prolapse. It has three important components which include controlled double row staple, circular anal dilator, and purse string suture anoscope. Purse string suture anoscope provided with the device causes simultaneous reduction of prolapse and supports placement of the purse string suture at least 4 cm above the dentate line which is nicely seen through the transparent anoscope.

3.1.1.2 Reusable PPH Stapler

This instrument is very economical and can be used in multiple patients after proper sterilization. The staple is made of pure titanium and the cartridge can be changed as and when needed. Detachment and cleaning of instrument is quite simple and convenient. It excises and anastomoses prolapsed mucosal tissue around the anal canal and rectum. The handle of the instrument has been designed in such a way that it is very easy to hold it. There is minimal loss of blood during the operation.

3.1.1.3 Disposable Three-Row-Staple PPH Stapler

The three-row-staple PPH stapler is used for anal hemorrhoidectomy and excision of rectal prolapse.

Advantages and Features

It has an extraordinary hemostatic effect and there is no need of manual suturing. The arrangement of PPH stapler cartridge is more compact and its outermost

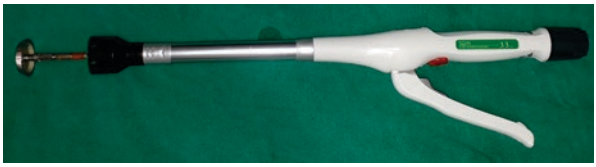

Fig. 3.1 Disposable PPH stapler

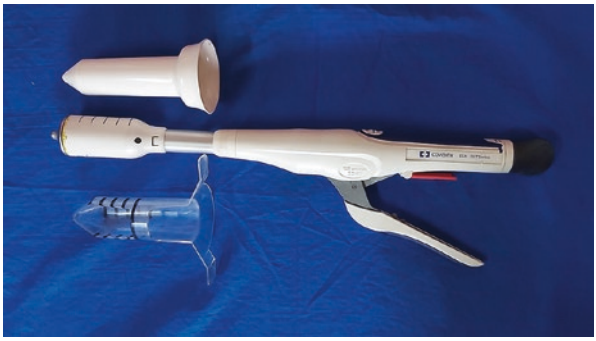

Fig. 3.2 Disposable PPH stapler with accessories

surface has a special design. The special design of the outer ring prevents anastomotic tissue from excessive squeezing. The three rows of titanium staples can effectively close the tissue. A greater lumen of the staple cartridge can hold more diseased tissue. The instrument has got a stainless steel anvil and guide shaft that makes the closing and firing stable and comfortable. The sharp circular knife fitted in the instrument can effectively cut the tissues. 0.75 mm suture clearance compresses the mucosa to achieve the best hemostatic effect. The anastomosis done by this type of stapler has got a higher tensile strength.

3.1.2 The Circular Stapler

This stapler is used for the reconstructive surgery of digestive tract and is used in general surgery, thoracic surgery, bariatric surgery, and in colorectal surgery, to perform end-to-end, side-to-end, and side-to-side anastomoses. This type of stapler could be curved or straight and is available in different diameters. The curved one is available from 21 mm up to 33 mm and the straight one is available from 33 mm up to 34 mm. The circular stapler uses titanium staples which are staggered in two concentric rings inside the staples-containing cartridge. The stapler is fitted with a circular blade which automatically cuts off any excess tissue during staple release and during creation of circular anastomosis. The stapler can be easily operated with the help of the trigger handle. The size of the selected circular staples to be used depends on the dimension of anastomosis. The instrument is very compact and designed on modern lines which makes it safe for the patient and comfortable for the user. Both disposable and reusable variants are available in the market.

3.1.2.1 Disposable Circular Stapler (Fig. 3.3)

It is the most convenient circular stapler available in the market at present. The curved intraluminal staplers are available in several sizes. Disposable circular stapler can be used throughout the alimentary tract for either end-to-end or end-to-side anastomosis. It has to be used only once, thereby avoiding the possibility of cross-infection. It has got a large cutting diameter and is equipped with an advanced and latest driving mechanism. It is provided with smooth and fast opening and closing mechanism which makes it very comfortable to use. Thickness of the tissue to be taken can be easily adjusted. The handle of the stapler has been designed according to human engineering, making it comfortable for the user.

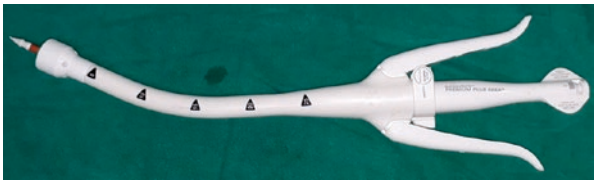

Fig. 3.3 Disposable circular stapler

3.1.2.2 Reusable Circular Stapler

The instrument is reusable, comfortable, convenient, and economical. The instrument can be easily detached and cleaned, making it surgeon friendly. The pure titanium material of the staples and the changeable cartridge makes it a reliable instrument. Four specifications are available in the market which are suitable for different stapler modes 25, 27, 29, and 32. Since this instrument is reusable, the body of stapler can be resterilized.

3.1.3 Linear Stapler

The linear stapler is used for transection and anastomosis of any part of the alimentary track. It has got utility in various abdominal, thoracic, gynecological, and pediatric surgical procedures. It has got certain specific features. The stapler can be easily operated by the complete squeeze of the trigger handle. Various types of linear staplers are available in the market ranging in size from 30 mm up to 90 mm (effective length of the anastomosis). For each size of the stapler, two staple heights are available for anastomosing a thick or thin tissue. The effective length of anastomosis is based on the size of selected stapler. While doing the procedure, two staggered rows of titanium staples are delivered by the linear stapler. These linear staplers may be automatic or manually operated and may be disposable or reusable.

3.1.3.1 Disposable Linear Stapler (Figs. 3.4 and 3.5)

It is used only once hence no chance of cross-infection. The height of closure nails can be adjusted depending on the thickness of the tissue. Disposable linear stapler

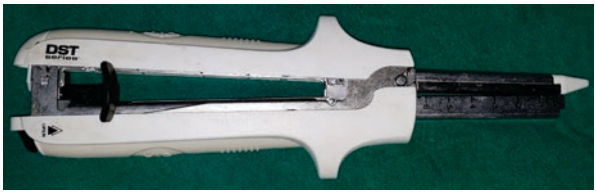

Fig. 3.4 Disposable linear cutting gastrointestinal stapler

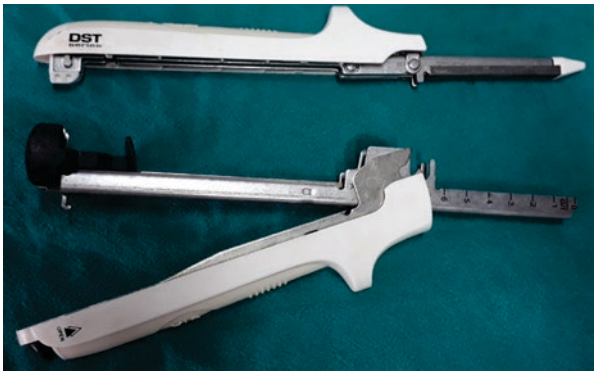

Fig. 3.5 Disposable linear cutting gastrointestinal stapler

is provided with a stand-by nail room which can be used in the same operation. Several specifications are available in the market depending on the suture lengths required.

3.1.3.2 Reusable Linear Stapler (Fig. 3.6)

The instrument is reusable, comfortable, convenient, and cost-effective. The instrument can be easily detached and cleaned, making it surgeon friendly. The pure titanium material of the staples and the changeable cartridge makes it a reliable and trustworthy instrument. Three specifications are available in the market which are suitable for different stapler modes 30, 60, and 90. Three cartridges of different specifications can fit for three different operation modes. Since this instrument is reusable, the body of stapler can be resterilized.

3.1.3.3 Disposable Linear Cutter

The linear cutter is commonly used for transection, resection, and anastomosis in gastrointestinal surgery, pediatric surgery, thoracic surgery, and urology. Different sizes of linear cutting stapler are available ranging from 55 to 100 mm (effective length of the anastomosis and transection). For each size of the stapler, two heights are available for thick and thin tissues. While using the stapler, two double-staggered rows of staples are delivered while simultaneously dividing the tissue between rows. An important feature of this instrument is its safety lock-out feature which is designed in such a way that it prevents a used reloading unit from being refired.

It has got a unique design that makes it sure that staple formation is consistent, and there is minimal bleeding. The stapler is provided with an inbuilt sharp knife. The stapler can be easily operated by complete squeeze of the handles followed by shifting of side knob forth and back. The handle has been designed according to human engineering. The instrument can be operated using only one hand. Cartridges of different sizes are available for different tissue thickness. It has got a longest cutline (98 mm) and can transect a larger organ in one firing. The effective length of anastomosis and transection is defined by the size of selected stapler. The linear cutting stapler is a cost-effective and a single patient use product because appropriate cartridges can be used.

3.1.3.4 Disposable Curved Stapler

It is both a stapling and cutting device and is quite suitable instrument for surgical treatment of anal wall diseases and for low anterior resection. In contrast to ordinary stapling devices, which cannot fit into the conformity of deep lower position of the

Fig. 3.6 Reusable Advant 55 linear cutting gastrointestinal stapler

pelvis, disposable curved cutting stapler can easily fit as they have been designed into arc shape according to the human anatomy. With the use of these types of staplers, both the operative time and the amount of bleeding are decreased markedly which can help to improve the quality of the surgery. The stapler is provided with three rows of crossing titanium staples, curved, cutting, and stapling part with a curved scalpel between the first and the second row. While three staggered rows of staples are delivered into the tissue, the transection of tissues between staple lines is done by a curved scalpel.

3.1.3.5 Disposable Endo Cutter Stapler and Reload Units (Figs. 3.7 and 3.8)

The endo-linear cutter staplers are again used in abdominal, gynecologic, pediatric, and thoracic surgery for resection, transection, and creation of anastomosis. Two, triple-staggered rows of titanium staples are placed by this stapler and simultaneously the tissues are divided between the two, triple-staggered rows. The size of the staples is determined by using either 2.5, 3.5, or 4.8 mm single cartridge. The instrument may be reloaded and fired up to 25 times in a single procedure. This disposable endo cutter stapler can accommodate as many as 60 cartridges of any size, whether 2.5, 3.5, or 4.8 mm. This stapler is supplied for clinical use in a sterilized packing and is sterilized by γ-ray.

3.1.3.6 Disposable Auto-purse String Forceps

The product is used for purse string suture in surgery by driving suture staples evenly around the patient's tissue, and pulling the thread. With the help of this

Fig. 3.7 Endo gastrointestinal reusable linear stapling device

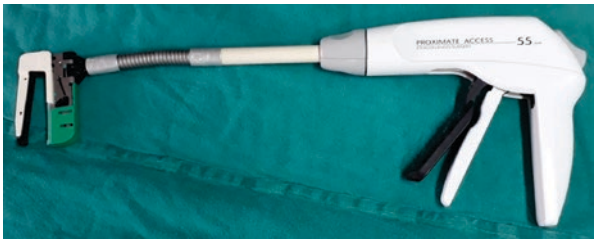

Fig. 3.8 Proximate Access 55 maneuverable rectal stapling device

instrument a purse is constructed in a mechanical manner, thereby saving the surgeon's time. This instrument is not used in certain conditions which include:

1. When the tissues are friable.
2. When the thickness of the tissue is less than 1.0 mm.

3.2 Controversy Regarding Use of Staplers in Gastrointestinal Surgery

The problem of foreign body reaction in stapled anastomoses was first reported by Lim et al. The foreign material eliciting this reaction was the stapler cartridges. Regardless of the level of anastomosis, there is little data available to demonstrate superiority of stapled over hand-sewn techniques in colorectal anastomosis. Although the results have been found to be comparable in terms of mortality, anastomotic dehiscence, and wound infection, the rate of stricture formation at the site of anastomosis has been found to be considerably higher with staples than with sutures for colorectal anastomosis (8% vs 2%, respectively). Matos systematically reviewed (Cochrane Database) nine studies involving 1233 patients which included 622 stapled and 611 hand-sewn patients and found that overall leaks were 13% vs 13.4%, with clinically evident leaks in 6.3% vs 7.1% and radiological leak in 7.8% vs 7.2%. They concluded that the use of a staple or hand-sewn technique must be decided on the basis of previous experience, clinical circumstances, and available resources (Ravitch and Rivarola 1966). Another systematic review showed that both stapler and hand-sewn techniques are equally effective and the choice may be based on personal preference (Lustosa et al. 2001; Malik et al. 2015). With regard to time taken for construction of anastomosis or occurrence of complications in colorectal anastomosis, no significant difference between the two techniques has been reported by several prospective and randomized trials (Halsted 1887; Myers et al. 2011). Although several studies have shown that with the use of stapling devices procedure takes less time to perform and anastomotic leakage occurred less often but routine use of stapling devices for intraperitoneal colorectal anastomosis cannot be recommended because of a higher incidence of mishaps and strictures (Schrock 1973; Offodile et al. 2010).

3.3 Laparoscopic Surgical Staplers

Laparoscopic staplers are longer and thinner as compared to those used in open surgery. They are designed in such a way that good access is achieved through trocar ports (Nazari 1990). There are currently two main global stapler manufacturers of laparoscopic surgical staplers, Covidien and Ethicon and they jointly hold a 69.3% share of the market. These laparoscopic staplers are frequently used in bariatric, colorectal, or thoracic surgery (Latimer 1975). Endo GIA provides articulation at a very narrow angle with a new knife each time. The Endo GIA technology also offers

a wide range of loads (ten rotating loads and ten straight loads). The staple line is also better and rotation is intuitive and easier to apply. Another advantage noticed is that these staplers are generally light-handed and more flexible and easier to handle (Kim et al. 2009).

3.3.1 Multifire Linear Endo GIA-30 Staplers and Reloads

The stapler is designed for using multifire Endo GIA 30—2.0, 2.5, and 3.5 reloads (Fig. 3.9). The stapler places two, triple-staggered rows of titanium staples and simultaneously divides the tissue between staggered rows. The size of staples is determined by the selection of the 2, 2.5, and 3.5 mm staple size. They are designed in such a way that they can be introduced through all appropriately sized trocar sleeves or larger sized trocar sleeves with the use of convertor.

3.3.2 Endo GIA Ultra Universal Staplers and Reloads

This stapler combines an ergonomic design, precise articulation, and one handed grasping for increased versatility (Fig. 3.10).

Fig. 3.9 Multifire linear endo GIA-30 staplers

Fig. 3.10 Endo GIA ultra universal stapler

Fig. 3.11 Endo GIA universal staplers

3.3.3 Endo GIA Universal Staplers and Reloads

It is a single use instrument (12 mm) used in abdominal, gynecological, pediatric, and thoracic surgery for resection, transection, and creation of anastomosis (Fig. 3.11).

3.4 Controversy Regarding Use of Staplers in Gastrointestinal Surgery

The problem of foreign body reaction in stapled anastomoses was first reported by Lim et al. The foreign material eliciting this reaction is believed to be the stapler cartridges. Regardless of the level of anastomosis, there is little data available to demonstrate superiority of stapled over hand-sewn techniques in colorectal anastomosis. Although the results have been found to be comparable in terms of mortality, anastomotic dehiscence, and wound infection, the rate of stricture formation at the site of anastomosis has been found to be considerably higher with staples as compared to sutures for colorectal anastomosis (8% vs 2%, respectively). Matos systematically reviewed (Cochrane Database) nine studies involving 1233 patients which included 622 stapled and 611 hand-sewn patients and found that overall leaks were 13% vs 13.4%, with clinically evident leaks in 6.3% vs 7.1% and radiological leak in 7.8% vs 7.2%. They concluded that the use of a staple or hand-sewn technique must be decided on the basis of previous experience, clinical circumstances, and available resources (Thokar et al. 2014). Another systematic review showed that both stapler and hand-sewn techniques are equally effective and the choice may be based on personal preference (Lustosa et al. 2001; Sozutek et al. 2012). With regard to time taken for construction of anastomosis or occurrence of complications in colorectal anastomosis, no significant difference between the two techniques have been reported by several prospective and randomized trials (Halsted 1887). Although several studies have shown that with the use of stapling devices procedure takes less time to perform and anastomotic leakage occurred less often but routine use of stapling devices for intraperitoneal colorectal anastomosis cannot be recommended because of a higher incidence of mishaps and strictures (Schrock 1973).

There is still a controversy between the surgeons as far as the ideal method of anastomosis is concerned and the research is still going on.

The aim should be to lower the incidence of dangerous complications and to avoid the need for a colostomy or ileostomy. In order to establish a link between new technology and practice, multi-center, well-designed, large cohort, randomized controlled trials are needed. Every effort should be made to use newer techniques to improve the quality of patient care. It is now a well-established fact that staplers have an important place in the armamentarium of colorectal surgeons.

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Total Mesorectal Excision (TME) in Rectal Cancer

4

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Abbreviations

APE	Abdominoperineal excision
APR	Abdominoperineal resection
AR	Anterior resection
CDH	Circular dilator head
CRM	Circumferential resection margin
DRE	Digital rectal examination
DVT	Deep venous thrombosis
IMA	Inferior mesenteric artery
IMV	Inferior mesenteric vein
LAR	Low anterior resection
LARS	Low anterior resection syndrome
NOME	Nerve-oriented mesorectal excision
PANP	Pelvic autonomic nerve preservation
PME	Partial mesorectal excision
S4	Fourth sacral vertebra
SRA	Superior rectal artery
TI, T2, T3, T4	Tumor grade in TNM classification
TME	Total mesorectal excision

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4.1 Introduction

In medical science, the quest for doing better for the ultimate benefit of the patient stays on. In the treatment of rectal cancer, the surgeons right from the time of Czerny kept on devising so many surgical procedures, which all had their advantages and flaws. Most of the procedures could not stand the test of time and became orthodox with passing time. The popular procedures that stood the test of time for carcinoma rectum are transabdominal resection with restoration of continuity as anterior resection (AR) or low anterior resection (LAR) or abdominoperineal resection or excision (APR/APE). However, the big mile stone was achieved by introduction of total mesorectal excision (TME) for the treatment of rectal cancer.

As the name signifies, the concept of TME evolved as an innovative surgery to eradicate rectal cancer by not only removing the involved rectum but also the mesorectum associated with it. In the literature, Thomas Jonnesco, a Romanian surgeon and anatomist, gave the first description of mesorectum. This description got published for the first time in *Traite d'Anatomie Humaine published by* Poirier and Charpy in 1896. In 1901, the second edition of book also mentioned Jonnesco's description in the same way (Jonnesco 1901). The thin fibrous sheath encapsulates rectum and allows it to be lifted from sacrum without any injury to presacral vessels as per the new evolved concept (Chapuis et al. 2002).

Abel first described the procedure of TME in 1931 (Abel 1931), but it was ultimately Heald who invited a worldwide attention of surgical fraternity to this procedure in 1979 (Heald 1979). He laid emphasis on direct vision and sharp dissection to excise mesorectum while doing a proctectomy by dissecting between the visceral and parietal pelvic fascia. Even though Heald had to face a sharp criticism from contemporary surgeons that the technique was practiced even before this for carcinoma rectum, the fact remains that Heald's article was the one to establish it as a standard in writing and popularizing it worldwide.

TME is an oncologically correct procedure for carcinoma rectum. This is at present considered to be the "Gold Standard" surgery for this disease. The age old concept of operating on carcinoma rectum was the use of blunt dissection for surgery and usually dissecting close to rectum, but it would definitely result in leaving behind a lot of residual disease in the mesorectum and lateral margins; hence, there was always a higher risk of recurrence (Havenga et al. 1996). Heald after revisiting the embryology of rectum came to a conclusion that hindgut and its mesentery (mesorectum) develop as a single unit. Since the unit is single, the chances of the carcinoma to involve the whole unit primarily are more. Excision of this whole tissue as a single unit by dissecting in a plane posterior to it is safe, bloodless, and natural to which Heald gave the name of "Holy Plane." This concept of dissection was widely practiced and markedly decreased the local recurrence rates (Heald et al. 1982). Besides histopathological examination of such specimens revealed that circumferential resection margin (CRM) positivity dropped to less than 5% from 10 to 25%, which obviously was biggest contributory factor for higher local recurrence rates. Decrease in local recurrence after TME has an obvious impact on improved 5-year survival and disease-free survival rates.

Quirke in 1986 rejuvenated the concept of lateral tumor recurrence. He laid the foundation of the concept that CRM positivity is directly proportional to high recurrence rates and decreased survival.

Hida supported the concept that mesorectum is the main area of spread. He also popularized the concept that carcinoma of rectum is mainly the disease of supra levator area and differed with cylindrical concept of Mile (Hida et al. 1997). The significant advantages of TME surgery are now proved beyond doubt. The evidence shows that local recurrence rates have markedly decreased from 12–20% to 4%. It also allows us to send a complete specimen to histopathologist who can very comfortably comment on the completeness and quality of the resected specimen. Besides, this operation provides a room for coloanal anastomosis after low and ultra low resections (Heald 1995).

For tumors of the middle and lower rectum, it is imperative to resect rectum along with whole of mesorectum up to the pelvic floor muscles to label it as a complete TME. In an APR for a low carcinoma rectum, again the same principles of complete TME are applied for resection. However, in these cancers, if the tumor is below the level of pelvic floor muscles, then the lateral extensions of the tumor below the level of mesorectum nullify the benefits of TME. In cancers of upper rectum even if we mobilize the mesorectum and cut the mesorectum 5 cm below the level of lesion, it still amounts to leaving behind some amount of mesorectum; hence, the term partial TME is applied to this type of surgery (Heald et al. 1982). This procedure gained popularity worldwide and became a landmark in the development of surgical treatment of carcinoma rectum.

4.1.1 Indications

TME is indicated as a part of low anterior resection for patients with

- Adenocarcinoma of the middle and lower rectum.
- T2 Lesions
- T3, T4 lesions, or other locally advanced lesions after downstaging with neoadjuvant treatment

4.1.2 Contraindications

1. Lesions infiltrating the sphincter muscle
2. Very low sphincter tone
3. Elderly patients (relative contraindication).

The big advantage of these low and ultra low sphincter saving resections is the decrease in APR rates (15%). APR is now most of the time suited only for cancers, which have invaded the sphincter or where the preexisting sphincter tone is very low (Heald et al. 1997). In elderly patients, many a times a permanent stoma of APR

is better tolerated than a sphincter preserving surgery, which may result in lot of frequency because of low sphincter tone.

4.1.3 Patient Education and Counseling

Patients have a legal and moral right to know about their disease, treatment, and its all possible implications in detail. So, patient counseling should be taken very seriously and always lay significant emphasis on counseling. Discuss in detail about long-term benefit of TME for decreasing the local recurrence. Explain about possibility of anastomotic dehiscence, sexual and bladder dysfunction, anterior resection syndrome, deep venous thrombosis (DVT), chest infections, bleeding, pulmonary embolism, and colorectal sepsis. Also explain about the chances of having a permanent or a covering stoma as an ileostomy in spite of a surgical plan for a sphincter saving procedure. Involve a stoma therapist to mark the possible stoma sites and have a detailed interaction with the patient about stoma handling and to explain the benefits and complications of stoma.

However, while explaining all these possibilities, the doctor has to bear in mind that these possibilities are not to be explained in a pessimistic manner to demoralize the patient but rather to educate him with optimism. The patient should be listened to very carefully at this stage and one should try to allay all his anxieties before getting an informed consent for the procedure.

4.1.4 Pre-procedure Planning

Bowel preparation and stoma site marking are performed on the day prior to surgery. Bowel preparation is a must in laparoscopic surgery to make gut handling more comfortable. High risk patients need to be optimized before surgery. Deep venous thrombosis (DVT) prophylaxis and prophylactic antibiotics are administered as per protocol. The procedure is done under general anesthesia preferably with epidural analgesia. The standard position for the operation is an extended Lloyd-Davies position or lithotomy Trendelenburg position. Always put a Foley's catheter before the start of procedure to keep the bladder empty. A right-handed surgeon would be comfortable to operate from the left side of the patient in an open surgery but on the right side in a laparoscopic procedure.

First assistant should come from the opposite side. Second assistant is positioned between the patient's legs. Patient is given a head down and left up position to get small gut away from the field of surgery.

4.1.5 Technical Considerations

This operation involves the technique of using sharp dissection with scissors or diathermy or a harmonic probe. By sharp dissection, the surgeon can see the important structures in the operative field more confidently and thus avoid injury to them. This

dissection also helps in decreasing the preoperative blood loss (Junginger et al. 2003; Mynster et al. 2004). Handling of tissues of rectum-mesorectum and pelvic walls should be delicate. Try to open the planes gently by continuous traction and countertraction without breaking the mesorectal envelope. The Holy Plane that lies posteriorly between visceral and parietal layers of endopelvic fascia should be identified and exploited for dissection. Go for the circumferential excision of mesorectum without any breaks and breeches, and try to get the circumferential resection margin free from tumor. Always try to keep the lateral dissection planes inside the pelvic plexus.

The proof of a properly performed total mesorectal excision is the gross appearance of the specimen itself, which is being increasingly recognized as a reliable predictor of an adequate rectal cancer operation. The rectum does not have a true mesentery and only its anterior and anterolateral parts are covered by peritoneum. However, there does exist a clear visceral envelope that encloses the mesorectum laterally and posteriorly. This visceral layer is separated from the lateral pelvic fascia by a distinct layer of areolar tissue. In the posterior midline, the pelvic fascia visceral envelope and areolar tissue aggregate to form a dense anchoring fascia of the rectum referred to as the recto-sacral fascia or sacro-rectal ligament. As the recto-sacral fascia is sharply divided, the rest of the areolar tissue submits almost effortlessly to sharp dissection, allowing mobilization without breaching the mesorectum.

4.1.5.1 Laparotomy and Exploration

A lower midline incision with a need based extension to upper midline or laparoscopic ports for Lap TME. Explore peritoneum, liver, and other viscera for any distant spread. Assess locoregional disease and decide about feasibility for surgery. Small gut is packed in upper abdomen by using three blade abdominal retractors. Dissection is carried out in an organized manner.

Identify ureters in a bloodless field at the start. Pull the sigmoid colon upward and toward left to make its mesentry taut. Divide the peritoneum near its base lateral to sigmoid colon. Go behind in the Holy Plane by traction and countertraction (Fig. 4.1). Go for posterior dissection in this avascular Holy Plane taking care of

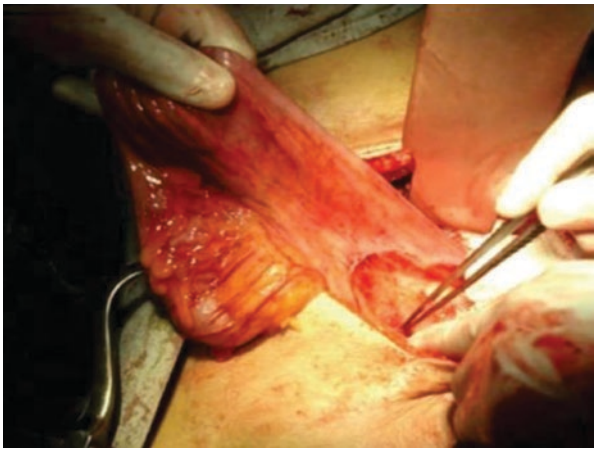


Fig. 4.1 Operative photograph showing mobilization of rectosigmoid

nerves and venous plexus. Go in a plane anterior to nerves but posterior to superior rectal artery (SRA). Create a complete window by joining both sides of lateral mesentric attachments taking care of ureters on both sides. Continue to dissect up to the level of mid sacrum (S4) level where you encounter a dense connective tissue layer known as sacro-rectal ligament. Divide the ligament by sharp dissection and then you continue dissecting till pelvic floor.

Again see left ureter and hypogastric nerves at the "V" formed by sigmoid mesocolon (bifurcation of common iliac artery at the base of sigmoid mesentry). SRA, which is a continuation of inferior mesenteric artery (IMA), is divided distal to left colic artery after skeletonization (Fig. 4.2). High ligation of IMA gets a full lymph node yield and decreases the tension on mobility of colon but can injure superior hypogastric plexus. Low ligation saves the nerve plexus from injury but may not give a good nodal yield. One can divide the vessel distal to its origin after dissecting down the nodes and skeletonizing the vessel, which serves both the purposes of plexus safety and good lymph node yield. However, whatever method you adopt, there is no effect on survival. Inferior mesenteric vein (IMV) is divided as high as possible near duodenojejunal flexure. For lateral dissection, identify the hypogastric nerves, preserve them till you reach lateral ligaments where you encounter middle rectal artery, which in a small percentage may even be absent. Lateral ligaments also contain nerves from pelvic plexus so one should come closer to rectal wall for dissection as soon as you start turning anterolateral and take away seminal vesicles by retraction to preserve autonomic nerve plexuses at 11 and 2'o clock position around rectum. Go between two layers of Denonvilliers' fascia and with St Marks retractor go for anterior dissection under proper light. In anterior dissection, you can use cautery taking care of bleeders after opening the pouch of Douglas and avoiding any injury to posterior wall of vagina in females. Cut sigmoid colon proximally using Zachary cope 3 bladed clamp to avoid any spillage. Lift the cut end of mobilized

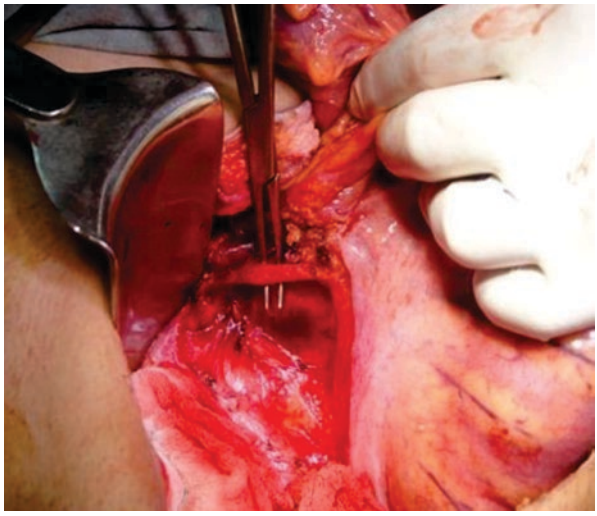


Fig. 4.2 Skeletonization of IMA

rectosigmoid and look for any further 3-dimensional mobilization and hemostasis. Before going for anastomosis, ensure complete mobilization and complete hemostasis. Sometimes, you may need even to mobilize splenic flexure of the colon to gain sufficient length for anastomosis. An objective parameter used in our setup is that if lower end of mobilized colon should be 6 cm from pubic symphysis, then it can reach down for any anastomosis comfortably (Figs. 4.3 and 4.4).

The rectum is divided at the level of the levators. At this level, there is no further mesorectum and the rectum is largely seen as a muscular tube. Cut rectum with the help of a roticulator/access 55/contour/contour or endostaplers at the level of levators. Examine the excised TME specimen for any breaks in the envelope. Tell your assistant to cut open the specimen longitudinally to examine macroscopically the distal margin, which ideally should be more than 2 cm (Fig. 4.5). An occlusion clamp is applied proximal to the stapler, and the rectum is divided on the stapler with a knife before releasing the stapler. Injury to autonomic nerves during total mesorectal excision is quite likely. The four areas described as most vulnerable to operative injury are the (1) origin of the inferior mesenteric artery, (2) anterior to sacral promontory, (3) lateral walls of the pelvis, and (4) postero-lateral corners of the prostate (Acar and Kuzu 2012).

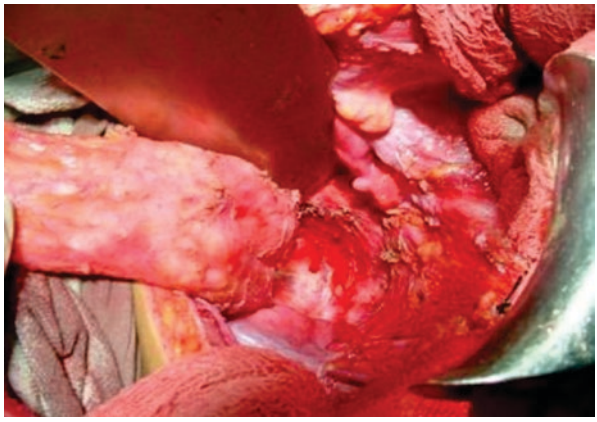


Fig. 4.3 Posterior mobilization in Holy Plane

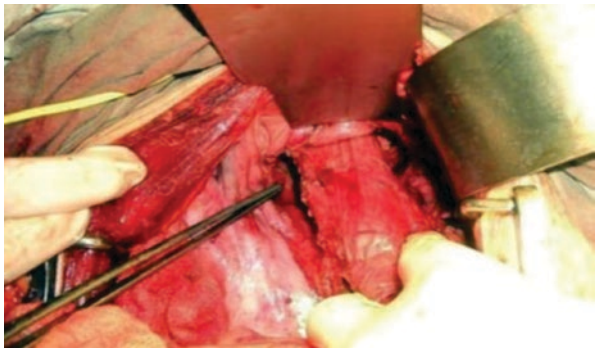


Fig. 4.4 Operative photograph showing anterior dissection

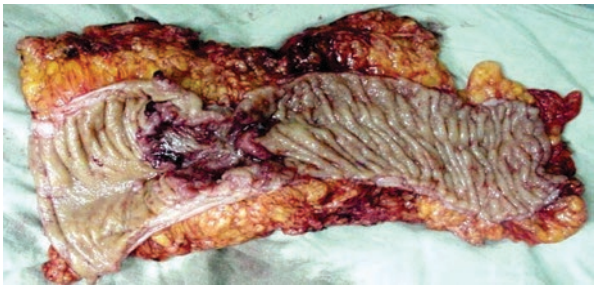


Fig. 4.5 TME specimen cut open to examine distal resection margin

4.1.5.2 Anastamosis

Anastamosis using stapling devices is the current standard for low anterior resection. Although a sutured anastomosis is technically feasible, stapled anastomosis is more consistent, ergonomically superior, and is easier to teach or learn. Stapling is a skill and practicing the correct technique is essential to ensure proper reconstruction. The colon is anastomosed to the rectum either as

- Straight colorectal anastomosis
- End to side anastomosis
- Colonic J pouch rectum anastomosis
- Coloplasty pouch anastomosis

For straight colorectal anastomosis, the anvil of CDH stapler is disengaged and put in colonic limb with the knob outside. The anvil is fixed with a 1° Prolene purse string suture in the colonic segment. The assistant goes between the legs of the patient and gently dilates the anal canal with two fingers using 2% xylocaine jelly. Then CDH is put in rectal stump, and the knob is rotated to get the pointed trocars pierce the stapled rectal stump till you see the orange mark becomes visible. Engage the trocars with the locking spring mechanism of the anvil till you hear a click, ensuring that the assembly is locked. Now keep on closing the adjustment knob till one notices a green mark in the firing indicator window. Disengage safety lock and ensure before firing that you have not taken any surrounding structures like vaginal wall, bladder, or ureter in the staple. Also check the orientation of the bowel loop. Fire the stapler under vision. Hold the fired stapler for 2 min to ensure better hemostasis. For disengaging the stapler, make two complete unlocking rotations of the knob and remove the stapler gently by fishtailing movements of the stapler. Examine the donuts for their completeness and send them for histopathological examination after properly labeling them. The pouch is actually a short J pouch with a 6- to 8-cm limb. For further details about colonic J pouch, please refer to our open access book chapter in rectal cancer book published by Intech publishers and the section on neorectum to follow in this book (Parray et al. 2011). Coloplasty pouch anastomosis is more physiological, easy to construct. For further details, refer to our publication on coloplasty (Parray et al. 2014). Anastomosis is tested by an air leak test after

filling the pelvis with saline. Repair or a complete takedown and re-anastomosis are indicated only in very large leaks. A small leak is taken care by a proximal diversion. The choice of diversion in the absence of a leak is trickier. Centers with a high volume of low anterior resections are more selective in the use of proximal diversion. Most other surgeons routinely perform a proximal diversion by a loop ileostomy. The loop ileostomy is closed after 6–8 weeks after confirming the integrity of rectal anastomosis and patency of distal loop by a water-soluble contrast study. One should not forget to do a routine digital rectal examination (DRE) to assess the patency of anastomotic site before planning a closure. Our routine is to do a diversion ileostomy for any anastomosis, which is lower than 6 cm from anal verge or wherever we have some risk factors like incomplete donuts, tension on anastomosis, obesity, or a narrow pelvis. The loop ileostomy can be closed with the use of staplers or hand sewn anastomosis. In our set up, we routinely close it with staplers using a purse string closure for skin with 1° Prolene, which heals with a minimal scar.

However, the operating surgeon should be well trained and acquainted with the use of various types of staplers. The circular stapler commonly used for colorectal or coloanal anastomosis is 29, 31, or 33 mm. For ensuring a very low catch at least 4 cm beyond malignant lesion in a low rectal cancer, one should use a roticulator, contour, laparoscopic endo stapler, or access 55. By taking it at least 4 cm down, you can then ensure at least 2 cm resection margin distally as 2 cm are usually lost in accommodating the instrument in the lower reaches of pelvis. For constructing a neo reservoir like J pouch, we can use green 55, 60, or 75 mm cartridge and ensuring a 5–7.5 cm long limb and at the same time ensuring the hemostasis on the staple line, which many a times may need a running hemostatic suture with an absorbable suture. The advantages of the stapled anastomosis are

- Easy to perform
- Double layered
- Less time consuming
- Standardized technique
- Increasing the possibilities of a sphincter saving procedure

The staplers at times may give problems like

- Failure to fire
- Unzipping
- Bleeding and hematomas from staple line
- Perforations
- Entangling other structures like vaginal wall, urinary bladder, or small bowel, which may later on present with unpleasant fistulae and lead to increase in morbidity and mortality
- Anastomotic stricture at a later date, which may present with features of subacute intestinal obstruction or painful defecation

Such patients will need a regular dilatation with anal dilators under local anesthesia to achieve a comfortable dilatation. In some patients, the anastomotic stricture may be so tight that it needs dilatation under general anesthesia or a formal repair like a stricturoplasty. The obstruction following a stricture at times may be so severe that you will have to resort to a temporary stoma followed by a definitive repair at a later date.

A very important thing to do after TME surgery is to examine your excised specimen for the completeness by examining the mesorectal surface.

4.1.5.3 Complete/Mesorectal Plane

In this type of specimen, the mesorectal surface is smooth with minor irregularities in surface not more than 5 mm in size. The specimen does not show any type of coning near the tumor site. The bulk of mesorectum is good anteriorly and posteriorly.

4.1.5.4 Nearly Complete/Intramesorectal Plane

Here, the mesorectal surface is irregular. It has irregular surface, but muscularis propria is not visible except near levator ani insertion. The bulk of mesorectum is moderate, and there is moderate coning of the specimen distally.

4.1.5.5 Incomplete/Muscularis Propria Plane

In this type of specimen, the mesorectum bulk is very less. The surface of mesorectum is irregular with lots of irregularities extending up to visible muscularis propria.

Even though this may not be a fool proof way to examine the specimens because of the fallacies like lack of good bulk of mesorectum anteriorly or improper identification of fascial planes. Also the surgeons may try to examine his specimens always some amount of bias and overrate his surgeries to some extent. The best way to improve your quality of TME surgery is to get yourself audited by a pathologist about the completeness of specimen and by a radiologist on a later date by getting a check MRI done. This is a routine that we usually follow in our system, and this really works over a period of years to improve the quality of surgery.

4.2 Complications of TME

Even though TME is considered to be an oncologically correct procedure for carcinoma rectum, many times the innovations in surgery always come at a cost like increased anastomotic leaks, higher incidence of low anterior resection syndromes, sexual and urinary dysfunction, long operative time, and poor results in elderly.

4.2.1 Anastomotic Leaks

Removal of whole of mesorectum in TME makes the anastomotic site less prone to healing and more prone to leaks; the lower the anastomosis, greater are the chances

of leak. Literature reports a leak rate of more than 20%, even though partly some leaks may be related to learning curve period of surgeons (Carlsen et al. 1998). Law and Chu in 2004 in his prospective study on 622 patients concluded that any rectal cancer treated by a TME is more complex technically and has a higher leakage rate (8.1% vs 1.3%; $p < 0.001$) than that of partial mesorectal excision (PME), which provides adequate mesorectal clearance in higher tumors with same survival and local control. Besides significantly longer median operating time, more blood loss, and a longer hospital stay were found in patients with TME. The overall operative mortality and morbidity rates were 1.8% and 32.6%, respectively, and there were no significant differences between those of TME and PME. Anastomotic leak occurred in 8.1 and 1.3% of patients with TME and PME, respectively ($p < 0.001$). Independent factors for a higher anastomotic leakage rate were TME, the male gender, the absence of stoma, and the increased blood loss. Even though the increased leak rates in males can be because of technically difficult anastomosis in narrow pelvis. Diversion stoma in any anastomosis below 6 cm is worthwhile and greatly helps in decreasing the leak rates.

4.2.2 Low Anterior Resection Syndrome (LARS)

LARS is a collection of symptoms seen in patients after resection of entire rectum or part of it and is characterized by urgency, frequent bowel movements, emptying difficulties, and incontinence and even at times no stool for a day or two and then numerous bowel movements another day and/or increased gas. Factors that predispose to LARS are low anastomosis, straight anastomosis, nerve injury, or use of radiotherapy. The pathophysiology is a complex of anatomical, sensory, and motility dysfunction. Many of these patients can be addressed by avoiding a straight anastomosis or making a neo reservoir by fashioning a J Pouch or coloplasty, which is discussed in detail in next chapter (Emmertsen et al. 2014).

4.2.3 Sexual and Urinary Disturbance

This used to be a major concern in the early years after the TME was practiced. The close proximity of autonomic nerves and plexuses supplying urinary bladder and sexual organs would always make patients more prone to have problems of urinary dysfunction, erectile dysfunction, or retrograde ejaculation. With more and more stress laid on the importance on identifying the plexuses and nerves, which is discussed in the later part of this chapter, negotiation of learning curve, use of better magnifying gadgets, laparoscopy and robotic surgery, the visualization of these nerves has improved under magnification; hence, the incidence of these complaints is decreasing.

4.2.4 Long Operation Time

The anatomy of pelvis always comes in the way of surgeon as an obstacle as soon as he has to dissect lower and lower; obviously the difficulty is more in a narrow pelvis. Dissecting for a low anterior resection or ultra low resection with sharp dissection at times is a neck breaking and time-consuming exercise in open TME; even though the problem of seeing in depths improves remarkably in laparoscopy and robotic, still it is going to take long operation hours than PME.

4.2.5 Elderly Patients

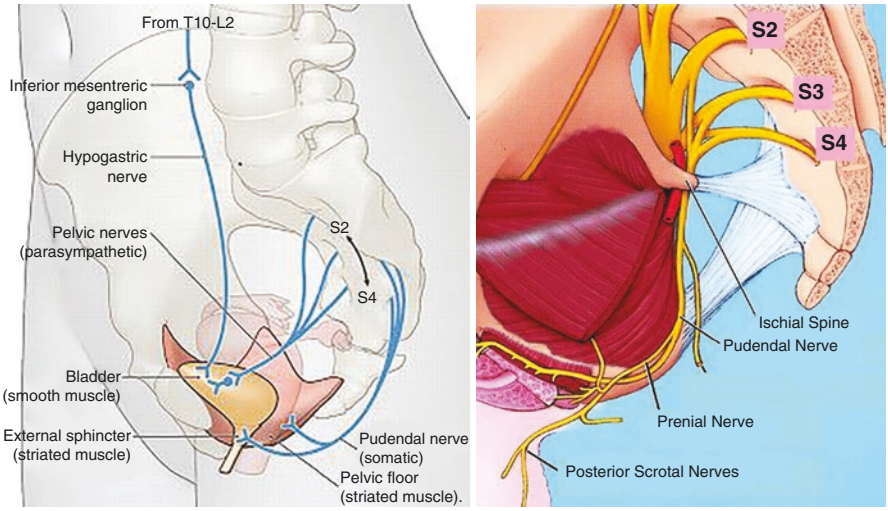
Patient assessment by the operating surgeons is very important before surgery by doing a digital rectal examination. It gives us an assessment of the location, size, mobility, luminal compromise, and the sphincter tone. Very often an extensive procedure like TME is selected for a patient with a low anal tone, which ultimately gives disastrous results. The patients with a sphincter saving procedure almost behave like a perineal colostomy because of frequency and soiling, which is quite distressing for the patient. This problem is quite frequent in elderly age group who most of the time will suffer from the low sphincter tone and TME may yield disastrous results.

Role of laparoscopy and robotic surgery will be discussed in detail in separate chapters.

4.3 Total Mesorectal Excision with Pelvic Autonomic Nerve Preservation in Rectal Cancer (TME with PANP)

TME with PANP is in fact not a separate entity. TME procedure in itself encompasses nerve preservation. In reality, most of the surgeons in the learning curve of TME will forget to focus on nerve preservation. It is usually after mastering the technique that colorectal surgeons then start going to the next step of pelvic autonomic nerve preservation. By defining this entity separately as TME with PANP automatically will motivate more and more surgeons to learn the synchronous craft of TME with nerve preservation, which will definitely help many patients not to become sexual cripples. Hojo and Moriya from Japan were the pioneers to introduce the concept of autonomic nerve preservation to urogenital organs (Figs. 4.6 and 4.7) (Hojo et al. 1991; Moriya et al. 1995; Yasutomi 1997). This was further popularized by an American Surgeon Enker who blended the concept of TME with nerve preservation. His studies showed an overall preservation of sexual function in approximately 90% patients. He also reported an excellent oncological outcome in his studies (Enker 1992; Havenga and Enker 2002).

Even though nowadays many surgeons undergo training in high volume colorectal centers to learn the craft of TME with nerve preservation, in spite of that sexual dysfunction, bladder disturbances and fecal incontinence continue



Figs. 4.6 and 4.7 Surgical anatomy of pelvic nerves

to be problems of concern in a small percentage of patients (Rees et al. 2007; Vironen et al. 2006). We undertook a study at *Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, J&K, India in Colorectal Department* on prospective basis. The study comprised of 47 male patients of carcinoma rectum (4–12 cm from anal verge). The incidence of overall sexual dysfunction at 3 months post surgery was 30.23%. This decreased to 8.5% at 1 year. Incidence of erectile dysfunction functions, i.e., 37.20% at 3 months decreased to 10.7% at 1 year (Dar et al. 2016). The main aim of the colorectal surgeon while performing TME should be to go in the real avascular Holy Plane and at the same time trying to identify the plexus and pelvic nerves after a meticulous sharp bloodless dissection. Laparoscopy is definitely a superior technique in identifying the nerves because of magnification; however, in open technique, a routine use of an optical loop will be a great help in identifying the pelvic nerves with more confidence. In spite of all the modern gadgets, what is of prime importance is that the surgeon at the helm of affairs keeps himself abreast with the knowledge of surgical anatomy and at the time of surgery is aware about the areas where he has to exercise precautions in order to save a nerve injury like some of the areas mentioned earlier. The emphasis again needs to be laid in this part of chapter that injury to superior hypogastric plexus or hypogastric nerves can be prevented by avoiding a high ligation at the root of IMA. Similarly one needs to be careful in lateral dissection in the area of 11 and 2'o clock position to avoid injury to inferior hypogastric plexus and efferent nerves. The best way to prevent the damage at these positions is to come close to rectum during dissection. In perineal dissection in APR, we can should try to take care of pudendal nerves, which can get damaged indirectly (Moszkowicz et al. 2011).

4.3.1 Intraoperative Neuromonitoring

It is an emerging technique. Early reports suggested that the use of neuromonitoring during TME is associated with significantly lower rates of urinary and anorectal dysfunction (Kneist et al. 2013).

4.3.2 Nerve-Oriented Mesorectal Excision (NOME)

It is described as a novel technique wherein autonomic pelvic nerves serve as landmarks for a standardized navigation along fascial planes. This is claimed to achieve high-quality mesorectal specimens and a high rate of preservation of autonomic nerve function. NOME achieves high-quality mesorectal specimens and an excellent quality of life by avoiding damage to autonomic nerves.

The key steps are

- Preparation of the splanchnic nerves at the mid-posterior sidewall
- Hypogastric nerves at the upper sidewall
- Urogenital nerve branches (Walsh) at the caudal-anterior sidewall
- Dissection of the lateral ligament is strictly performed as the last step

The concept of using nerves as laparoscopic landmarks may help to standardize and master laparoscopic rectal cancer surgery (Runkel and Reiser 2013).

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Neo-Reservoirs in Rectal Cancer

5

Fazl Q. Parray, Mushtaq A. Laway, and Shaheem Parray

Abbreviations

APR	Abdomino perineal excision
ARS	Anterior resection syndrome
LAR	Low anterior resection
LARS	Low anterior resection syndrome
PME	Partial mesorectal excision
QOL	Quality of life
TME	Total mesorectal excision
ULAR	Ultralow anterior resection

Sphincter saving surgeries in patients of carcinoma rectum was seen as a major technical advance of recent years. These surgeries like low anterior resection (LAR), ultralow resection (ULAR), coloanal anastamosis, partial mesorectal excision (PME), and total mesorectal excision (TME) not only improved survival but also decreased grossly the local recurrence rates. Besides, the fear associated with

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having a permanent stoma with surgeries like abdomino perineal resection (APR) also got decreased and this indirectly lead to increased acceptability for sphincter saving surgeries. The psychosocial fear associated with a permanent stoma would even refrain many patients coming forward for the treatment. The sphincter saving surgeries became more popular with the newer generation of circular staplers which made anastamosis technically possible in inaccessible areas of pelvis. Nowadays, many patients who are subjected to sphincter saving surgeries would have been definitely subjected to a sphincter sacrificing surgery just two decades back. In surgery most of the new technologies develop at a cost and at a price. The price patients have to pay for sphincter saving surgeries is in the form of buying staplers and facing problems like anterior resection syndrome (ARS) or low anterior resection syndrome (LARS) which at times may grossly deteriorate their QOL but all this has been accepted very gracefully with the benefits of radical cure of carcinoma and an improved psychosocial image by a stoma free life. In order to get rid of ARS or LARS secondary to loss of rectal reservoir a new thought process for the formation of a neo-reservoir was felt.

5.1 Anterior Resection Syndrome (ARS); Low Anterior Resection Syndrome (LARS)

Loss of a natural reservoir (rectum) after sphincter preserving surgeries after rectal cancer is a significant loss. This loss reservoir in many patients manifests in the form of a complex problem known as ARS or LARS which may present with increased stool frequency, increased urge, difficulty in evacuation of stools, increased soiling of under garments, feeling of incomplete evacuation, and many associated functional disorders. This anorectal dysfunction is usually quite frustrating for the patient in the first year of adaptation (Lewis et al. 1995; Miller et al. 1995). Even though this complex disorder is an established entity for many years but till date no standard definition is established. A very acceptable and pragmatic definition to this entity was given by Bryant et al. as "disordered bowel function after rectal resection, leading to a detriment in quality of life" (Bryant et al. 2012). In most patients these symptoms gradually start improving toward the completion of 1 year and steady state is achieved by 1–2 years postsurgery. The symptom complex has a significant impact on QOL of these patients. In many studies severe bowel function disorder was observed in up to 75% patients on a long-term follow-up after low anterior resection (LAR) (Hallbook and Sjodahl 2000; Bryant et al. 2012; Fazio et al. 2007).

Anorectal manometry studies in these patients frequently showed reduced anal tone, loss of rectoanal inhibitory reflex (RAIR) (Iwai et al. 1982), and reduced rectal compliance (Batignani et al. 1991). Alteration of rectal volume primarily effects rectal compliance, hence the symptoms. The studies which aimed at investigating the urgency and incontinence in patients of ARS/LARS depicted a wide variation in the range of 4–68% (Oya et al. 2002) and similar variation in the range of 2–74% were reported for evacuation difficulties, incomplete emptying, and clustering (Bryant et al. 2012). Some of the studies have tried to address issues like QOL after various types of surgeries for carcinoma rectum and better QOL was observed in

patients of sphincter saving surgery than in patients subjected to a permanent stoma (Pachler and Wille-Jorgensen 2005). These observations, however, on QOL did change in anastamosis as low as 6 cm from anal verge; even though in areas of body image and sexual performance, sphincter saving procedures still scored better but these lower scores are balanced better in symptom, cognitive, and social scores (How et al. 2012).

5.2 Management

5.2.1 Conservative

Patients with ARS/LARS at times are quite difficult to manage conservatively; however, the attending surgeon should have some important considerations on mind which should be excluded in these patients:

- Recurrence of an excised tumor
- Pelvic sepsis
- Chronic constipation
- Spurious diarrhea
- Anastamotic stenosis
- Sphincter weakness

All the above mentioned conditions can at times mimic the symptomatology of ARS/LARS and one may really make a big blunder by not excluding them.

The most important step in managing patients of ARS/LARS is:

- *Reassurance about adaptation*: Patients should be explained that these symptoms are going to settle over a period of approximately 18 months till the colon adapts to new changes after surgery and takes over as reservoir (Ho et al. 2001).
- *Dietary Advice*: Avoid foods that cause bowel dysfunction which will vary from patient to patient. Patients with increased frequency can be given codeine, bile salt binding agents or diphenoxylate to decrease frequency. Laxatives or enemas are given to patients with problems of rectal emptying.
- *Biofeedback*: Some of the patients who show no response to reassurance or dietary modification should be referred for biofeedback. Biofeedback may show successful results in such patients. This type of treatment is a special form of behavioral modification that aims to control body function (Goldenberg et al. 1980; Ho et al. 1996). Some studies on biofeedback point to possibility that biofeedback works by improving rectal and/or anal canal sensation, rectal liquid retention, and anal sphincter coordination. It is not that biofeedback only helps patients with increased frequency but has been reported to help >90% of patients with constipation following LAR (Ho and Tan 1997).
- *Surgical*

5.2.1.1 Postanal Sphincter Repair

Use of circular stapling instruments trans-anally for anastamosis inflicts permanent sphincter injuries in some patients which can be demonstrated by anorectal physiological tests and trans-rectal ultrasound. Some of these patients may present as intractable type not responding to any conservative treatment. In these patients a postanal sphincter repair is recommended. The studies conducted in these patients after repair have shown a marked improvement in stool frequency and continence (Ho 2001).

With the recent advent of bulking agents implanted intersphincterically by injection, another option for managing internal sphincter injuries in patients after low anterior resection is now available. Clinical studies are awaited.

Most important precaution which can be taken is prevention rather than treatment. This prevention can be in the form of a replacement of reservoir surgically, hence a need for an artificial neo-rectal reservoir was felt in order to get rid of these distressing symptoms of ARS/LARS, and the reservoirs designed from time to time to get rid of these distressing symptoms are described as under:

5.2.1.2 Colonic J-Pouch (CJP)

In order to give relief to patients from these distressing symptoms Lazorthes et al. and Parc et al. in 1986 presented the concept of neo-reservoir to the world. They designed the neo-reservoir by making a J shaped pouch from the last part of colon which may be sigmoid or descending colon and it is popularly known as "Colonic J-Pouch" (CJP). This CJP was found to improve the quality of life (QOL) in patients of carcinoma rectum; however, it cannot be considered to be an equivalent of a natural reservoir (Parc et al. 1986; Hida et al. 1996). Other Pouches like S, W can also be used but J-pouch is more popular because of technical ease of construction. The neo-rectal reservoir in the form of J-pouch would be of benefit to patients of low and mid-rectal cancer with T2/T3 lesions or T3/T4 after down-staging with neo-adjuvant treatment. This procedure however is contraindicated in patients with a poor sphincter tone, pregnancy, poorly differentiated cancers, locally advanced carcinomas, and narrow pelvis (Parray et al. 2011).

Technical Considerations

After performing the sphincter saving surgery mobilize the descending colon to an extent that its lower end can go 6 cm beyond symphysis pubis in downward direction.

Pouch will invariably reach pelvis comfortably but in some patients you observe difficulty because of:

- Obesity
- Adhesions
- Inadequate mobilization
- Thick mesentery
- Short vessels
- Small gut resection

For gaining this length, many maneuvers like:

- Mobilization of splenic flexure,
- Making windows in mesentery,
- Skeletonizing vessels, or
- Cutting vessels under tensions (after clamping them in vascular clamps and ensuring that there are no color changes in gut)

Advantages

- It saves a patient from anterior resection syndrome in the first year after surgery.
- The pouch can be constructed with a 60- or 80-mm linear cutter or hand sewn.
- Anastamosis in a pouch is end to side so has better vascularity and lesser leak rates.
- Pouch limbs occupy the dead space in the pelvis; hence decrease the chances of pelvic collection.
- Small gut coils may not get enough place to migrate in pelvis, hence makes them less prone to radiation injury during adjuvant treatment and adhesion obstruction.
- Only problem with the pouch can be evacuation difficulty which again is not seen much with smaller pouches with 6–8 cm limbs.

Technique

J-pouch is made by folding the last part of the colon in the form of 2 "J" limbs. Each limb should be 6–8 cms long. Put 3 stay sutures in the J limbs at two apices and in the center and hold them in clips to have the limbs in proper orientation. Make a small colostomy at the base of J and push two limbs of disengaged linear stapler in the two limbs of gut. Engage the two parts of stapler ensuring that mesentery of the gut is pushed down and does not impinge in the area to be stapled. Ensure proper approximation of the linear stapler and fire in one go and come back. Hold on the stapler for some time to cause some compression on the bleeders of cut ends. Disengage the stapler and examine the inside for any bleeding. If there are any oozers, overrun them with 3° catgut (Fig. 5.1). The same colostomy site is used for pushing in the anvil of

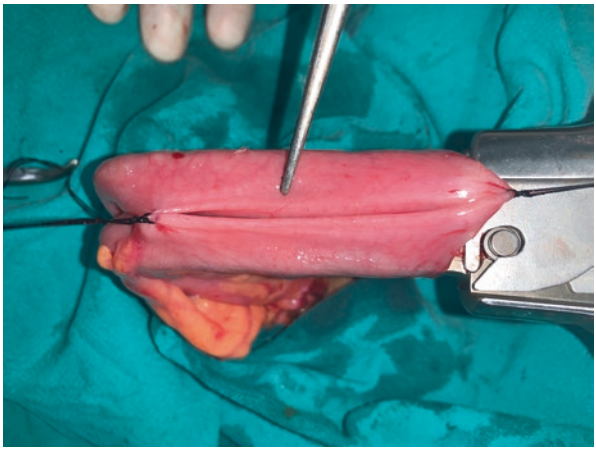

Fig. 5.1 Linear stapler for J-pouch

circular stapler (CDH/CEEA). Fix it in the colotomy with 1° prolene. Push closed circular stapler in the anal canal after using 2% xylocaine and dilating it with two fingers. Now ensure that the circular head is abutting against stapled line. Select anterior or posterior to staple line, the appropriate place of entry of the knob. Now start opening the rotator cuff till pointed knob pierces the rectum and you see the orange cuff on the knob from abdominal side. Assemble the anvil and knob by engaging them with each other till you hear a click of spring loaded self-lock (Fig. 5.2). Continue closing the knob till you see the green line appearing in the gap setting scale of circular stapler which indicates the proper approximation of the abdominal and rectal tissue. Disengage the safety knob and fire the stapler. Hold it for 2 min for compressing the oozers. Release the pressure and unlock the knob. Make two complete 180° turns of the knob before removing the stapler from the anorectum with fish-tail movements. Examine both the doughnuts for completeness. Send the resected specimen and two doughnuts for histopathological examination (HPE) after labeling the proximal and distal doughnut. Ideal would be to send the last upturned part of J as upper doughnut as that is the representative part of proximal doughnut in a J-pouch and not the one which we routinely sent from the bottom of J. Perform a leak test by filling the pelvis with saline and inject air per rectum. Look for any air bubbles in pelvis. Cover it with a temporary stoma in case of any doubt about leaks and for very low anastamosis as leak rates are quite high for very low anastamosis.

We prefer to cover all anastamosis below 6 cm from the anal verge with a covering Ileostomy. However, the literature does not prove that covering stomas can decrease the leak rates but the contents of the leak vary after the covering stoma which saves the patient from developing fecal peritonitis in case of any leaks from the anastamosis. In the postoperative or follow-up period, a contrast study of J-pouch is done with water soluble contrast media to know about the shape, angulations, and any leaks in the J-pouch (Parray et al. 2011). Our experience with colonic J-pouch has been very encouraging and we have been continuously performing this procedure whenever indicated for last more than 12 years.

A J-pouch can also be constructed after total proctocolectomy for diseases like familial adenomatous polyposis or ulcerative colitis. In these patients' terminal loops of small gut with 12–15 cm limb length are used for construction of J-pouch

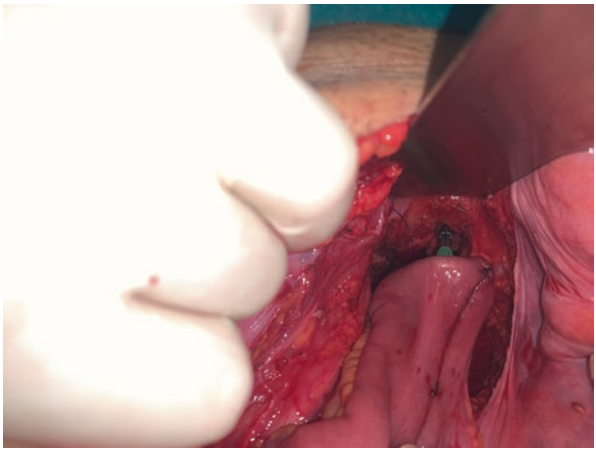

Fig. 5.2 CDH engaged

and thus is called an ileal J-pouch. Here it would be beyond the scope of this chapter to go in the details of this topic.

Complications

- Evacuation Problems
- Leaks from anastamosis
- Anastamotic Strictures
- Pouchitis (Ileal Pouch)
- Pouch Failure

Evacuation problems are usually seen in patients where you try to make J limbs more than 8 cm. Besides, the advantage of a reservoir, pouches have less leak rates because of end-to-side anastamosis. We also prefer to fix the pouch with two stitches to presacral fascia to prevent the horizontal angulations during the act of defecation which may lead to failure of pouch evacuation.

Long-term follow-up should continue on the lines of carcinoma rectum and colo-anal anastamosis should be assessed in follow-up with digital rectal examination (DRE) for any stenosis or strictures and if any such tightness is detected early, it can be addressed by regular anal dilatations. Pouch evacuation failures may at times need supportive treatments like laxative suppositories, oral laxatives, pouch irrigation or manual evacuation, or very rarely pouch excision.

In most of the patients this is a very well accepted procedure with quite less frequency of ARS and better QOL.

Even though CJP is getting quite popular as a neo-reservoir, still some surgeons feel quite skeptical about its routine use apprehending its outcome and evacuation problems. But most of the literature suggests that CJP is a safe procedure as it has produced better functional outcome, decreased anastamotic leak rates, decreased stool frequency, and given better continence to patients (Dennett and Parry 1999). Decrease in leak rates automatically decreases the incidence of anastamotic strictures. Besides, it is always wise to ensure that there is no tension on anastamosis by ensuring a good vascularity of ends to be anastamosed, sound technique, and avoiding any tension on anastamosis. Tension can be decreased by complete mobilization of the splenic flexure of colon and blood supply is improved by use of colonic J-pouch as was proved by the use of laser doppler flowmetry during surgery (Hallbook et al. 1996).

Most of the time surgeons prefer to use descending colon for construction of J-pouch. Evidence suggests that sigmoid colon can cause excessive functional problems for being a high-pressure segment and is more prone to develop severe motility dysfunction (Seon Choen and Goh 1995). Sigmoid colon is also more prone to diverticulosis, hence not suitable for anastamosis or pouch formation. Besides, high ligation of inferior mesenteric artery may render the sigmoid colon ischemic and not fit for use.

The comparative studies have proved time and again that colonic J-pouch has the inherent disadvantage of decreased daytime and nocturnal frequency of bowel as compared to straight anastamosis. The stool frequencies may vary from 1 to 6 when the patients with colonic J-pouch are assessed on follow-up on 1 month, 3 months,

and at 1 year (Lazorthes et al. 1986; Parc et al. 2011). This was further substantiated by studies of Ho et al., Seon Choen et al., and Nicholls et al. Harris et al. in their study found that the median frequency of bowel movements at night time was zero in the CJP patients compared to SA group. This was at 0–4 years and 5–9 years duration on follow-up. Routine work schedule in the busy life makes it imperative for the person to be able to hold his stools for some time till he finds a toilet to ease out. Inability to do so has its own social and psychological stigmas. Even though still the consensus does not exist whether one should make a CJP routinely or can directly skip to SA. Based on the conclusions drawn from Dennet and Parry 1999 and 14 studies which report on postoperative urgency after CJP, it appears that CJP is almost a near perfect solution to postoperative urgency but Ho et al. reports no significant improvement. Incontinence is one of the major determinants of functional outcome after low anterior resection and it was found from most of the studies that continence to gases, liquids, and solids improves significantly after the construction of colonic J-pouch especially in very low rectal cancers. It was further substantiated by observing a significant difference in their composite incontinence score at 2 months and 1 year (Hallböök et al. 1996). Most of the studies definitely are in favor of a better functional outcome with CJP as compared to SA especially when the rectal cancer is of low variety and post-resection the anastamotic line is below 8 cm on DRE. For higher lesions usually the lower or some part of mid-rectum may be preserved hence the reservoir is not needed and the functional outcome may not show any advantage over SA (Table 5.1).

Table 5.1 Functional outcome after coloanal J-pouch anastomosis (Dennett and Parry 1999)

Author	Num	Stool freq/24 h	Continent no. (%)
Lazorthes et al. Pouch Control	15 36	1.7 ± 0.67 3 ± 1.25	12 (80) 28 (78)
Cohen Hallbook et al. Pouch Pouch Control	23 42 47	• 4 2 (1.3–2.3) Median (interquartile range) 3.5 (2.4–4.50)	19(83) [a] [a]
Hida et al. (5 cm) Pouch (10 cm) Pouch	20 20		[a] [a]
Lazorthes et al. (6 cm) Pouch (10 cm) Pouch	14 17	1.8 ± 1.1 2 ± 1.6	8 (57) 12 (70)
Joo et al. Pouch Control	26 30	2.4 ± 1.3 4 ± 2	[a] [a]

Unless otherwise stated the stool frequency is mean (range) or ± standard deviation
Values that are statistically significant
Num = Number; Freq = Frequency
[a]A functional score is given for continence is given rather than raw data

Colonic Reservoir

Even though many surgeons may outrightly reject the formation of pouches but the evidence from meta-analysis (Heriot et al. 2006) suggests that CJP after anterior resection has significant functional advantages over SA and this persisted over time and seems to be the procedure of choice.

Another study on *colonic J-pouch anal anastomosis* after ultralow anterior resection proved that colonic J-pouch anal anastomosis decreases the severity of fecal incontinence and improves the quality of life (Park et al. 2005). One study compared colonic J-pouch versus coloplasty following resection of distal rectal cancer and found similar functional results in the coloplasty group compared to the J-pouch group (Fürst et al. 2003).

Problems with CJP

Surgeons need proper training before adopting any new procedure in order to avoid on table technical snags, failures, and complications. Many a times surgeons try new procedures in technology boom without properly learning them in animal laboratories which is a dangerous trend and puts their patient at a greater risk which may at times be life threatening. We should also take learning curve into consideration as rectal cancer surgeries as such are technically demanding procedures. The problems are further compounded in presence of obesity, narrow pelvis, redosurgery, and low rectal cancers. Hence all surgeons go through a long learning curve to master these procedures and then only they should think of going for any further advances like CJP or coloplasty. Patient selection is very important from technical point of view. In case you have selected a very obese patient with previous adhesions, narrow pelvis, bulky sphincters, or diverticulosis, you will definitely get discouraged to adopt the procedure; hence a proper patient selection especially in the initial days is very important. Volume of the center is one of the biggest contributory factors which can make you to master a particular surgery. Ideal pouch size would be a 5 cm limb to get rid of evacuation problems. We believe this size compromises with the neorectal volume, hence we prefer a limb of 6–8 cm which balances between the volume and evacuation.

Evacuation problems—arise because of the peristaltic wave to other limb of J rather than going in the direction of anal canal. The problem gets further aggravated by the long size of a limb, so the remedial measures are already discussed in the preceding paragraph. Besides these patients may many a time need the support of a bulk laxative to facilitate the evacuation. Horizontal angling of the pouch during the act of defecation can become another contributory factor in failure of pouch evacuation; however, this problem can be overcome by fixation of the pouch with presacral fascia. Technically, CJP may not be possible in all patients. Many factors like thick mesocolon, adhesions, failure to gain adequate length, narrow pelvis, poor vascularity may pose some technical difficulties to construct a pouch.

Pouch failure—Some pouches inspite of a good construction may fail to evacuate and inspite of the support of enemas and laxatives may not be helped so may need a revision surgery in the form of APR.

Cost factor—This continues to be a concern in resource poor countries. The staplers cost a good bit of money which still is out of reach of the most in this part of globe.

Is CJP a Gold Standard?

As per the evidence present in literature at present, CJP still cannot be considered a gold standard. It will need larger trials and long-term follow-up. Many surgeons still believe that there are only some perceptible differences seen between CJP and SA patients in the first year of adaptability, and then both groups almost behave in the same manner.

5.2.1.3 S Pouch

Usually most of the colorectal surgeons will prefer to construct a J-pouch because of the technical ease. Rarely, a surgeon is encountered with problems of tension on a planned J-pouch anastamosis in spite of all maneuvers of mobilization and gaining length. The S-pouch can reach up to 2–4 cm further compared with a J-pouch, so it is usually created if there is excessive tension in the anastamosis. An S-pouch is constructed using three limbs of 6–8 cm of colon for each limb with a 2-cm exit conduit. The colonic segments are approximated by continuous seromuscular sutures. An enterotomy is performed in an S shape. Continuous running full thickness sutures or staplers are applied to the two posterior anastamotic lines. The anterior wall is closed with continuous seromuscular sutures or staplers. It is then reinforced using interrupted sutures. Same type of pouch can be made from terminal part of small gut for disorders as described earlier but again it is not relevant to describe the details of S Ileal Pouch in this chapter. Since the construction of this pouch is technically a little difficult and time consuming so it did not gain much favor with surgeons.

5.2.1.4 Transverse Coloplasty Pouch (TCP)

In spite of all the methods of mobilization mentioned above, one may still come across a patient where it will still be not feasible technically to construct a J- or S-pouch; in those cases we prefer to use a coloplasty pouch. This concept of construction of neo-rectal reservoir was given by Z'graggen K and his colleagues in 2001. They introduced a technically simpler transverse coloplasty pouch (TCP), a novel pouch which has a much smaller capacity than J-pouch but is more physiological.

Z'graggen et al. in their study confirmed the safety of transverse coloplasty pouch after low anterior resection. Their study showed a favorable early functional outcome following TCP with avoidance of late evacuation problems seen with colon pouch (Z'graggen et al. 1999, 2001).

Technique

After performing a sphincter saving procedure, last segment of resected colon is selected for the construction of this novel pouch. About 5–6 cm proximal to the cut

end, a colotomy is made. The colotomy is 8 cm long and is ideally between the two taenia (Fig. 5.3). Two stay sutures are given in the center of colotomy on two sides and pulled outward which help in transverse orientation of the gut and the colotomy is then closed in a transverse fashion using 1-0 vicryl as is done in pyloroplasty, thus fashioning a reservoir (Fig. 5.4). In the distal open end of colotomy, we fix the anvil of circular stapler with 1° prolene. Circular stapler is introduced per anum and engaged with anvil. The stapler is fired to make the final anastamosis. The pelvis is filled with normal saline and air insufflated per anum blocking the colon proximal to anastamosis gently between fingers to check for any anastamotic leak. Ileostomy for temporary fecal diversion usually will allow the TCP to heal nicely and decrease leak rates.

Advantages

- It is technically easier to construct
- Problems of evacuation are quite less
- More physiological
  - (Parray et al. 2014).

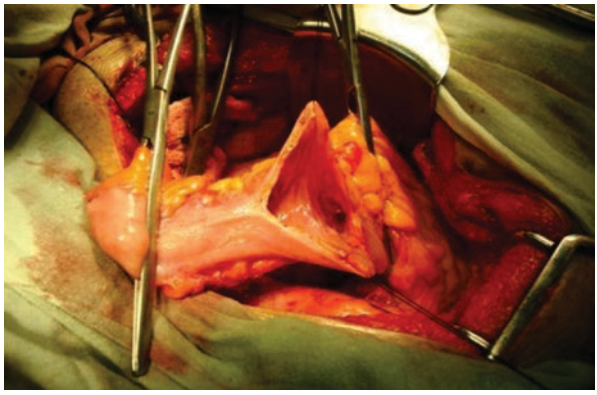

Fig. 5.3 Colotomy made (8 cm)

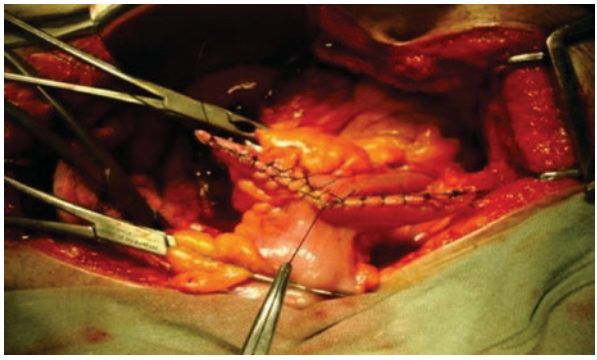

Fig. 5.4 Transverse coloplasty pouch

Disadvantages

- Anastamosis is end to end so leak rates are more
  – (Parray et al. 2014).
- Colotomy becomes one more area for potential leak

However, the meta-analysis of the colonic J-pouch versus transverse coloplasty pouch after anterior resection for rectal cancer does not support any study of increased leak rate in coloplasty and report similar results for both the procedures and suggests the use of coloplasty as a useful alternative to J-pouch because of its safety, less time consumption, and technical ease (Liao et al. 2010).

TCP reconstruction after rectal cancer resection and coloanal anastomosis is functionally similar to CJP both in short- and long-term outcomes. The TCP technique does not seem to improve significantly the incomplete defecation symptom respect to CJP (Biondo et al. 2013).

Important Considerations

- Pouches should be preferably covered with a covering or a temporary stoma for at least 6–12 weeks so that pouches heal well.
- Pouchogram is a must before closure of the stoma to rule out any obstruction in the distal segment.
- DRE is also a must before stoma closure to rule out any anastamotic stenosis or stricture.

End-to-Side Anastamosis

Colonic J-Pouch, Coloplasty, Side-to-End Anastomosis

Even though J-pouch is quite frequently used and accepted as one of the standard forms of a neo-reservoir but meta-analysis proved that CJP even though is able to obviate some of the functional problems of straight anastamosis, it comes with problems of pouch evacuation. Therefore, other techniques, such as transverse coloplasty pouch and side-to-end coloanal anastomosis, have also been adopted (Ooi and Lai 2009).

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Pathology in Colorectal Malignancy

6

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Abbreviations

APC	Adenomatous polyposis coli
BRAF	Oncogene involved in RAS signal transduction
CDX2	Homeobox gene that encodes nuclear transcription factor
CK 20	Low molecular weight keratin
CK7	Low molecular weight keratin
CRC	Colorectal cancer
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
FAP	Familial adenomatous polyposis
IHC	Immunohistochemistry
KRAS	Oncogene involved in signal transduction
MAP	Mitogen activated protein
MLH-1	Mut L homolog 1 gene
MMR	Mismatch repair gene
MSI	Microsatellite instability
MUTYH	MutY DNA glycosylase gene
P53	Tumor suppressor gene
PMS 2	Name of DNA repairing gene
SSA	Sessile serrated adenoma
TME	Total mesorectal excision
WHO	World Health Organization

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6.1 Colorectal Carcinoma

Colorectal carcinoma represents the third most common cancer in the United States. It is the third commonest cause of cancer-related deaths in the United States (Siegel et al. 2011). With advancement in the era of personalized medicine, the role of pathologists in the management of patients with colorectal carcinoma has grown from traditional morphologists to clinical consultants for gastroenterologists, colorectal surgeons, oncologists, and medical geneticists. Besides providing accurate histopathologic diagnosis, pathologists are responsible for assessing pathologic stage, analysing surgical margins, assessing prognostic markers, and therapeutic effect in patients who have received neoadjuvant therapy. Pathologists also play an important role in analysing tumors showing microsatellite instability (MSI), selecting representative tissue sections for MSI testing and mutation analysis for KRAS, BRAF, and interpreting results of these important therapeutic and prognostic tests (Wang et al. 2010).

6.2 Histopathologic Diagnosis of Colorectal Carcinoma

WHO classifies colorectal carcinomas as under (Hamilton et al. 2010):

6.2.1 Epithelial Tumors

6.2.1.1 Premalignant Lesions

Adenoma
- Tubular adenoma
- Villous adenoma
- Tubulovillous adenoma
- Glandular intraepithelial neoplasia, low grade
- Glandular intraepithelial neoplasia, high grade

6.2.1.2 Serrated Lesion

Hyperplastic polyp
- Sessile serrated adenoma/polyp
- Traditional serrated adenoma

6.2.1.3 Carcinomas

Adenocarcinoma
- Cribriform comedo-type adenocarcinoma
- Medullary carcinoma
- Micropapillary carcinoma
- Mucinous carcinoma
- Serrated adenocarcinoma
- Signet ring cell carcinoma

Adenosquamous carcinoma
Spindle cell carcinoma
Squamous cell carcinoma
Undifferentiated carcinoma

6.2.1.4 Neuroendocrine Neoplasms

Neuroendocrine tumor G1 (NET G1)/Carcinoid
Neuroendocrine tumor G2 (NET G2)
Neuroendocrine carcinoma,
Large-cell neuroendocrine carcinoma
Small-cell neuroendocrine carcinoma
Mixed adenoneuroendocrine carcinoma
Enterochromaffin cell (EC), serotonin-producing
Neuroendocrine tumor (NET)
L cell, Glucagon-like peptide-producing and
PP/PYY-producing NET

6.2.1.5 Mesenchymal Tumors

Leiomyoma
Lipoma
Angiosarcoma
Gastrointestinal stromal tumor, malignant
Kaposi sarcoma
Leiomyosarcoma
Lymphomas
B-cell lymphoma unclassifiable with features intermediate between diffuse large
B-cell lymphoma and Burkitt lymphoma
Burkitt lymphoma
Diffuse large B-cell lymphoma
Mantle cell lymphoma
Marginal zone lymphoma of mucosa associated lymphoid tissue
Secondary tumors

Adenocarcinoma is the predominant cancer type in colorectal carcinomas accounting for more than 90% of all the colorectal cancers (Hamilton et al. 2010). Other types of colorectal cancers are listed.

Adenocarcinomas are the tumors characterized by formation of glands; the differentiation is dependent on the percentage of glandular formation within the tumor. In well-differentiated adenocarcinomas more than 95% of the tumor is gland forming. In moderately differentiated adenocarcinomas 50–95% of the gland shows gland formation and poorly differentiated tumors are usually solid with less than 50% gland formation.

Tumor grade, although subjective is considered as a stage independent prognostic variable—a poorly differentiated tumor is associated with poor survival (Compton 1999). Tumor grade however, may not be applied in the form as discussed above. Many studies have shown that a two-tier grading system combining

well and moderately differentiated adenocarcinomas calling it as low-grade adenocarcinoma and defining poorly differentiated adenocarcinoma as high grade decreases the inter-observer variations and improves prognostic significance of grading (Compton 2000).

According to WHO, grading should be based on the evaluation of the worst area, excluding the areas of focal differentiation present at the invasive margin of the tumor.

Besides tumor grade, the other features evaluated for prognosis are as follows.

6.3 Depth of Tumor Invasion

Majority of colorectal carcinomas are diagnosed initially by endoscopy or polypectomy. Looking for evidence of invasion is important for a pathologist. However, comment on invasion may be difficult if the biopsy is superficial or orientation is not proper. An invasive carcinoma disrupts the muscularis mucosae (Fleming et al. 2012) and goes into the submucosa sometimes in close proximity to submucosal blood vessels. An important additional feature of invasion is the presence of desmoplasia—which is defined as a type of fibrous proliferation surrounding tumor cells secondary to an invasive tumor. In addition, invasive colorectal carcinoma shows characteristic necrotic debris in glandular lumina called "dirty necrosis." This feature may be helpful to distinguish a colorectal primary from a metastatic tumor (Fleming et al. 2012).

For colorectal cancers, the diagnosis of invasive carcinoma is made when carcinoma has at least invaded into the submucosa of colorectum. Submucosal invasion is required for the diagnosis of a pT1 tumor, whereas in other parts of gastrointestinal tract the presence of mucosal invasion is sufficient for the diagnosis of an invasive carcinoma. It is because of relative paucity of lymphatics in colorectum that the invasion restricted to lamina propria and muscularis mucosae has no risk of nodal or distant metastasis. Thus, intra-mucosal carcinoma is preferably called high-grade dysplasia by pathologists for colorectal cancers in order to avoid a surgical intervention in such situations. However, cancer staging manual for American Joint Committee on Cancer (AJCC) classifies mucosal invasion as "Carcinoma in situ (Tis)" (Edge et al. 2010). The outer edge of muscularis propria represents the line of demarcation between pT2 and pT3. pT3 indicates spread in continuity beyond the bowel wall and does not imply lymphatic or venous invasion. Tumors that have penetrated the visceral peritoneum as a result of direct extension through the wall and subserosa are assigned pT4 category, like the tumors which directly invade other organs or structures whether or not they penetrate the serosal surface. To comment on the visceral peritoneal involvement adequate tumor sampling, multiple levels of tissue sectioning and subsequent microscopic examination are mandatory. The histological features considered to represent carcinomatous serosal involvement are (Shepherd et al. 1997):

- Tumor involvement at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and an erosion or ulceration
- Free tumor cells on the serosal surface associated with underlying ulceration of the visceral peritoneum

6.4 Margins of Resection

Proximal, distal, circumferential, and mesocolic margins of resection should be evaluated in colorectal cancer surgical specimens. It is very useful to mark the margin(s) closest to the tumor with ink after careful examination of the serosal surface. Proximal and distal resection margins are rarely involved unless close (<2 cm) to the tumor or if the tumor shows histologically poor differentiation or a diffusely infiltrating pattern of growth. Sections to assess proximal and distal margins can be obtained either by longitudinal sections perpendicular to the margin or by en face sections parallel to the margin. The distance from the tumor edge to the distal resection margin is important for low anterior resections and a clearance of 2 cm (1 cm for T1 and T2 tumors) is considered optimum. The circumferential (radial) margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically.

6.5 Regional Lymph Nodes

The number of metastatic lymph nodes and the total number of lymph nodes examined must always be reported. Regional lymph node status should be assessed according to the new TNM classification. Histological examination of a regional lymphadenectomy specimen ordinarily includes 12 or more lymph nodes. If the lymph nodes are negative, but if the number ordinarily to be examined is not met, the tumor will be classified as pN0. All macroscopically evident lymph nodes in the surgical specimen should be dissected and examined histologically. Many factors influence lymph node recovery and evaluation, such as extent of surgical resection, quality of pathologic examination, patient factors, and the tumor characteristics. The mean number of nodes detected in a series of dissections is now considered to be indicative of colon cancer quality care and should be between 12 and 15. As nodal metastases in colorectal cancer are often found in small lymph nodes (<5 mm in diameter), a meticulous search is needed on gross examination by the pathologist. If less than 12 lymph nodes are retrieved, reexamining the specimen can be useful. Specimens from patients treated with neoadjuvant therapy, the number of recovered lymph nodes is usually lower than 12 despite meticulous search. Many studies have reported that the total number of lymph nodes evaluated after surgical resection is an important prognostic factor in colorectal cancer (Chang et al. 2007). Peritumoral deposits (satellite nodules) are defined as macroscopic or microscopic carcinomatous nests or nodules in the pericolo-rectal adipose tissue lymph drainage area of a

primary carcinoma without histologic evidence of residual lymph node tissue. They may represent discontinuous spread of the tumor venous invasion with extravascular spread or totally replaced lymph nodes.

6.6 Response to Neoadjuvant Therapy

Preoperative (neoadjuvant) chemo- and radiotherapy for rectal cancer induces several secondary changes including tumor regression and downstaging (Ryan et al. 2005). In rectal cancers treated with neoadjuvant therapy, pathologic staging should be performed according to the pTNM system and based on evaluation of viable cancer cells. Marked tumor regression, especially complete tumor eradication is associated with a better clinical outcome. Thus, specimens from patients treated with neoadjuvant therapy should be carefully examined and sampled thoroughly to demonstrate complete tumor regression.

6.7 Vascular Invasion

Several studies have shown venous invasion to be an independent negative prognostic factor in colorectal cancer. Invasion of large extramural veins particularly has been associated with increased risk of cancer-related death. The prognostic value of intramural venous invasion or the invasion of lymphatics or thin-walled vessels is less clear.

6.8 Molecular Prognostic and Predictive Factors

In clinical practice, KRAS mutational analysis and evaluation of proficiency of the DNA mismatch repair system by IHC and microsatellite instability analysis are employed (Zlobec and Lugli 2008; Walther et al. 2009).

6.8.1 KRAS Mutation

Only those patients whose tumor shows absence of KRAS mutations can be treated with anti-EGFR antibiotic (Cetuximeb and Panitumumab) and only a fraction of patient with KRAS wild-type carcinomas respond to anti-EGFR antibody treatment. There is a need for an active search of predictive molecular markers.

6.8.2 DNA Mismatch Repair

Genetic or epigenetic inactivation of MMR genes is always associated with loss of expression of the corresponding protein. Also, as MMR proteins work as

heterodimers, so, whenever one protein is abnormal, it leads to proteolytic degradation of their dimer and loss of both obligatory and secondary partner protein. Thus, IHC pattern of MMR protein expression allows identification of gene that is most likely inactivated. IHC and MSI analysis are used for identification of MMR-deficient colorectal carcinomas. MMR status has been shown to be an independent prognostic factor in colorectal carcinoma. Several studies have shown higher survival rates for patients with stage II and stage III MSI carcinomas with respect to patients with non MSI tumors, MSI tumors don't benefit from adjuvant S-Thiouracil based chemotherapy.

6.9 Additional Histologic Prognostic Factors

Several other histopathologic variables, including the pattern of growth, perineural invasion, lymphocytic infiltration at the tumor margin, the presence of tumor infiltrating lymphocytes (TILs), Crohn-like reaction, and tumor budding have been proposed as prognostic factors in colorectal cancer. These parameters are not routinely employed in the clinical setting and their reporting is optional. Nowadays, tumor budding and the grade of intratumoral lymphocytic infiltration represent promising prognostic factors which should be introduced in the pathologic evaluation of these tumors, provided their assessment is standardized and their prognostic value clearly defined.

6.10 WHO Classification

In World Health Organization (WHO) Classification many variants of adenocarcinomas are discussed; we list here a few important ones and the value for a pathologist to recognize them because the histological subtype plays a role in tumor biology (Nitsche et al. 2013).

6.10.1 Mucinous Adenocarcinoma

It is a special type of colorectal carcinoma defined when >50% of tumor mass is comprised of extracellular mucin. Tumors with a mucinous component of more than 10% but less than 50% are termed as adenocarcinomas with mucinous differentiation. Mucinous carcinomas may be categorized as colloid carcinomas or signet ring carcinomas. In colloid carcinoma mucin is extracellular and in signet ring carcinoma mucin is seen both extracellularly as well as intracellularly (Fenoglio-Preiser et al. 2008).

Mucinous carcinomas account for nearly about 10% of all colorectal cancers and signet ring cancers account for about 1% of colorectal tumors. When compared to adenocarcinomas, both mucinous and signet ring carcinomas have been associated with younger age, female preponderance, advanced tumor stage, and distinct

molecular pattern, i.e., microsatellite instability and activated mutations of BRAF gene (Verhulst et al. 2012). Mucinous carcinomas also occur in patients with hereditary non-polyposis colorectal cancer (HNPCC) (Leopoldo et al. 2008).

6.10.2 Signet Ring Cell Adenocarcinoma

Signet ring cell adenocarcinoma is defined by the presence of more than 50% of tumor cells which show signet ring cell features characterized by prominent intracytoplasmic mucin vacuole that pushes nucleus to the periphery. Signet ring cells may demonstrate an infiltrative pattern or may be present within the pools of extracellular mucin. It is a high-grade tumor with the worse outcome (Verhulst et al. 2012).

6.10.3 Medullary Carcinoma

Medullary carcinoma is a rare tumor characterized by the presence of epitheloid neoplastic cells with a large vesicular nuclei, prominent nucleoli, and abundant cytoplasm. It has a pushing border and is associated with tumor infiltrating lymphocytes. Medullary carcinoma is associated with MSI-H instability and has excellent prognosis.

6.10.4 Other Types—Anaplastic Carcinoma, Undifferentiated Carcinoma

These are rare tumors which lack morphological evidence of differentiation beyond that of an epithelial tumor and have variable histological features (Leopoldo et al. 2008).

6.11 Role of Immunohistochemistry in Colon Adenocarcinomas

The most commonly used immunohistochemical markers for colorectal adenocarcinoma are cytokeratins—CK20, CK7, and CDX2. Colorectal adenocarcinomas are usually positive for CK20 and negative for CK7. However, on an average 20% of tumors may show CK7 positive/CK20 negative or CK7negative/CK20 negative staining pattern. It has been demonstrated that decreased or absent CK 20 expression is associated with high levels of microsatellite instability. High levels of microsatellite instability result from abnormal nucleotide mismatch repair.

CDX2 is a marker of enteric differentiation and is positive in more than 90% of colorectal adenocarcinoma. CDX2 is a homeobox gene that encodes an intestine-specific transcription factor. It is expressed in the nuclei of epithelial cells throughout the intestine from duodenum to rectum. CDX2 is thus positive in any carcinoma that shows enteric differentiation and is not thus entirely colorectal specific.

6.12 Pathological Reporting of Colorectal Tumors

The details to be included in pathology report are—specimen size and type, site of tumor, size of tumor, macroscopic tumor perforation, histological type of tumor as per the WHO classification-its grade (a four-grade system or a two-grade system), tumor extension, tumor margins, (proximal, distal, radial), lymphovascular invasion, perineural invasion, treatment effects, tumor deposits, TNM staging (which should include total number of nodes examined and total number of nodes involved) heading edge of the tumor, tumor budding, and histological features suggestive of MSI may also be reported if feasible (Fleming et al. 2012).

6.12.1 Precursor Lesions

Some of the common precursor lesions of colorectal carcinoma are as follows.

6.12.2 Conventional Adenomas

Adenomas are glandular neoplasms which may precede colon cancer development. They are histologically defined by the presence of dysplastic epithelium. Dysplasia may be low grade or high grade. Low-grade dysplasia is defined as stratified dysplastic epithelium which retains its columnar shape. The nuclei may be spindle or oval shaped. The stratified nuclei tend to remain in basal epithelium extending no more than three quarters of height of epithelium. There is minimal nuclear pleomorphism. All adenomas contain at least low-grade dysplasia. High-grade dysplasia is defined as dysplasia with nuclei consistently coming to the surface of epithelium. It includes loss of columnar shape, cellular rounding, increased nuclear-cytoplasmic ratio, nuclear irregularity, loss of polarity, cellular pleomorphism, and heaping up of cells. The cells may remain confined to the basement membrane or they may extend to surrounding lamina propria (Fenoglio-Preiser et al. 2008).

Conventional adenomas are sub-classified as tubular, tubulovillous, and villous based on their architectural features. Tubular adenomas are composed of simple crypt-like dysplastic glands and contain less than 25% of villous component which are dysplastic cell collections that resemble finger-like projections. Villous adenomas contain more than 75% of villous component, tubulovillous adenomas are intermediate lesions with 25–75% villous component.

6.12.3 Malignant Polyp

It is used to describe a polyp that contains invasive adenocarcinoma in the submucosa. In a malignant polyp the histological grade, the status of resection margins, the presence or absence of lymphovascular invasion needs to be assessed. For polyps with a negative margin, low-grade histology, and lymphovascular invasion, a surgical resection is recommended.

It is important to receive polypectomy specimen intact if the margins are to be accurately evaluated by the pathologist. In case there is piece meal resection and an inability to assess a margin, surgical resection is recommended. A pathologist should also be aware of the pseudo-invasion in which adenomatous elements are displaced into the submucosa secondary to traumatization or torsion of stalk, however lack of high-grade dysplasia, absence of desmoplastic response, and presence of hemosiderin help to distinguish the two (Ramirez et al. 2008).

6.12.4 Serrated Lesions

This is a heterogenous group of lesions characterized morphologically by serrated (sawtooth or stellate) architecture of the epithelial compartment. It includes hyperplastic polyp, sessile serrated adenoma/polyp, and traditional serrated adenoma. Hyperplastic polyps are often small <10 mm sessile polyps microscopically composed of elongated or hyperplastic crypts that have sawtooth or serrated architecture. This serrated architecture usually extends down from the surface to involve half to two-third of the crypt. These show infolded epithelial tufts with microvesicular cells sometimes enlarged goblet cells are seen in the upper zone of the crypts. However, importantly there is no nuclear dysplasia.

Sessile serrated lesions show a hyperplastic or serrated polyp-like appearance with some unusual architectural features that includes the presence of horizontal orientation of deep part of the crypts just above muscularis mucosa forming L-shapes or inverted T-shape. This pattern of serration extends down to the base of the crypts. No nuclear dysplasia is noted, however mild nuclear enlargement is seen.

Traditional serrated adenoma (TSA) is a lesion characterized by an overall complex and villiform growth pattern, with cells often showing cytological features of dysplasia. They are pedunculated and limited to left side of colon and in the rectum. These lesions usually show prominent serration, diffuse low-grade dysplasia with approximately 10% showing high-grade dysplasia. The dysplastic epithelium shows luminal infoldings oriented perpendicular to the main axis of the crypt termed as ectopic crypt formation or short ectopic budding crypts (Torlakovic et al. 2008). TSA is generally not associated with carcinoma with high MSI but may be associated with low MSI.

6.12.5 Juvenile Polyp

Juvenile polyp contains edematous granulation tissue that surrounds cystically dilated glands laden with mucin. These glands are lined by cuboidal to columnar epithelial cells with reactive change. Dysplasia is rare in sporadic juvenile polyps but there is an increased risk of colorectal carcinoma in patients with juvenile polyposis syndrome.

Peutz–Jeghers Polyp: These are hamartomatous gastrointestinal polyps with a central core of smooth muscle that shows tree-like branching. This is covered by mucosa drawn into folds producing a villous pattern.

6.13 Other Lesions

Neoplasia in chronic inflammatory bowel diseases: The risk of colorectal carcinomas in ulcerative colitis and Crohn's disease increases after 8–10 years of disease and is highest in patients with early onset and extensive involvement of the colorectum especially pancolitis.

6.13.1 Ulcerative Colitis

Ulcerative colitis affects children and adults with a peak incidence in early third decade of life. A risk of CRC of 30% after 30 years is reported in patients with pancolitis in whom the disease began before the age of 15 years. Ulcerative colitis associated colorectal carcinomas are often multiple, flat, infiltrative, and mucinous or signet ring cell type. Low-grade tubuloglandular adenocarcinoma occurs almost exclusively in ulcerative colitis or Crohn's disease and is quite problematic to diagnose because of its well-differentiated nature.

6.13.2 Crohn's Disease

The risk of colorectal carcinoma appears to be about threefold in individuals with Crohn's disease than without chronic inflammatory bowel disease (Freeman 2008). Long duration and early onset of the disease are risk factors. The characteristics of CRC in Crohn's disease are similar to those in ulcerative colitis. However, there is also an increased frequency of adenocarcinoma within perianal fistulae and of squamous cell carcinoma of the anus.

6.13.3 Intestinal Polyposis Syndromes

Many polyposis syndromes involve the gastrointestinal tract. The hereditary gastrointestinal polyposis syndromes include:

6.13.3.1 Familial Adenomatous Polyposis (FAP)

It is an autosomal dominant disorder characterized by development of hundreds to thousands of colorectal adenomatous polyps and also the inevitable occurrence of colorectal adenocarcinoma if the colon is not removed. Classical FAP is defined clinically by the finding of at least 100 colorectal adenomatous polyps in a patient

in whom the syndrome is fully developed. Finding of fewer adenomas in a first-degree relative of an affected person is also diagnostic, especially in younger individuals.

6.13.3.2 Gardner Syndrome

Gardner syndrome is a variant of FAP that includes epidermoid cysts, osteomas, dental anomalies, and desmoids tumor.

The term Turcot syndrome is applied to a variant of FAP with typical intestinal polyps and also brain tumors, i.e., medulloblastoma.

An attenuated form of FAP called attenuated FAP is characterized by an average of 30 colorectal adenomas however, the number of polyps is extremely variable.

6.13.3.3 MUTYH-Associated Polyposis (MAP)

MUTYH-associated polyposis (MAP) is an autosomal recessive disorder characterized by a variable number of colorectal polyps with different histological phenotypes that have tendency to progress to malignancy. MAP is suspected in patients with multiple (>10) synchronous colorectal adenomas of late onset in the absence of a germ line mutation in the adenomatous polyposis coli (APC) gene and a pedigree suggestive of autosomal recessive inheritance. Conventional colon adenomas are the predominant type of polyps found in MAP. The unusual feature of MAP is their association with serrated polyps of all kinds. Some MAP patients have an excess of hyperplastic polyps.

6.13.3.4 Serrated Polyposis Syndrome

In this syndrome patients have five serrated polyps proximal to the sigmoid colon with two or more of these being >10 mm or any number of serrated polyps proximal to the sigmoid colon with a first-degree relative with serrated polyposis or >20 serrated polyps of any size but distributed throughout the colon. The lesions of serrated polyposis are predominantly SSA/P with fewer microvesicular hyperplastic polyps. Untreated serrated polyposis is thought to be associated with a substantial (although undetermined) increased risk of developing colon cancer (Noffsinger 2009; Bettington et al. 2013).

6.13.3.5 Juvenile Polyposis

Juvenile polyposis is a familial cancer syndrome with an autosomal dominant trait characterized by multiple juvenile polyps of the gastrointestinal tract, predominantly the colorectum but also stomach and small intestine. Although polyps in patients with juvenile polyposis are considered to be hamartoma, they do have a malignant potential.

6.13.3.6 Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an inherited cancer syndrome characterized by mucocutaneous melanin pigmentation and hamartomatous gastrointestinal polyposis which preferentially affects the small intestine. PJS is associated with a 10–18 fold excess of gastrointestinal and non-gastrointestinal cancers.

6.13.3.7 Cowden Syndrome

Cowden Syndrome is an autosomal dominant disorder characterized by multiple hamartomas involving organs derived from all three germ-cell layers. The classical hamartoma associated with CS is trichilemmoma. Affected family members have high risk of developing breast and epithelial thyroid carcinomas.

6.13.3.8 Bannayan–Riley–Ruvalcaba Syndrome

Previously thought to be clinically distinct, BRRS is characterized by macrocephaly, lipomatosis, hemangiomatosis, and speckled penis, is likely to be allelic to Cowden syndrome. The association and risk of gastrointestinal malignancy with CS is unknown but appears to be likely.

6.14 Molecular Classification of Colorectal Carcinoma

Attempts have been made to classify colorectal cancers based on location, histology, etiology, and molecular mechanisms of tumor genesis. It has been noted that cancers arising in the proximal and distal colon involve different genetic mechanisms. Familial forms of colorectal cancer have served as prototypes for understanding distinct molecular mechanisms of tumor genesis. Two pathways which are molecularly distinct namely the mutator pathway and the suppressor pathway are known to exist and believed to cause colonic carcinoma. Lynch syndrome results from loss of function in one of the MMR genes and follows the MSI pathway ("mutator" pathway) and FAP arises in patients with inherited mutations in APC gene (Fearon and Vogelstein 1990) that forms the basis of chromosomal instability (CIN) pathway ("suppressor" pathway). Epigenetic instability has gained considerable attention and is now implicated in the pathogenesis of almost one-third of colorectal cancers (Snover 2011). One of the best characterized epigenetic modifications associated with colorectal tumor genesis is silencing of genes (tumor suppressor and/or MMR genes) through hypermethylation of their promoter regions. Promoter hypermethylation of the MLH1, one of the MMR genes, is demonstrated in majority of sporadic colorectal cancers with a MSI phenotype (Veigl et al. 1998). CIN pathway is implicated in both sporadic and syndromic colorectal cancers. CIN tumors are characterized by karyotypic abnormalities, chromosomal gains, and losses, which are determined by DNA ploidy or loss of heterozygosity (LOH) analyses. These tumors almost always have APC mutations, frequently show KRAS and *p53* mutations, and often have 18q allelic loss (Ogino and Goel 2008). MSI pathway is implicated in both sporadic and syndromic colorectal cancers, MSI tumors are characterized by loss of the DNA mismatch repair function. In sporadic colorectal cancers, the loss of function is primarily due to methylation of the *MLH1* gene promoter that leads to epigenetic inhibition of protein expression of MLH1 and its binding partner PMS2. These tumors usually show *BRAF* mutation, but only rarely *KRAS* mutations (Ogino and Goel 2008).

6.14.1 Importance of Molecular Testing in Colorectal Cancers

In order to predict prognosis and to determine need for family counseling, MSI, KRAS, and BRAF are the most commonly performed tests in pathology laboratories.

6.14.2 MSI Testing

Microsatellites are repetitive DNA sequences that are prone to errors during DNA replication if the MMR system is defective. MSI is defined as alterations in the length of the microsatellite sequences. It is typically assessed by analyzing two mononucleotide repeats and three dinucleotide repeats, known as the Bethesda panel by comparing DNA samples extracted from normal and tumor tissues from the same patient (Umar et al. 2004). The test is a polymerase chain reaction (PCR)-based test, and can be performed on formalin-fixed paraffin-embedded tissues. A tumor is designated as MSI-H if two or more (>40%) of the five microsatellite markers show instability, MSI-L (low-level) if only one marker shows instability, or MSS if none of the markers show instability (Umar et al. 2004). An indirect analysis of MSI status can be done by immunohistochemical stains for MMR proteins. These proteins are ubiquitously present in normal cells but show loss of expression in MSI tumor cells. Several staining patterns may be observed based on the underlying genetic or epigenetic abnormalities. Loss of MLH1 protein expression is almost always accompanied by the loss of its binding partner PMS2, but loss of PMS2 expression may occur by itself. Same holds true for MSH2 and its binding partner MSH6. Immunohistochemistry is a reliable substitute for MSI with a concordance rate of >90%. It provides additional information over PCR-based MSI test, in that it allows gene-specific DNA sequence analysis based on the staining pattern but may miss rare MSI cases that are caused by germ line mutations by other genes. Thus, it is recommended to perform both PCR-based MSI test and immunohistochemistry in order to minimize the chance of missing the diagnosis of Lynch syndrome. It is best to test all newly diagnosed colorectal cancers regardless of patient's age for either immunohistochemistry or MSI analysis, so that we do not miss the diagnosis of Lynch syndrome (Weissman et al. 2012). MSI tumors account for ~15% of colorectal adenocarcinomas. These tumors tend to show unique clinicopathologic features, tend to have a better stage-adjusted prognosis when compared with MSS tumors, but are resistant to treatment with 5-fluorouracil (Ogino and Goel 2008).

6.14.3 KRAS Testing

Mutations in the KRAS (Kirsten rat sarcoma viral oncogene homolog) gene lead to expression of a constitutively activated KRAS protein, which is detected in ~40% of colorectal cancers. As a critical downstream molecule in the epidermal growth factor receptor (EGFR) signaling pathway, mutant KRAS renders tumors resistant to EGFR-targeted therapies. Mutation analysis of the *KRAS* gene is recommended for patients who will receive anti-EGFR therapies (Allegra et al. 2009).

6.14.4 BRAF Testing

In addition to KRAS, mutations in other members of the EGFR signaling pathway can also cause resistance to anti-EGFR therapy. BRAF (v-raf murine sarcoma viral oncogene homolog B1) gene mutation, has been reported in ~10% of colorectal cancers (Samowitz et al. 2005). Mutation testing of the BRAF gene should be done following a negative KRAS mutation analysis. BRAF mutation is almost exclusively seen in sporadic MSI tumors that are believed to develop through the serrated tumorigenic pathway, but has never been reported in Lynch syndrome. To be specific, activating mutation of the BRAF gene is associated with a high level of global DNA methylation and epigenetic silencing of the MLH1 gene, found in 70–90% of sporadic colorectal tumors with a microsatellite unstable phenotype. Therefore, testing BRAF mutation in a MSI tumor will help clarify the sporadic or syndromic nature of the tumor. Also, BRAF wild-type MSI-H tumors have the better prognosis, whereas BRAF-mutated MSS tumors are associated with the worst outcome. Therefore, testing for both MMR abnormalities and BRAF mutations offers additional prognostic information (Fleming et al. 2012; Samowitz et al. 2005).

6.15 Special Considerations in Grossing-Helpful to Diagnose Tumors

Small carcinomas (1–2 cm) are red, granular, button-like lesions slightly elevated above the tan mucosal surface, sharply circumscribed, resembling adenomas. Their consistency depends on proportion of carcinoma, pre-existing adenoma and amount of stromal desmoplasia. When carcinoma replaces adenoma, the tumor will become firmer and pale. Gross appearance of CRC is either polypoidal, fungating, ulcerating, stenosing, or infiltrating.

The polypoidal form appears nodular lobular or papillary and contains residual adenomas. Two-thirds of all CRCs are ulcerating and one-third appears fungating.

Bulky, fungating cancers appear in the caecum and ascending colon. They have raised or rolled margins. They grow into the lumen and extend along one wall only. They occupy a large proportion of lumen but rarely cause obstruction. They remain asymptomatic until blood loss results in late anemia. Intraluminal mass is far voluminous than the intramural part.

Ulcerating carcinomas invade deeply into the colonic wall. The edge of an infiltrating carcinoma is only slightly elevated. It involves whole circumference adenocarcinomas of transverse colon and descending colon usually are infiltrative and ulcerating producing annular constricting tumor. They appear irregularly round with raised edges and a central excavated part.

Beginning as locally infiltrative lesion they progressively encircle the bowel wall. These tumors obstruct lumen and exhibit characteristic apple core or napkin ring appearance on barium contrast radiograph. Proximal to tumor, bowel dilates and the mucosal folds atrophy. These tumors induce desmoplasia and hence are firm on consistency. The tumor volume in luminal portion is same as that of intramural portion. Surrounding structures like small intestine might get involved if the tumor extends completely through the bowel wall. Further necrosis and ulceration may cause perforation and peritonitis.

Diffuse infiltrating CRCs are uncommon, they convert colon into a rigid tube resembling gastric linitis plastica. Another pattern of growth is recognized which appear as flat plaque on the mucosal surface with extensive intramural invasion.

6.15.1 Grossing of Colon and Rectum (Key Points)

- Surgeons should refrain from opening the specimen as it would distort important structures such as serosa or non-peritonalized surface with respect to tumor.
- Nature of surgical procedure should be known.
- Quality of total mesorectal excision should be assessed.

The quality of mesorectal excision is assessed as follows (Nagtegaal et al. 2002; Maugham and Quirke 2003).

6.15.2 Complete TME (Grade 3)

Plane of surgery is mesorectal fascial plane. Mesorectum is intact and bulky with a smooth surface. There are only minor irregularities of the mesorectal surface with no surface defects greater than 5 mm in depth. No coning toward the distal margin of the specimen. Smooth CRM (circumferential resection margin) on transverse slices.

6.15.3 Nearly Complete TME (Grade 2)

Plane of surgery is through the mesorectum. Bulk of mesorectum is moderate. There is irregularity of the mesorectal surface with defect greater than 5 mm but none

extending to the muscularis propria except at the insertion site of levator ani muscles. Moderate coning is seen toward the distal margin of the specimen. Moderate irregularity of CRM is seen in transverse slices.

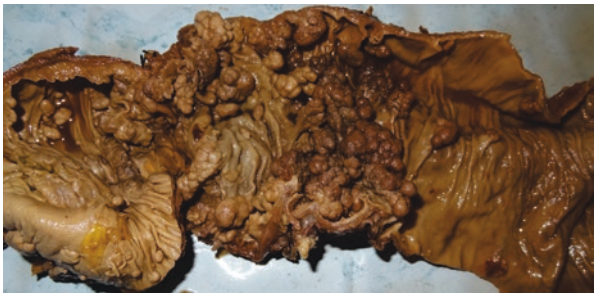
6.15.4 Incomplete TME (Grade 1)

Plane of surgery through muscularis propria. Little bulk of mesorectum is present. Non-peritonalized surface is to be painted with ink with special reinforcement to the NPS related to the tumor (Nagtegaal et al. 2002).

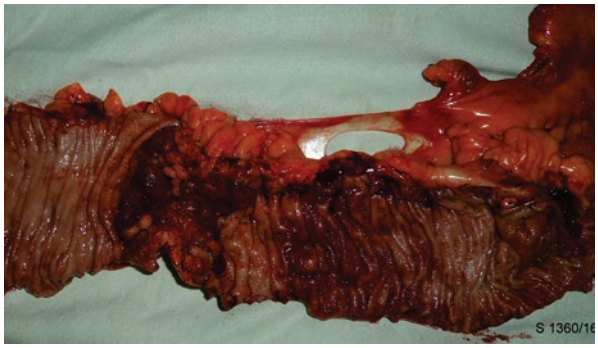
6.16 Grossing a Colorectal Polyp

Polyp should be received intact. If it has a stalk, the base of stalk should be inked and 2-mm-thick end should be sampled as excision margin. In case of broad-based sessile polyp the entire base is inked. Serial parallel sections of the polyp should be obtained each containing the inked base. The excision margin in a sessile polyp is sampled in a perpendicular manner.

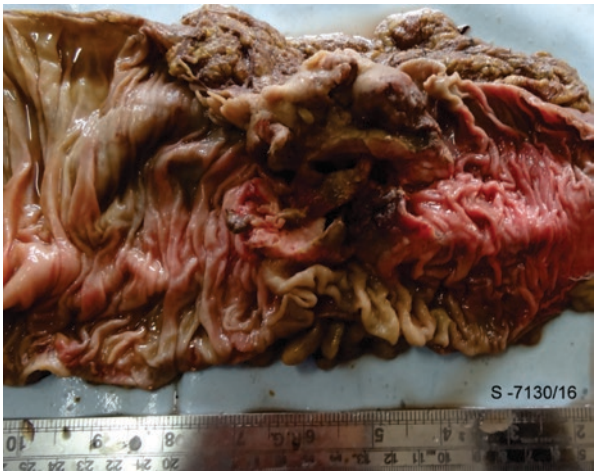
Multiple polypoidal lesions seen over entire length of colon



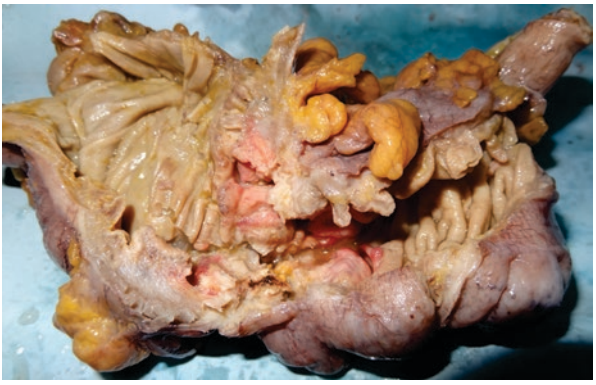
A polypoidal button -like growth with overlying ulcerated and hemorrhagic mucosa



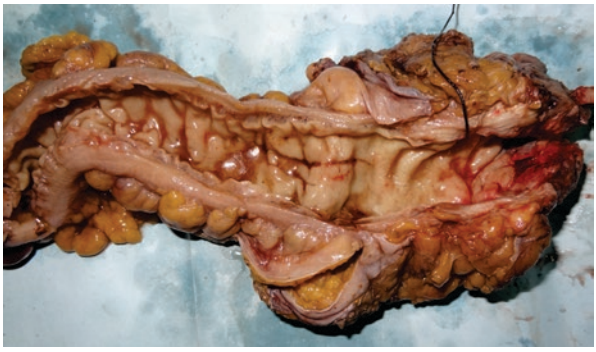
A Fungating necrotic mass involving whole circumference of colon

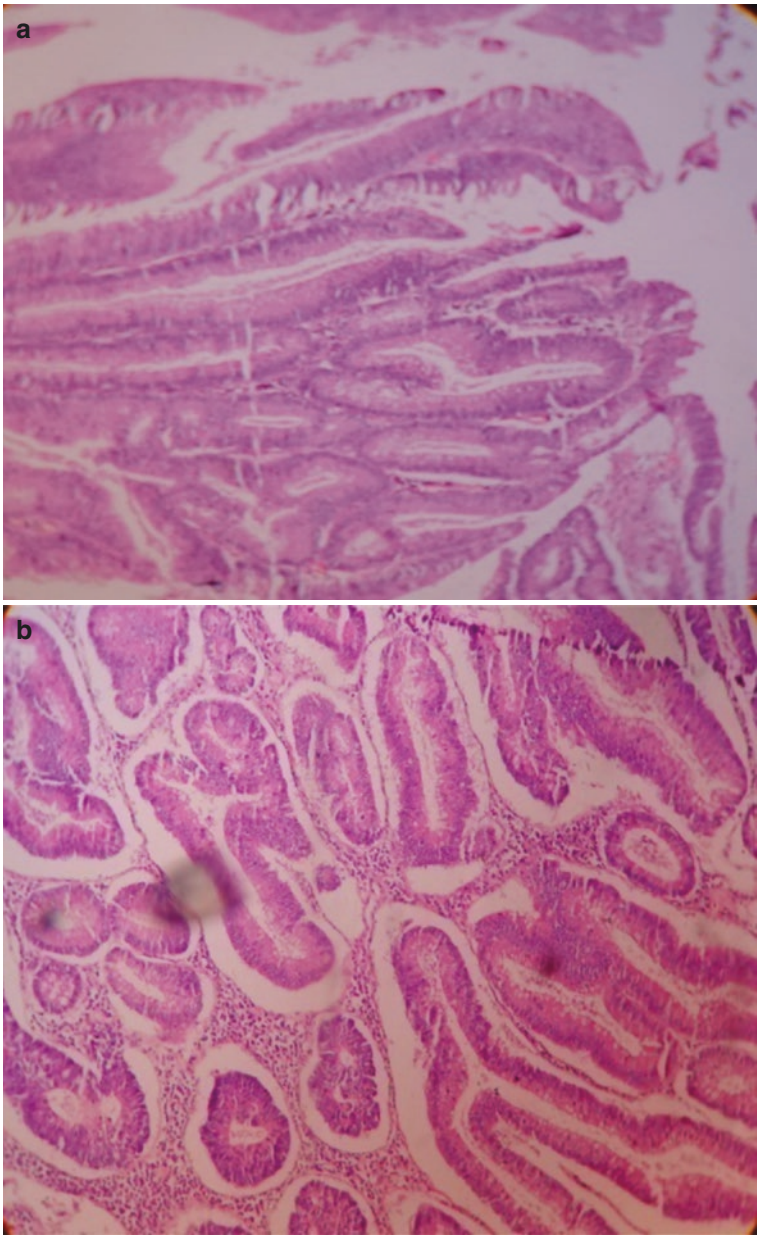


An infiltrative lesion encircling whole bowel wall causing rigidity, unable to straighten it postoperatively

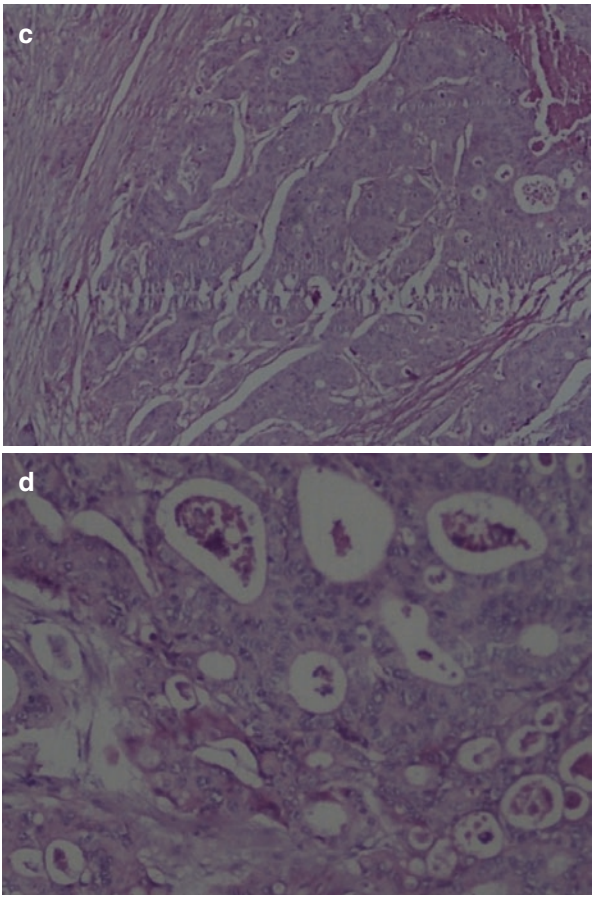


Colonic wall is grossly thickened with loss of haustrations

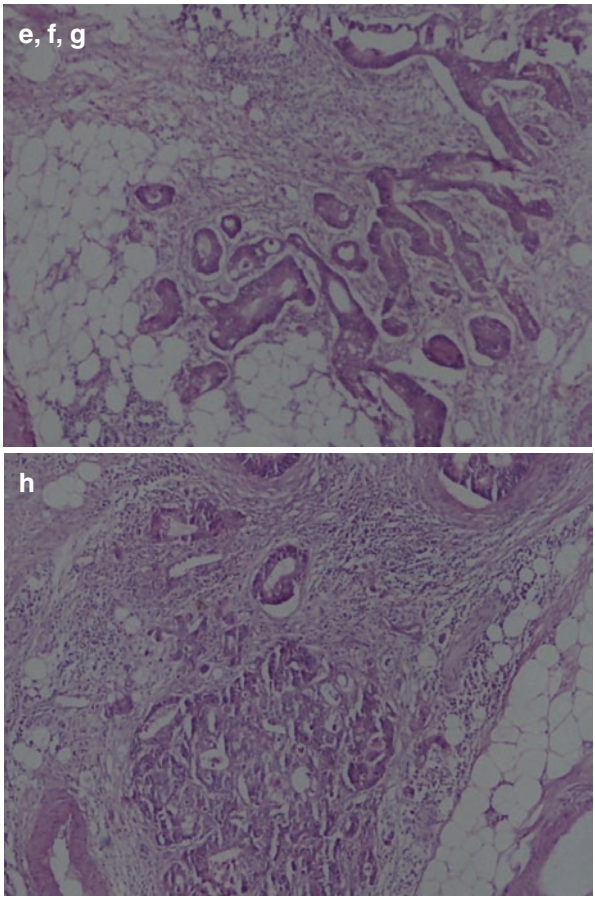




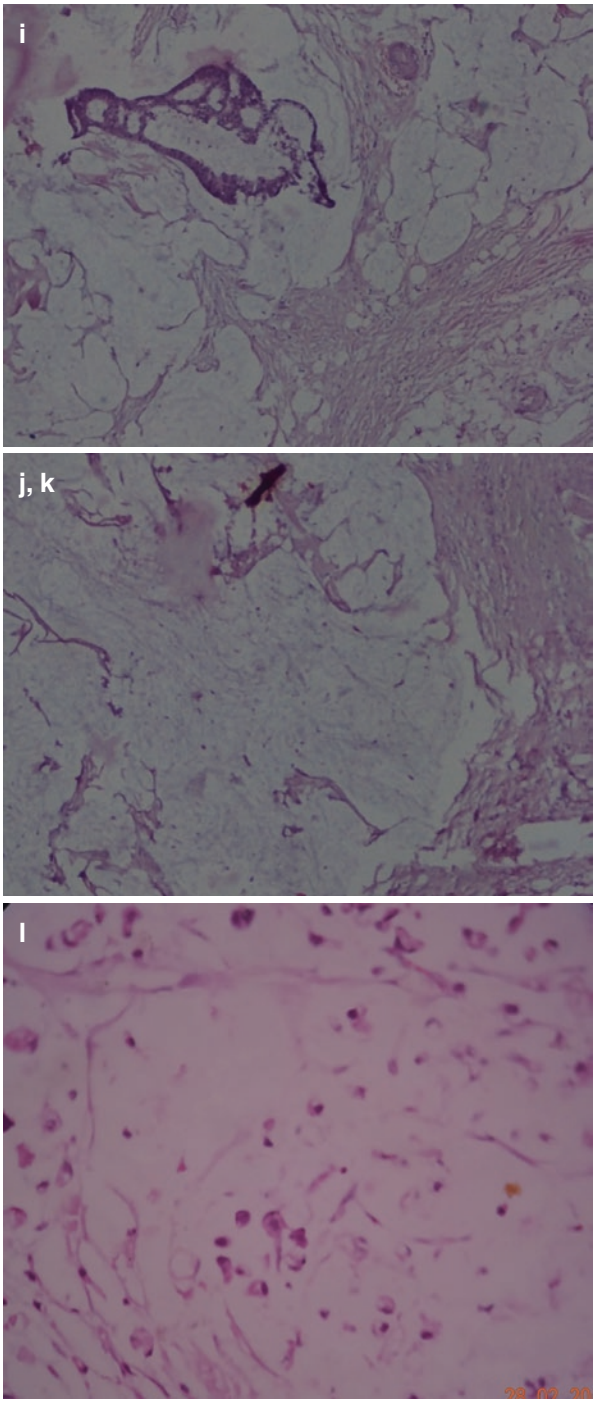
(**a**) Well-differentiated adenocarcinoma, elongated hyperchromatic nuclei seen. Tumor arising from previous adenoma are well differentiated. (**b**) Tumor glands showing architectural dysplasia and cytological atypia seen beneath lamina propria.



(**c**) Necrotic debris present in the gland lumen of tumor glands and tumor necrosis seen on one side of field. (**d**) Poorly differentiated adenocarcinoma form few glands but are mostly composed of infiltrating nests of tumor cells.



(**e**–**g**) Tumor glands seen infiltrating into colorectal fat. (**h**) Tumor glands separated by dense fibroblastic proliferation infiltrated by lymphocytes.



(**i**) Single tumor gland seen in pools of mucin. (**j**, **k**) Acellular pools of mucin seen in muscle layer in colloid carcinoma. (**l**) Mucinous adenocarcinoma with signet ring cells and extracellular mucin pools

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Nucleotide Excision Repair (NER) and Role in Colorectal Carcinogenesis

7

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Abbreviations

BER	Base excision repair
CAK	Activating kinase
CDK	Cyclin-dependent kinase
CETN2	Centrin 2
Chl1	Chromatid cohesion in yeast
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CPD	Cyclobutane pyrimidine dimmers
CRC	Colorectal cancer
CS	Cockayne's syndrome
CTD	C-terminal domain
DDB1	Damage-specific DNA-binding protein 1
DDB2	Damage-specific DNA-binding protein 2
DinG	Damage-inducible G
DNA	Deoxyribose nucleic acid
ER	Excision repair
FancJ	Fanconi's anemia complementation group J
GG-NER	Global genome NER
hRAD23B/HR23B	Human RAD23 homolog B

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TFIIH	Transcription factor II H
MGMT	O6-methylguanine DNA methyltransferase
MIN	Microsatellite instability
MMR	Mismatch repair
NER	Nucleotide excision repair
RNAPII	RNA polymerase II
RR	Recombination repair
RTEL	Regular of telomere length
SF2	Superfamily 2
SNPs	Single nucleotide polymorphisms
TC-NER	Transcription-coupled NER
TTD	Trichothiodystrophy
XP	Xeroderma pigmentosum
XPB and XPD	Subunits of TFIIH; both ATP-dependent DNA
XPC	Xeroderma pigmentosum C
XPE	Xeroderma pigmentosum E

7.1 Introduction

Colorectal carcinogenesis is a multifactorial and multigene process that is determined by the gatekeeper and caretaker molecular pathways, referred to as the adenoma–carcinoma sequence/model (Vogelstein et al. 1988). The development of colorectal cancer (CRC) occurs as a result of cumulative amassing of mutations in oncogenes and tumor-suppressor genes. Several genetic changes are required for the initiation and progression of cancer (Migliore et al. 2011). CRC is classified into three specific phenotypes based upon the molecular profiles (Cunningham et al. 2010). These phenotypes involve three major genetic instability pathways, which are: chromosomal instability (CIN), microsatellite instability (MIN), and CpG island methylator phenotype (CIMP) (Sameer 2013; Ogino et al. 2011). One of the important causes of genetic instability is the inefficient repair of DNA lesions that sneak into the cellular genome via various DNA-damaging agents affecting the normal cellular functioning, which in turn lead to tumorigenesis.

7.1.1 DNA Repair Mechanisms

A wide variety of DNA-damaging agents (physical and chemical) which affect the structure and functioning of the genes constantly pose a potential threat to the eukaryotic genome. Eukaryotic cells constitutively express an array of different molecules which take part in repair mechanisms specifically responsible for identification and removal of different specific types of DNA lesions that may otherwise lead to various repair diseases like cancers (Michailidi et al. 2012). These repair mechanisms help to prevent the effect of DNA modifying agents on the functioning

of the genome and allow smooth functioning of the fundamental cellular processes. Each of the DNA repair pathway has a constitutive specificity for the specific DNA lesion. Therefore, the mechanism of restoration of intact DNA is dependent upon various factors like the cell cycle phase, type of DNA lesion, and other environmental factors. However, all types of repair mechanisms use the cell's intact complementary DNA strand as a template to restore the original strand.

The various repair mechanisms which are known to operate in the cell, are divided broadly into direct and indirect ones, based on the proteins which are primarily used for the repair process and also the time period of repair (Sameer et al. 2014; Michailidi et al. 2012).

Direct repair mechanisms take place during the replication process itself, when the daughter DNA is still being synthesized by polymerases. Direct repair is mostly carried out by direct DNA interacting enzymes which may be either DNA polymerases or O6-methylguanine DNA methyltransferase (MGMT) (Hoeijmakers 2001). Indirect repair takes place after the synthesis process and involves the DNA lesions which have been created during the synthesis of new daughter DNA. Indirect repair is actually a post-replication process and it functions to overcome the inability of the direct repair to fix all lesions during the DNA synthesis process (Sameer et al. 2014). Thus, essentially, it is a post-synthesis process of fixing the DNA lesions. It is assisted by many proteins of the DNA replication factory as well. Indirect repair mechanisms are further divided into three categories: excision repair (ER), recombination repair (RR), and mismatch repair (MMR). ER is further classified into two subcategories: base excision repair (BER) and nucleotide excision repair (NER). BER is utilized by cell for excision of abnormal bases such as uracil and breaks found only in one DNA strand, while as NER is used for the removal of bulky adducts within the DNA (Sameer et al. 2014; Michailidi et al. 2012).

7.1.2 NER: Structure and Function

The NER mechanism is one of the essential and important systems that cells use in protection against genotoxic damage like the ones induced by UV-irradiation or exposure to chemical carcinogens, which are known to incorporate DNA lesions into the cell's genome (Benhamou and Sarasin 2000, 2002). The most common DNA lesions which NER system identifies and restores are bulky covalent adducts. These are produced by nitrogenous bases affected by UV light, ionizing radiations, electrophilic chemical mutagens, drugs, and chemically active endogenous metabolites (Petruseva et al. 2014). NER is utilized by cells to overcome the inability of BER to remove the bulky lesions from the duplex DNA. In general, NER corrects the helix-distorting base lesions within the DNA that arise because of exposure to sunlight or bulky chemicals such as benzo[a]pyrene, benzo[c]anthracene, diol-epoxide, aromatic amines such as acetyl-aminofluorene, aflatoxin, nitrosamines such as MNNG, and 4-nitroquinoline oxide (Petruseva et al. 2014; Michailidi et al. 2012; Nouspikel 2009).

The NER pathway repairs the defective DNA strand by deleting about 24–32 nt DNA fragments containing the DNA lesion (Petruseva et al. 2014). The repair of the damaged DNA strand involves five main steps: first is the damage recognition step, followed by the opening of double helix at the lesion site, third is the demarcation of the actual DNA lesion and assembly of a pre-incision complex over it, fourth is the actual excision of the lesion containing damaged strand, and finally the synthesis of the DNA in the gap (Benhamou and Sarasin 2000, 2002; Hoeijmakers 2001). Each of these steps of NER requires the specific and coordinated functioning of the specialized protein complexes to carry out the repair efficiently and specifically (Spivak 2015). Almost 30 different polypeptides have been identified so far which play an important role in one or more steps of the NER mechanism (Petruseva et al. 2014).

Functionally, for the initial damage recognition process NER utilizes two distinct mechanisms for dealing with DNA helical distortion lesions. One repairs the bulky lesions throughout the genome (i.e., global genome NER, GG-NER) including the un-transcribed regions and silent chromatin while the other works in cooperation with the transcription machinery of the cell to remove lesions from actively transcribed regions of genes during the transcription process (i.e., transcription-coupled NER, TC-NER) (Spivak 2015; Petruseva et al. 2014).

GG-NER works under the control of specialized protein called XPC (xeroderma pigmentosum C). XPC locates and recognizes the helix-distorting DNA lesion in the genome and starts the repair process. However, some lesions like cyclobutane pyrimidine dimers (CPD) which are too small to destabilize the DNA helical structure are recognized first by damage-specific DNA-binding protein 1 (DDB1) and DDB2/XPE complex (Spivak 2015). XPC is functional as a heterotrimer in complex with two other proteins—human RAD23 homolog B (hRAD23B/HR23B) and centrin 2 (CETN2). HR23B helps to stabilize the complex, protects it against proteasome degradation, and also stimulates the DNA-binding activity of XPC. It plays an important role in the recruitment of other repair proteins into the GG-NER process (Spivak 2015; Petruseva et al. 2014; Nouspikel 2009).

TC-NER, on the other hand is primarily dependent upon cellular transcription machinery for its initial recognition of the DNA lesion. In TC-NER, DNA lesion is identified by the elongating RNA polymerase II (RNAPII) when it meets a bulky DNA lesion within the coding region of the gene that is being transcribed (deLaat et al. 1999). Blocking of the RNAPII by coding region DNA lesion constitutes the first step for the damage repair via TC-NER (Spivak 2015). The arrested elongation complex then recruits CSB (ERCC6), a transcription elongation factor that translocates along template DNA with RNAPII. CSB serves as master recruiter, which in turn recruits complexes of proteins required for repair mechanism like the CSA complex, NER factors (not including the GGR recognition factors XPC and XPE), and p300 to sites of arrested RNAPII. Both pathways of NER: TC-NER and GG-NER then converge on a single mechanism, with the recruitment of transcription factor II H (TFIIH) to the repair site (Spivak 2015) (Table 7.1).

Table 7.1 Composition of the human NER system

Factor	Subunits	Function	Additional role	Interactions with
XPC	HR23B	Stimulates XPC activity	Protects XPC complex from proteasome degradation	TFIIH; XPA; DDB
	XPC	Recognition of a distorted DNA lesion	Works in GG-NER only	
	CEN2	Stabilize the binding of XPC to DNA lesion	Regulates recruitment of TFIIH	
DDB	DDB1	Recognition of damage, interaction with chromatin		XPA; RPA
	DDB2			
XPA	XPA	Structural function, binding to a damaged strand and facilitating repair complex assembly		XPA; RPA; TFIIH; ERCC1
RPA	RPA70	Stabilizes single-stranded DNA and positions nucleases	Replication and recombination	XPA; XPG; PCNA/RFC
	RPA32			
	RPA14			
XPF	ERCC1	Endonuclease, catalyzes formation of single-strand break in DNA on the 5′ side of the damage	Interstrand cross-link repair	XPA; TFIIH
	XPF		Recombination via single-strand annealing	
XPG	XPG	Endonuclease, catalyzes formation of single-strand break in DNA on the 3′ side of the damage	Member of FEN-1 family of nucleases	TFIIH; PCNA; RPA
RFC	RFC1	ATP-dependent connection of PCN A		PCNA; RPA
	RFC2			
	RFC3			
	RFC4			
	RFC5			
PCNA	PCNA	Factor ensuring processivity of DNA polymerases		RFC; XPG; Pol δ
Pol δ	pI25	DNA polymerase		PCNA
	p66			
	p50			
	p12			
Pol ε	p261	DNA polymerase		PCNA
	p59			
	p17			
	p12			
Ligase I	Ligase I	Ligation of a single-strand break		
Ligase III	Ligase III			
TFIIH		Discussed in Table 7.2		XPA; XPC; XPF; XPG

Adapted from Petruseva et al. (2014)

Defects in NER usually results in UV-sensitivity and high-carcinogenic pathologies. NER defects have been demonstrated to cause at least three human genetic disorders: xeroderma pigmentosum (XP), Cockayne's syndrome (CS), and trichothiodystrophy (TTD), in addition to neurodegenerative manifestations (Spivak 2015; Petruseva et al. 2014; Iyama and Wilson III 2013).

7.1.3 TFIIH: Structure and Function

TFIIH is an incredible dual function multisubunit protein complex that plays a fundamental role in the transcription of protein-coding genes, and has a significant role in the NER system (Compe and Egly 2012; Oksenych and Coin 2010). During the process of transcription, TFIIH is essentially required for two main functions—first for the correct binding of RNA polymerase I and II at their specific promoter regions located in the upstream region of the gene and second for the promoter clearance of polymerases to culminate the initiation phase and proceed into the elongation phase of transcription via its C-terminal domain (CTD) phosphorylation (Compe and Egly 2012; Mydlikova et al. 2010). In TC-NER, TFIIH forms an essential component of the core incision machinery without which NER mechanism would cease to function properly (Egly and Coin 2011).

The TFIIH complex constitutes two sub-complexes: core complex and cyclin-dependent kinase (CDK)—activating kinase (CAK) complex. The 3D structure of TFIIH reveals to be of ring-like core from which the CAK module projects out (Chang and Kornberg 2000). Core complex in turn is composed of seven subunit core (XPB, p62, p52, p44, p34, and TTD-A) associated with a three subunit—CAK module by the XPD helicase (Oksenych and Coin 2010) (Table 7.2). CAK module constitutes CDK7 (p40), cyclin H (p34), and menage á trois 1 (MAT1; p32). Three important enzymatic subunits are located within the TFIIH complex, two ATP-dependent DNA helicases: XPB and XPD and one kinase CDK7 (Mydlikova et al. 2010; Zhovmer et al. 2010). Proteins p62, p52, p44, and p34 originally regarded just as "structural" subunits have been demonstrated to contain regulatory functions within TFIIH complex. Protein p52 moderates XPB activity by upregulating its ATPase activity via direct XPB/p52 interaction and it also anchors XPB to the core TFIIH. Protein p44 regulates XPD via direct p44/XPD interaction and also functions as ubiquitin ligase and protein p62 has been demonstrated to interact with thyroid hormone receptor TRβ (Compe and Egly 2012; Egly and Coin 2011; Mydlikova et al. 2010).

The two subunits of TFIIH—XPB and XPD, are both ATP-dependent DNA helicases with $3' \rightarrow 5'$ and $5' \rightarrow 3'$ DBA helicase activity, respectively (Mydlikova et al. 2010). XPB and XPD with opposite functional polarities have been suggested to cooperate in the opening of the damaged DNA helix on opposite sides of a lesion. XPB works on the $3'$ side of the lesion while its counterpart - XPD works from the $5'$ side (Fuss and Tainer 2011; Compe and Egly 2012; Oksenych and Coin 2010). However, the differential role played by both proteins has been demonstrated to switch its functionality between transcription and repair (Oksenych and Coin 2010).

Table 7.2 Composition of the human TFIIH complex

	Human	Yeast	Function	Related human disorders
CORE COMPLEaX	XPB	Ssl2	3′ to 5′ ATP-dependent helicase	Trichothiodystrophy and combined xeroderma pigmentosum and Cockayne syndrome
	XPD	Rad3	5′ to 3′ ATP-dependent helicase and forms a bridge between the CAK and the core	Trichothiodystrophy, xeroderma pigmentosum, and combined xeroderma pigmentosum and Cockayne syndrome
	P62	Tfb1	Structural function and interacts with transcription factors and NER factors, stimulates XPB	
	P52	Tfb2	Regulates the XBP ATPase activity	
	P44	Ssl1	E3 ubiquitin ligase[a], stimulates XPD	
	P34	Tfb4	Structural function and strong interaction with p44	
	P8	Tfb5	Interaction with P52, stimulation of XPB ATPase activity	Trichothiodystrophy
CAK MODULE	CDK7	Kin28	Kinase	
	Cyclin H	Ccl1	Modulates the CDK7 kinase activity	
	MAT 1	Tfb3	CAK stabilization and regulates cullin neddylation[a]	

CAK, cyclin-dependent kinase-activating kinase subcomplex; Ccl1, cyclin C like 1; CDK7, cyclin-dependent kinase 7; MAT1, ménage à trois 1; NER, nucleotide excision repair; Ssl, suppressor of stem–loop protein; Tfb, RNA polymerase II transcription factor b; XPB, xeroderma pigmentosum group B complementing protein

[a]Activity found in yeast only

XPB ATPase activity is essentially required for DNA opening in both NER and transcription but its helicase activity is committed specifically to polymerase promoter escape during transcription. XPD helicase activity plays a small role in transcription process but it is essential in NER system for the removal of DNA lesions (Oksenych and Coin 2010; Richards et al. 2008; Coin et al. 2007; Winkler et al. 2000; Tirode et al. 1999). Opening of the DNA double strand around the DNA lesion by these two helicases in an ATP-dependent manner is the first catalytic reaction of NER system. This in turn leads to the conformational changes that allow the recruitment of additional NER proteins to the site of lesion for its repair (Wolski et al. 2010).

Within the core complex of TFIIH, XPB protein is the biggest subunit of seven helicase motifs and it belongs to helicase superfamily 2 (SF2). XPD comprises of a

RecA-like fold that belongs to the SF2 family of helicases with distinct 4Fe4S (FeS) cluster which is central for its function as a helicase differentiating into two helicase domains, HD1 and HD2 (Mydlikova et al. 2010; Wolski et al. 2010; Rudolf et al. 2006; Zurita and Merino 2003).

In CAK domain, CDK7 protein constitutes the biggest subunit. It has bi-functional activity—one phosphorylase via which CDKs participate in the cell cycle, and second as a component of the TFIIH, which is essential for CTD phosphorylation of the largest subunit of RNA polymerase II (Mydlikova et al. 2010). MAT1 protein functions to link CAK to the core TFIIH in a complex interaction facilitated also by both XPD and XPB helicases. MAT1 interacts with the CDK7-cyclin H complex and stimulates the CDK7 kinase activity (Busso et al. 2000).

The role of TFIIH in transcription is via its joining the other general transcription factors like TFIIA, TFIIB, TFIID, TFIIE, and TFIIF to form the pre-initiation complex (of more than 30 polypeptides) together with central RNPII at the promoter region of the gene which is to be transcribed (Fig. 7.1). Promoter recognition is primarily carried out by TFIID which then recruits TFIIA and TFIIB. Eventually TFIIH entry into the complex is mediated via TFIIF/E (Compe and Egly 2012; Mydlikova et al. 2010). During the process of transcription, TFIIH plays a wide variety of roles: it is involved in initiation, promoter escape, and early elongation stages, to transcription reinitiation and formation of gene loops (Zhovmer et al. 2010). TFIIH controls transcription initiation and enhances the association of the RNPII CTD with the 7-methylguanosine (m7G) RNA capping machinery (Serizawa et al. 1993). The TFIIH kinase activity toward the CTD of Pol II can be regulated by different factors, including MAT1 (ménage à trois 1) and cyclin H, which are two binding partners of CDK7 within the CAK subcomplex (Komarnitsky et al. 2000). TFIIH also plays important role in the RNPI transcription of ribosomal genes (Iben et al. 2002).

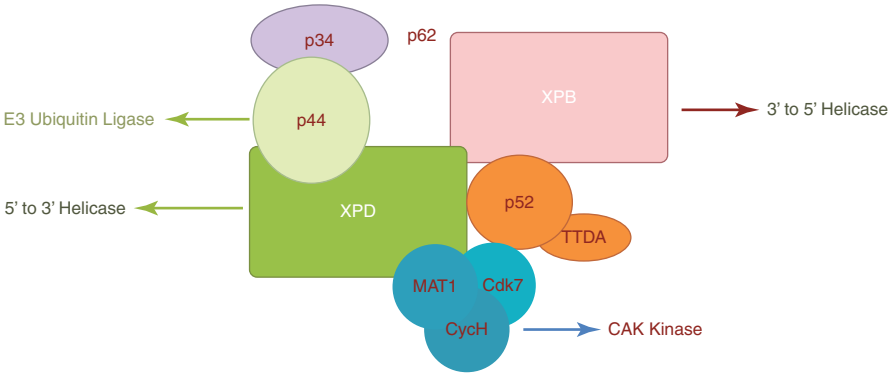

Fig. 7.1 A multisubunit functional complex of TFIIH. The TFIIH complex is composed of 11 subunits, with XPB making its one face and XPD another. The complex also contains CAK kinase domain of three subunits (Blue). Functionally TFIIH possess four enzymatic activities; XPB and XPD have helicase activity, Cdk7 has kinase, and p44 serves as E3 ubiquitin ligase

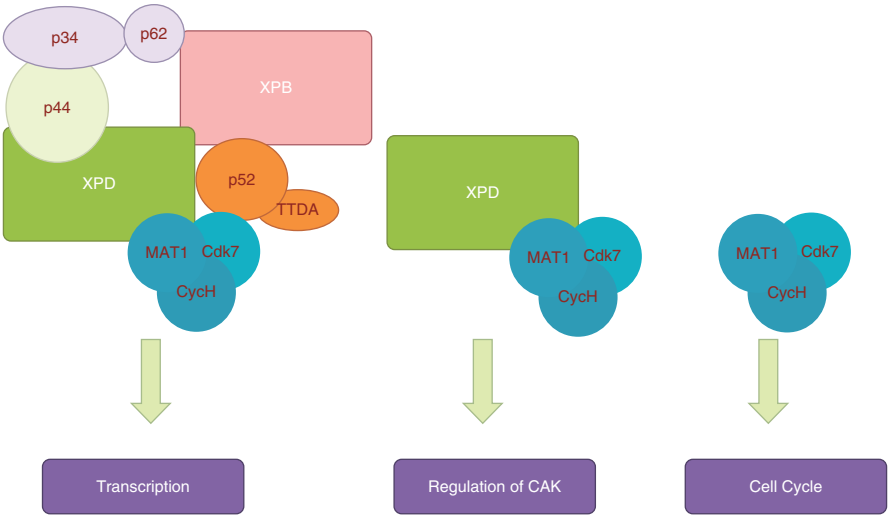

Fig. 7.2 TFIIH complexes vs non-TFIIH complexes and differences in their functions

Furthermore, depending upon the branches of the NER whether GG-NER or TC-NER, the recruitment of TFIIH to the lesion site in DNA is mediated either by XPC or the stalled RNPII. After recruitment, TFIIH opens the DNA around the lesion and allows the excision of long stretch of 24–32 nt DNA fragment (containing the lesion) and its subsequent replacement by a new DNA fragment (Compe and Egly 2012; Egly and Coin 2011; Oksenych and Coin 2010). In GG-NER, TFIIH forms a part of the dual incision complex constituting XPC-HR23B, centrin2, XPA, replication protein A (RPA), XPG, and excision repair cross-complementation group 1 (ERCC1)-XPF, and is involved in the opening of the DNA around the lesion (Fig. 7.2). Because of its high sensitivity for the recognition of damage sites, XPC not only rapidly detects the various DNA lesions but it also promotes the kinks in DNA helix forming a transient recognition intermediate, allowing the other proteins of NER to be recruited to the site (Compe and Egly 2012). XPA serves as a scaffold protein devoid of any enzymatic activity that nevertheless shows preferential association to damaged DNA and is indispensable for DNA incision (Missura et al. 2001). Soon after TFIIH correctly gets seated at the damaged DNA, it mediates the excision of the DNA lesion with the help of XPB and XPD ATPase/helicase activities (Oksenych et al. 2009).

7.1.4 XPD: Structure and Function

XPD (also known as ERCC2) is a helicase protein with a molecular weight of 86.9 kDa and constituting 761 amino acids (Benhamou and Sarasin 2002). XPD is one of the two essential ATPase/Helicase located in the core unit of THIIF molecular assembly. It helps to form a connection between the TFIIH core complex and the

CAK module—which otherwise also exists as a free trimeric complex with its own distinct functions (Cameroni et al. 2010; Wolski et al. 2010; Chen and Suter 2003). XPD belongs to an ATP-dependent 5′-3′ superfamily 2 (SF2) helicases, characterized by seven "helicase motifs" (walker motif I, Ia, II, III, IV, V, and VI) constituted of highly conserved amino acid sequences (Oksenych and Coin 2010). XPD protein also constitutes a 4Fe4S (FeS) cluster that is essential for its helicase activity. Because of this cluster XPD becomes a founding member of a family of related SF2 helicases (Rudolf et al. 2006, 2010; Liu et al. 2008). SF2 family helicases also includes various important family members like bacterial DinG (damage-inducible G) and the eukaryotic XPD paralogs FancJ (Fanconi's anemia complementation group J), RTEL (regular of telomere length), and Chl1 (chromatid cohesion in yeast) (Wolski et al. 2010). The exact function of the FeS cluster is not known but a number of explanations for its role have been given—a purely structural part which provides stabilization to the FeS domain; direct interaction with the damaged DNA lesion and acting as a damage sensor and acting as a regulatory center for XPD helicase (Wolski et al. 2008, 2010; Rudolf et al. 2006; Fan et al. 2008).

Furthermore, XPD serves as the authenticator of the DNA lesion initially sensed by XPC-HR23B which preludes the binding of TFIIH at the site of lesion (Oksenych and Coin 2010). The opening of the DNA duplex at the site of lesion requires the dual ATPase function of both XPB and XPD. However, the helicase activity of XPD plays a critical role in the opening of the DNA helix at the lesion site. The biochemical data vividly demonstrates that mutations in the motif I (containing ATPase activity) of either XPB or XPD inhibits the formation of DNA bubble at the lesion site but the mutations in the motif III and IV (containing helicase activities) of XPB impairs its functionality but does not inhibit NER in vivo (Coin et al. 2007). However, some specific mutations in both XPB and XPD can completely prevent opening and dual incision of the DNA lesions site in NER (Evans et al. 1997). Additionally, it has also been demonstrated that binding of N-terminal p44 subunit with XPD stimulates its helicase activity by almost tenfold. Furthermore, mutations in the C-terminal domain (CTD) of XPD prevents the interactions with p44 resulting not only in decrease in the overall TFIIH helicase activity but also modulates TFIIH composition and contributing to further transcription defects (Coin et al. 1998, 1999). XPD has also been demonstrated to control the cell cycle via its interaction with CAK domain of the TFIIH complex. Downregulation of XPD, as happens at the beginning of the mitosis, initiates the disengagement of CAK module from TFIIH complex and its eventual role as regulator of cell cycle independent of TFIIH core complex (Chen et al. 2003).

7.1.5 XPD Gene SNPS

XPD gene is located at chromosome 19q13.3 and comprises of 23 exons which span around ~54.3 kb in length; cDNA of this gene is about 2400 nt (Benhamou and Sarasin 2002). Point mutations in the human XPD protein are known to cause DNA repair-deficiency diseases (like xeroderma pigmentosum, trichothiodystrophy, and

Table 7.3 Most common mutations affecting XPD protein

S. no	Human	Sulfolobus acidocaldarius	Motif affected	Disease
1	T76A	T56A	Ia	XP
2	D234N	D180N	II	XP
3	Y542C	Y403C	IV	XP
4	R601L/W	K446L	V	XP
5	R638W/Q	R531W		XP
6	K507Q	K369Q	Channel	
7	G47R	G34R		XP/CS
8	G602D	G447D		XP/CS
9	R666W	R514W	VI	XP/CS
10	G675R	C523R		XP/CS
11	R112H	K84H		TTD
12	R592P	K438P	V	TTD
13	D673G	D521G		TTD
14	C116	C88S	4Fe-4S	
15	C134	C102S	4Fe-4S	

Adapted from Fan et al. (2008)

Cockayne syndrome). These diseases are characterized by high ultraviolet-light hypersensitivity, a high mutation frequency, and cancer-proneness, as well as some mental and growth retardation and probably aging. So far 100 different mutations have been reported in the XPD gene (Itin et al. 2001; Fan et al. 2008) (most important are given in Table 7.3); most of which are clustered in the C-terminal domain of the protein, which is the pivotal interaction domain of XPD for p44 (Fan et al. 2008; Tirode et al. 1999; Coin et al. 1998, 1999).

In addition to the lethal point mutations, a number of single nucleotide polymorphisms (SNPs) have also been reported in the *XPD* gene in both exonic and intronic regions. Researchers have defined 17 different SNPs in the XPG gene; seven of which affected the coding regions of the gene (exons 6, 8, 10, 17, 22, and 23) and hence affected XPD enzymatic activity (Shen et al. 1998; Mohrenweiser et al. 2002). Among all, four SNPs result in amino acid changes: isoleucine to methionine in codon 199 (C > G), histidine to tyrosine in codon 201 (C > T), aspartic acid to asparagine in codon 312 (G > A), and lysine to glutamine in codon 751 (A > C). Out of these four, only two are the most commonly occurring ones—codon 312 and 751 while as other two—codon 199 and 201 are rare (Benhamou and Sarasin 2002; Shen et al. 1998).

7.1.6 XPD SNPS, DNA Repair Capacity, and CRC

Among all the reported SNPs of XPD, most of the population-based case-control studies have focused on studying the effects of SNPs affecting codons 156, 312, and 751 only, partly because of their high occurring frequency and partly because of their effects on XPD helicase activity (Benhamou and Sarasin 2002; Shen et al. 1998; Coin et al. 1998).

XPD Asp312Asn and Lys751Gln are two of the most common SNPs located within the exon 23 of the *XPD* gene which affects the C-terminal domain of XPD helicase that is known to interact with p44 protein of TFIIH complex, thereby stimulating XPD helicase activity (Coin et al. 1999). Thus, these two SNPs may therefore affect different protein interactions and diminish the activity of TFIIH complexes (Shen et al. 1998). In addition, XPD Lys751Gln SNP is also known to reduce the XPD protein expression by decreasing the mRNA stability (Moisan et al. 2012).

Lunn et al. (2000) was the first to report the reduced repair of X-ray-induced DNA damage by XPD Lys751Lys genotype. It was reported that individuals with the XPD 751 Lys/Lys genotype had a higher number of chromatid aberrations than those having a 751Gln allele. Possessing a Lys/Lys751 genotype increased the risk of suboptimal DNA repair by almost sevenfolds, suggesting that the Lys751 (common) allele may alter the XPD protein product resulting in suboptimal repair of X-ray-induced DNA damage.

Furthermore, it has been also reported that the XPD Lys751 allele is associated with a high level of UVC-induced formation of DNA strand breaks (Møller et al. 2000). Also, Lunn et al. (2000) suggested that XPD Lys751 may alter the XPD protein product resulting in the suboptimal repair of X-ray-induced DNA damage. However in contrast, two studies reported that the cells containing the homozygous Lys/Lys XPD protein had the elevated repair capacity than the cell containing XPD protein with Gln in either of the two forms (Spitz et al. 2001; Qiao et al. 2002).

A large number of epidemiological studies have been carried out recently to understand the effects and role of XPD SNPs on the modulation of risk of CRC; while some studies found a significant association between the two (Paszkowska-Szczur et al. 2015; Procopciuc and Osian 2013; Gan et al. 2012; Rezaei et al. 2013; Huang et al. 2013; Skjelbred et al. 2006); others failed to link them (Zhang et al. 2011, 2014; Du et al. 2014; Moghtit et al. 2014; Yeh et al. 2005).

Two important recent meta-analyses—one by Zhang et al. (2011) on 15 case-control studies (including a total of 3042 cases and 4627 controls) and another by Zhang et al. (2014) on 11 case-control studies (including a total of 32,961 cases and 4539 controls) did not find any evidence of a link between the XPD Lys751Gln polymorphism and risk of CRC. A recent study by Moghtit et al. (2014) on Western Algerian CRC patients (consisting of 129 cases and 148 controls) reported no association of the XPD Lys751Gln with CRC risk. Furthermore, Sliwinski et al. (2009) in their study on polish CRC cases did not find any significant association between any genotype of XPD 751 codon SNP and the occurrence of CRC; they also did not observe any relationship between XPD 751 SNP and any of the clinicopathological parameters.

Paszkowska-Szczur et al. (2015) in their study on polish CRC patients observed a significant association of XPD 312 SNP with the risk of developing CRC and strongly in men. Also, the study of Rezaei et al. (2013) in their study on Iranian CRC cases observed that individuals with heterozygous variant (Lys/Gln) SNP of XPD gene may have an increased susceptibility to CRC compared to other SNPs

(Lys/Lys and Gln/Gln). Furthermore, they observed that heterozygous variant (Lys/Gln) was more frequent in CRC patients than in the control group. Similar results were also reported previously by Skjelbred et al. (2006) and Moreno et al. (2006) in their own respective populations. Also, Stern et al. (2006) have demonstrated lower risk of developing CRC in homozygous (Lys/Lys) SNP carriers. Contrarily, the study of Wang et al. (2010) on Indian CRC patients found that XPD 751Gln allele demonstrated the 3.5 times increased risk of rectal cancer.

However, meta-analysis by Mandal et al. (2014) of 13 case-control studies (including 3087 cases and 3599 controls) reported the likely association of the XPD Lys751Gln polymorphism with the risk of development of cancer in Indian population. Their meta-analysis concluded that XPD Lys/Gln and XPD Gln/Gln genotypes had had 1.3- and 1.6-fold increased risk of developing cancer as compared with the wild XPD Lys/Lys genotype, respectively. Similarly, another meta-analysis of 37 case-control studies (including 9027 cases and 16,072 controls) by Du et al. (2014) suggested that the XPD 751Gln/Gln genotype was a low-penetrative risk factor for developing digestive tract cancers, especially in Asian populations.

My own study in ethnic Kashmiri population (Sameer 2018; Unpublished data) indicated that XPD Lys751Gln SNP may predispose our population to the development of CRC. Furthermore, it was also found the XPD Gln allele frequency to be about 26% among controls and almost 33% among CRC patients, this frequency was in accordance with the study of Moghtit et al. (2014).

7.2 Conclusion

Since XPD is one of the major molecules which connects the two essential processes of sustenance of life –NER pathway and transcription process, it is one of the most analyzed molecules of NER in various epidemiological studies carried out on CRC. However, even though a decade of research on XPD gene and its SNPs, no clear relationships between its various SNPs and the risk of CRC has been established till date. To establish a cohesive data on XPD SNPs, well-designed studies with large statistical power is warranted to clarify the ambiguity associated with the current data on XPD SNPs.

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Laparoscopy in Colorectal Cancer

8

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Abbreviations

ALaCart	Australian laparoscopic cancer of rectum
APR	Abdomino perineal resection
AR	Anterior resection
ASCOG	American College of Surgeons Oncology Group
CI	Confidence interval
CLASSIC	Conventional vs. Laparoscopic Assisted Surgery in Colorectal Cancer
COLOR	Colon Cancer Laparoscopic or Open Resection
COREAN	Comparison of open vs. laparoscopic surgery for mid- or low rectal cancer after neoadjuvant chemoradiotherapy
COST	Clinical outcome of surgical therapy
CRM	Circumferential resection margin
EMR	Endoscopic mucosal resection
ERAS	Enhanced recovery after surgery
HALS	Hand-assisted laparoscopic surgery
IH	Incisional hernia
Lap	Laparoscopic
MAS	Minimal access surgery

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MRC	Medical Research Council
NOSE	Natural orifice specimen extraction
NSQIP	National Surgical Quality Improvement Program
QOL	Quality of life
RCT	Randomized controlled trial
SBO	Small bowel obstruction
SILS	Single-incision laparoscopic surgery
SLS	Standard laparoscopic surgery
SPLS	Single port laparoscopic surgery
T1, T3	Used for tumor staging in tumor, node, metastasis classification
TME	Total mesorectal excision
TUSE	Transumblical specimen extraction
TVSE	Transvaginal specimen extraction

8.1 Laparoscopy

The term "laparoscopy" is derived from the Greek words "lapara," meaning "the soft parts of the body between the rib margins and hips," and "skopein," meaning, "to see, view or examine."

The art and craft of laparoscopy describes the process of viewing the abdominal cavity using specially designed instruments and a camera system controlled by the surgeon outside the abdomen.

The concepts of open colorectal surgery date back to Sir William Arbuthnot-Lane at Guy's Hospital in London in early part of twentieth century for treatment of constipation. Following this the colorectal surgery saw a new dawn of rapid development and better understanding in the last part of century. However, in 1913 Lane was criticized and ridiculed for doing a total colectomy for a patient of chronic constipation. But his surgery ultimately proved to be a milestone for the management of a variety of benign and malignant colorectal diseases (Blackmore et al. 2014).

The era of laparoscopy in abdominal surgery heralded in 1985 with Muhe performing first laparoscopic cholecystectomy in Germany (Reynolds 2001). First laparoscopic-assisted colonic surgery was performed by Jacob in 1991 in Miami, Florida (Jacobs et al. 1991) and by Fowler in Kansas (Fowler and White 1991).

Laparoscopy is making its benchmark in every surgical field. To decrease the number of scars and aim at better cosmetic outcome is the main of laparoscopic surgery. Even though the laparoscopic surgery in colorectal pathologies is quite advanced and a demanding procedure, the commitment and dedication of surgeons and technical advances made by various industries has made it possible. Training in simulation (endo trainer) laboratories, dry and wet labs and high-volume centers made it possible for surgeons to learn and improve their skills and to perform such surgeries by laparoscopic means. Besides high-definition cameras and monitors helped all surgeons a

great deal in defining the anatomical planes more appropriately and operate with a greater degree of ease, comfort, and precision. Energy sources like harmonic scalpel, ligasure, bipolar and monopolar cauteries, and use of vessel sealing devices allowed a surgeon to work in a bloodless field and perform better surgeries. Use of liga clips, hema clips, endostaplers, and skin staplers has markedly cut short on the time of procedures and made advanced laparoscopic procedures more acceptable worldwide. In present day world, if a surgeon acts orthodox or is a little reluctant to welcome new technology, ultimately it is he who lags behind. Laparoscopic surgery has now made its inroads in colon and rectal cancer and all over the world laparoscopy has become an accepted procedure for such cancers (Figs. 8.1 and 8.2).

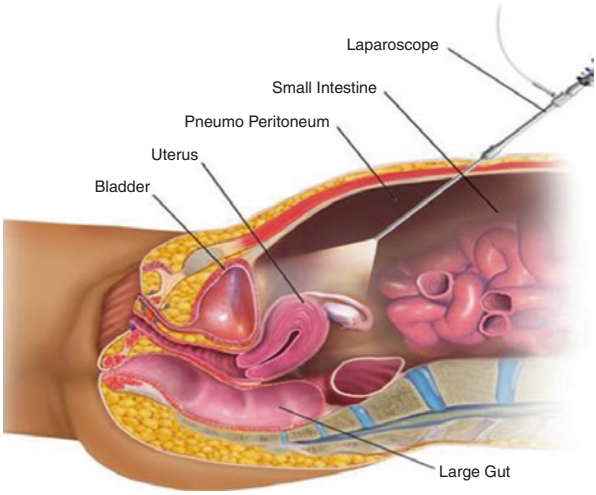

Fig. 8.1 Inside view of abdominal viscera at laparoscopy

Fig. 8.2 Operation theatre view for advanced lap surgeries

8.1.1 Laparoscopy in Colon Cancer

The art of laparoscopy in colonic cancer saw gradual evolution after Moises Jacob reported his first laparoscopic colectomy (Jacobs et al. 1991).

The initial years saw a very sluggish development in the popularity of this craft because of a steep learning curve and lack of widespread availability. The other concerns which heralded the development of the craft were the concerns about oncological safety and port site metastasis (Berends et al. 1994).

The acceptability of the laparoscopic craft went on increasing slowly and steadily with the help of evidence from landmark randomized controlled trials (RCTS) like Barcelona Trial, Color trial, and MRC Trial which are described in detail as under:

8.1.1.1 Barcelona Trial

This trial was conducted with a purpose to know about the overall safety of role of laparoscopy in colon cancers. It was conducted in early 1990s. The total numbers of patients included in the trial were 219. This trial reported a conversion rate of 11%.

The main flaws in the trial were: an underpowered trial, lesser acceptances by surgeons and patients, small sample size, steep learning curve, evolving technology, and lack of facilities for structured training for surgeons.

However, this trial did clear some of the confusions regarding cancer-free survival which was found to be same in open and laparoscopic group. Besides in this trial, the confidence interval (CI) was in the range of −3.2 and +7.2% which in simpler words would mean that in laparoscopic group the 3-year survival would be less by 7.2% than open group but in the worst possible case scenario. This was the only RCT of its kind to report benefits of laparoscopic surgery for oncological safety.

In 2008 Lacy et al. found that in stage III disease the laparoscopy offers better long-term survival and lesser tumor recurrences.

However, other RCTS did not report any beneficial oncological outcomes after laparoscopy (Fleshman et al. 2007; Jayne et al. 2007; Colon Cancer Laparoscopic or Open Resection Study Group et al. 2009).

8.1.1.2 The COLOR (Colon Cancer Laparoscopic or Open Resection) Trial

This trial included total of 1248 patients of colon cancer, which were randomized into two groups. One group assigned to laparoscopic resection (n = 627) and the other group assigned to open resection (n = 621). In laparoscopic group they reported a shorter hospital stay, an early return of peristalsis, lesser requirement of analgesia, decreased blood loss but a longer operating time.

It was also found that the histopathological reports of radical resection margins did not report any difference in the two groups. The conversion rate was 17%. The conclusion drawn was that laparoscopy is quite a safe way to operate on malignancy of colon (Veldkamp et al. 2005).

This trial also reported that there was no difference in the total cost between the two groups in 4 months to the society and disease-free survival remained same. But laparoscopic surgery definitely proved costlier to the health care system (Janson et al. 2004).

8.1.1.3 COST (Clinical Outcomes of Surgical Therapy) Study Group

This study included patients of colon cancer. The patients were randomly divided into laparoscopic resection group ($n = 435$) and open resection group ($n = 437$). The study period spread over 1994–2001. It included patients from 48 institutions. The criteria for participation of any surgeon's inclusion was that he has done more than 20 laparoscopic resections. However, the conversion rate in this trial i.e., 21% was a little higher than reported in earlier trials.

In laparoscopic resection group, the patients had a quicker recovery with a short hospital stay but operating times were longer and intraoperative complications were more; however, it did not reach a statistical significance. Also, the other parameters like tumor recurrence, overall survival and morbidity and mortality did not show any significant difference. The trial concluded that laparoscopic resection for colonic cancer is a safe method of resection (The Clinical Outcomes of Surgical Therapy Study Group 2004).

8.1.1.4 The MRC CLASICC (Conventional vs. Laparoscopic-Assisted Surgery in Colorectal Cancer) Trial

This was the first trial which included rectal as well as colon cancer patients. A total of 794 patients were randomized into two groups; laparoscopic resection group ($n = 526$) and open resection group ($n = 268$). The ratio was 2:1 in the study population. The study was conducted in 27 institutes of the UK. The study period was 1996–2002. Patients who needed conversion were found to have increased complication rate. CRM positivity incidence was also more in resection group for patients of carcinoma rectum who had anterior resection; however, it was not statistically significant. Conversion rates were higher for carcinoma rectum as compared to carcinoma colon; 32% and 25%. Hospital mortality and quality of life remained same in both the groups at 2 and 12 weeks after the surgery. The conclusion drawn was that laparoscopic surgery is as effective as open surgery but because of the availability of only short-term outcome, it is still not considered a gold standard in rectal cancer (Fleshman et al. 2007; Jayne et al. 2007; Colon Cancer Laparoscopic or Open Resection Study Group et al. 2009).

8.1.1.5 Meta-analysis from Trials

This is a meta-analysis of all the mentioned trials. This trial included 1765 patients. In this study, a confidence interval (CI) −5% to +4% is reported, which is an accepted difference clinically. The inference drawn from the meta-analysis was that laparoscopic surgery for colon cancer is oncologically a safe surgery (Transatlantic Laparoscopically Assisted vs. Open Colectomy Trials Study Group 2007).

8.1.2 Laparoscopy in Rectal Cancer

This craft still is considered to have a steep learning curve for dealing with rectal cancer. Most of the studies still report very high conversion rates like 18% (Morino), 27% (Poulin) for AR, and 3% for APR and 32% conversion by CLASSIC Trial. But there is a definite advantage of laparoscopy in patients of carcinoma rectum in

terms of shorter hospital stay, better stomal function, and early bowel movement (Aziz et al. 2006). Some studies showed a significant disadvantage in preservation of sexual function (lap 47%; open 5%) while the bladder dysfunction remained the same in both groups (Quah et al. 2002).

But the results of CLASSIC Trial report equal incidence of bladder and sexual dysfunction in both groups. In anterior resection group the CRM positivity was more in laparoscopic group, i.e., 12% vs. 6% (p-value 0.19) but in APR it was 20% vs. 26% (p-value 1.00) (Guillou et al. 2005). The local recurrence rate was 7.8% vs. 7% (p-value 0.70) for AR in lap vs. open group but for APR it was 21% vs. 15% (p-value 0.47%). Disease-free survival remained the same in both groups (Jayne et al. 2007).

A significant factor in decreasing the complication rate for advanced procedures still remains the learning curve in laparoscopy. Cleveland Clinic reports a marked decrease in complication rate over a period of years. The complication rate decreased from 29 to 11 to 7% from 1991 to 1993 to 1995, respectively, in laparoscopic colorectal surgery (Agachan et al. 1996). Even the conversion rates markedly decrease as soon as the surgeons negotiate the learning curve (Pandya et al. 1999). Most of the literature does not report clearly about port site metastasis. However, the comparison about port site recurrence in a multicenter RCT reports <1% recurrence ($p < 0.50$) (COST Study Group et al. 2004).

Even though the laparoscopic resection for rectal cancer are now picking up all over the world, the fact remains that robust evidence to conclude that laparoscopic surgery and open surgery have similar outcomes in rectal cancer is lacking. A COLOR 11 trial was designed to address the issue.

This international trial was conducted in 30 hospitals on 1044 patients (699 in laparoscopic group and 345 in open group). It included patients of solitary adenocarcinoma of rectum within 15 cm of anal verge without any invasion into adjacent tissue and metastatic disease. Patients were randomly assigned to two groups: laparoscopic or open in the ratio of 2:1. The primary end point was locoregional recurrence 3 years after the index surgery. Secondary end points included disease-free and overall survival.

At the end of 3 years, the locoregional recurrence was 5% in the two groups (difference, 0 percentage points; 90% confidence interval [CI], −2.6 to 2.6). Laparoscopic group showed a disease-free survival of 74.8% and in open group it was 70.8% (difference, 4.0 percentage points; 95% CI, −1.9 to 9.9). Overall survival rates were 86.7% in the laparoscopic group and 83.6% in the open group (difference, 3.1 percentage points; 95% CI, −1.6 to 7.8).

8.1.2.1 Conclusions

Laparoscopic surgery in patients with rectal cancer was associated with rates of locoregional recurrence and disease-free and overall survival similar to those for open surgery.

The limitations of COLOR 11 study are:

- Absence of centralized macroscopic and microscopic evaluation of the resected specimens.
- Different imaging methods to determine the location of the tumor.

Better alternative was to standardize the imaging technique of the pelvis and calibrate the measurements centrally by independent professionals (Bonjer et al. 2015).

8.1.2.2 TME

In the Dutch trial, 1805 patients with TME by open surgery, the locoregional recurrence was 5.3% at 2 years which resembled the results of COLOR 11 (Kapiteijn et al. 2001).

8.1.2.3 COREAN Study

COREAN study was conducted on 340 patients with middle and lower rectal cancer who were downstaged with neoadjuvant treatment. Rates of locoregional recurrence were 2.6% in laparoscopic group and 4.9% in open group. The circumferential resection margin (CRM) was involved in 2.9% in laparoscopic group and 4.1% in open group. In this study CRM was 1 mm whereas in COLOR 11 it was 2 mm (Jeong et al. 2014; van der Pas et al. 2013).

The disease-free survival rates in COLOR 11 were 74.8% after laparoscopic surgery and 70.8% after open surgery, as compared with rates of 79.2% and 72.5%, respectively, at 3 years follow-up period in the COREAN study (Jeong et al. 2014). In COLOR 11 study trail, disease-free survival rates were 64.9% after laparoscopic surgery and 52.0% after open surgery in patients of stage 2 disease and same thing was observed by Lacy et al. for lymph node positive colon cancers (Lacy et al. 2002). The reduced tumor recurrence may be explained on the basis that probably laparoscopic technique causes less tissue trauma (Bouvy et al. 1997). Even laparoscopic surgery was shown to have attenuated stress response and improved preservation of immune function as compared to open surgery in one of the studies (Veenhof et al. 2012). However, to draw a conclusive evidence whether laparoscopy is associated with improved survival, further randomized multicentric studies are needed.

Even today rectal cancer surgery is a technically demanding, what so ever surgical technique adopted especially for mid- and low rectal growths. Wisdom demands a proper training in high-volume centers before independently performing these surgeries by any technique. Laparoscopic surgery in rectum has a steep learning curve and expertise in this technique cannot be assessed objectively. However, conversion rates and operative time give an indirect assessment of the laparoscopic expertise (Harrysson et al. 2014). The median operative times for laparoscopic surgery were 245 min in COREAN Trial and 240 min in COLOR 11. The conversion rates in COREAN Trial was 1% (surgeries by highly skilled surgeons), 16% in COLOR 11, and in CLASSIC group it was 38% in first year but came down to 16% in last year (Guillou et al. 2005). Another important lesson drawn from COLOR 11 was that patients with T4 and T3 lesions within 2 mm of endopelvic fascia need to be excluded from laparoscopic resection as circumferential resection margin is threatened in such lesions.

To conclude, the long-term results of COLOR 11 trial label laparoscopic surgery in localized rectal cancer safe and effective.

8.1.2.4 RCT of Laparoscopic-Assisted Resection

This trial was conducted on patients of colorectal carcinoma. Three-year results reported that laparoscopic-assisted surgery for carcinoma of colon is equivalent to

open surgery. In both groups the oncological outcome and QOL is comparable. Even now there are reports available about the long-term outcome in patients of rectal cancer after laparoscopic resection. The results conclude that laparoscopic APR and AR has similar outcome as with open groups and laparoscopic use should be continued in such patients for carrying out the resection (Jayne et al. 2007).

8.1.2.5 Cochrane Systemic Review of RCT (COST Study Group et al. 2004)

This review of RCTS conveyed a message that outcome of surgery in colon cancer patients after laparoscopic resection is same as we see after open resection. About carcinoma upper rectum, the review says that even though at present laparoscopic resection in upper carcinoma rectum is acceptable but in order to assess the long-term outcome more RCTS need to be conducted. The new studies did not find any difference in QOL after surgery in the two groups (Kuhry et al. 2008).

In spite of so many favorable studies for laparoscopic resection, some studies still report a high incidence of intraoperative complication rate in laparoscopic surgery (Bartels et al. 2010; Tarik et al. 2011).

To conclude laparoscopy is definitely having the advantages of:

- Decreased hospital stay
- Cosmetic superiority
- Reduced need of postoperative analgesics
- Early bowel function recovery
- Same oncological clearance as with open surgery

Twelve trials on laparoscopy vs. open included more than 3346 patients confirmed that there is no difference in cancer-related mortality and overall recurrence rate also remains the same. However, one must remember that "Technical demands and steep learning curve can compromise expected oncologic Outcomes" (Parray 2012; Park et al. 2009).

8.1.2.6 Long-Term Follow-Up of CLASICC Trial

In order to assess the feasibility of a procedure application, long-term follow-up data needs to be analyzed. In patients enrolled for CLASSIC Trial the survival outcomes and recurrences were analyzed on long-term follow-up. The patients had a median follow-up of 62.9 months. The analyzed results did not show any overall survival difference in the laparoscopic resection and open resection group. Another important observation made in the study was that worst overall survival was observed in patients of colon cancer who were converted to open surgery. No significant difference was seen in terms of recurrence in two groups. However, at 10 years right colon cancers developed more recurrent cancers as compared to left colonic cancers.

8.1.2.7 Cochrane Review

A 2014 Cochrane review suggests that survival and recurrence rates are similar to those for the equivalent open procedure, though the evidence is not yet sufficiently precise to rule out the possibility that one approach may be superior to the other (Vennix et al. 2014).

The conclusion of the author of this Cochrane review is that there is moderate quality evidence that laparoscopic total mesorectal excision (TME) has similar outcome as with open TME on long-term survival outcomes for the treatment of rectal cancer. The quality of the evidence was downgraded due to imprecision and further research could impact on the confidence of authors in this result. There is moderate quality evidence that it leads to better short-term postsurgical outcomes in terms of recovery for nonlocally advanced rectal cancer. Currently, results are consistent with similar disease-free survival and overall survival and for recurrences after at least 3 years and up to 10 years. Although due to imprecision, the authors cannot rule out superiority of either approach. They await long-term data from a number of ongoing and recently completed studies to contribute to a more robust analysis of long-term disease free, overall survival, and local recurrence.

Conclusion

Laparoscopy for colon and rectal cancer continues to be a safe option on long-term results.

In two recent randomized controlled trial (ALaCart and ASCOG Z6051), the superiority of laparoscopic approach was challenged.

In the ASCOG Z6051 trial (American College of Surgeons Oncology Group), 92% of patients of carcinoma rectum had complete or near complete TME by laparoscopic approach with only 11% conversion rate but still failed to demonstrate non-inferiority of laparoscopic surgery as compared to open due to nonstatistically validated composite end point (Stevenson et al. 2015; Fleshman et al. 2015).

The purpose of conducting ALaCART trial (Australasian Laparoscopic Cancer of rectum) was to see the effect of laparoscopic-assisted resection vs. open resection on pathological outcomes in rectal cancer. The study included 475 patients with T1-T3 rectal cancer lesion <15 cm from anal verge randomized into open (n = 232) and laparoscopic group (n = 238). The objective was to determine whether laparoscopic resection is non-inferior to open rectal cancer resection for cancer clearance. Pathologists used standardized reporting and were blinded to methods of surgery. The conclusion was that in T1-T3 rectal tumors, there was no inferiority of laparoscopic surgery vs. open surgery for successful resection. Even though the overall quality of surgery was high but still it lacked sufficient evidence to promote laparoscopic surgery in routine practice. The trial recommends a longer follow-up to ascertain recurrence and survival (Stevenson et al. 2015).

The health expenditure in the USA has reached three trillion dollars and is expected to go uptown five trillion dollars by 2023; thus it becomes important for the health care system to get down the expenditure by way of introducing more of laparoscopy in colorectal surgery which can help in increasing efficiency, decreasing hospital stay, and postoperative complication rate (National health care expenditures n.d.).

The evolution in minimal invasive surgery is going beyond our imagination and the cutting-edge technology of present time might be the thing of the past very soon. In this process of evolution what is important for us as responsible treatment providers is that patient safety should get the highest priority and all new techniques need to undergo large trials before being put into practice. The bright future of minimally invasive technology in colorectal surgery needs to be practiced with caution to ensure patient safety.

8.2 Hand-Assisted Laparoscopic Surgery (HALS)

The acceptability for use of laparoscopy in colorectal pathologies is increasing all over the globe with each passing day. The procedure may be performed as a standard laparoscopic surgery (SLS) or hand-assisted laparoscopic surgery (HALS).

In HALS, a small incision is made at the start of the procedure in midline or Pfannenstiel for insertion of hand using a self-retaining Alex retractor sealed with a gel port. This hand is used to retract the bowel, feel for the growth if the need arises, and feedback tactile sensation while dissection is being done using laparoscopic instruments without the loss of pneumoperitoneum. The same port is used for specimen extraction and for performing the extracorporeal anastomosis which saves a lot of operative time.

In standard laparoscopic surgery (SLS), on the contrary whole bowel is retracted and mobilized with instruments and specimen is extracted through a very small incision only. The anastomosis can be performed intra or extracorporeal depending on the expertise and availability of endostaplers. Even though HALS seems to have a theoretical advantage in a way of having assistance of one hand which may be of benefit to have better orientation of gut during dissection and may provide a degree of comfort in complex procedures but the main established benefit remains to shorten the surgery time but even that failed to show up a substantial time difference in the first two RCTS which compared HALS and SLS (HALS Study Group 2000; Targarona et al. 2002).

But some studies have shown that HALS has real operative time advantages with more complex colonic procedures like total colectomy (Nakajima et al. 2004; Rivadeneira et al. 2004).

The literature further reports that in complex diverticulitis HALS not only reduces the operation time but also decreases the conversion rates (Lee et al. 2006).

In a recent review of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database 1740 matched patients in two groups were compared for open colectomy vs. HALS Colectomy. The open group had significant high morbidity, surgical site infection, urinary tract infection, hospital readmission, reoperation, and ileus as compared to HALS group. Hence, the authors after seeing the outcome of this study have suggested that HALS technique can be used as a bridge to laparoscopy or as a tool in difficult cases (Benlice et al. 2016a, b).

Two recent papers published after reviewing the American college of Surgeons NSQIP database comparing HALS to standard laparoscopy, one review of 7843 patients who underwent one of the procedures showed that operation time was marginally shorter in HALS group but surgical site infection and ileus rates remained slightly higher in this group (Benlice et al. 2016a, b).

In year 2012–2013 the review of 13,949 propensity matched patients on the same database for the same procedures were compared. HALS group had significantly higher rates of postoperative ileus, wound complications and 30 day readmission without any difference in the operating time (Gilmore et al. 2016).

A prospective multi-institutional randomized study showed that operative time got decreased substantially in segmental and total colectomy with HALS. The only disadvantage with the HALS is a little larger incision as compared to SLS but otherwise all other RCTS are showing similar short-term outcome in both the groups for return of gastrointestinal peristalsis and duration of hospital stay (HALS Study Group 2000; Targarona et al. 2002; Marcello et al. 2008).

Whether to use HALS or not is actually subjective and will remain controversial. Surgeons who are comfortable with SLS will never favor the use of HALS while as those who are regularly practicing HALS always supports its use.

Comparative studies were conducted to know the long-term complication profile after HALS and SLS to know the incidence of incisional hernia (IH) and small bowel obstruction (SBO) after colon and rectal resection and the conclusion drawn was that HALS does not increase the incidence of these long-term complications (Sonoda et al. 2009).

HALS at present is considered to provide maximum benefits of laparoscopic surgery and at the same time is considered to be a safe and effective technique (Figs. 8.3 and 8.4) (Samalavicius et al. 2013).

Fig. 8.3 Alexis port system for hand retraction and specimen retrieval with air-seal technology

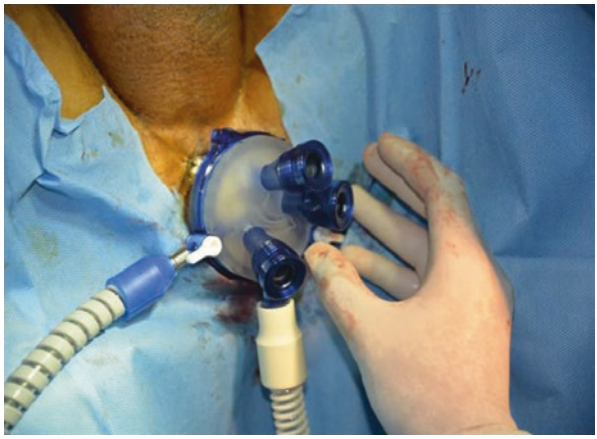

Fig. 8.4 Use of Gelport with ports inserted (used for transanal and transabdominal lap surgeries)

8.2.1 Advantages

- Restored tactile feedback
- Preserving the main idea of MAS
- Reduced conversion rate
- Enhanced safety and efficiency
- Improving the steep learning

8.2.2 Limitations

- Fatigue
- Impaired tactile feedback in long procedure
- Crowding of the hand with the instruments
- Fewer acceptances because of mini laparotomy
- Cosmetically inferior
- Increased duration of ileus
  Proponents of standard laparoscopy, however, criticize HALS technique because it may encourage blind and blunt dissection of the holy plane in posterior mobilization of the rectum, which contradicts the fundamental principles of TME. As per the TME principles we need to go for precise, sharp dissection in the embyronic areolar tissue plane under direct visualization, emphasizing the avoidance of violation of the mesorectal fascia and preservation of the autonomic nerves.

HALS, even though, is still advocated by some surgeons in technically demanding cases, it has been shown to be clearly inferior to standard laparoscopy. At present HALS demonstration in laparoscopic high-volume institutes should be limited to an educational tool.

8.3 Single-Incision Laparoscopic Surgery (SILS)

The concepts of minimal invasive surgery are evolving more and more and with each passing year we want to do more with best cosmesis, hence the concept of SILS, also known as single-port laparoscopic surgery (SPLS), emerged and it was utilized in colorectal surgery also. In this technique, we approach the abdomen through a small incision around umbilicus which remains cosmetically almost as a hidden scar (Fig. 8.5). A SILS Port is negotiated through this incision and all working instruments are pushed through the port to carry out the procedure.

Whether SILS is better than SLS is still under evaluation and all the data available at present still have not set aside the controversy.

A systemic review and meta-analysis comprising of more than 1000 colorectal operations suggest that SILS is a safe and feasible option for colorectal patients (Maggiori et al. 2012).

Fig. 8.5 Single incision laparoscopic surgery (SILS) port

Another meta-analysis proved that SILS if performed by experienced hands can be more feasible and safe option in malignancies but the conversion rates will be higher. SILS will definitely benefit more than SLS with its cosmetic superiority (Lv et al. 2013).

8.3.1 Technique

A single incision is made around umbilicus which is a potential embryological defect. A SILS multi-lumen port is negotiated through the incision. Different types of specialized instruments with different curvatures and articulations are used for dissection. This special design of instruments helps the surgeons to come over the principles of triangulation. SILS is emerging as a new technique aimed at better cosmesis, minimizing operative trauma, and lesser morbidity.

SILS is now becoming more and more evidence based as studies prove that this method of surgery is not only feasible but also safe (Raman et al. 2009; Podolsky and Curcillo 2010).

In SILS surgery for rectum we need a 30° high definition with 5 mm diameter laparoscopic camera, a tissue grasper, and an energy source. Energy source can be used for hemostasis and dissection. Endostaplers and multi-fire clip applicators will be of great help to facilitate the procedure.

Sometimes cost of the single port might prove a limiting factor in establishing the craft in underdeveloped or developing world but some technical modifications in the available things may help to overcome these factors as shown in Figs. 8.6 and 8.7 (Bulut 2011).

The main advantages of SILS surgery are superior cosmesis, less morbidity, less pain, and less number of port site complications. The final length of the incision will depend on the size, bulk, thickness of mesorectum, and stool content within the rectal lumen. Same SILS incision is utilized for retrieval of specimen. Most of the studies,

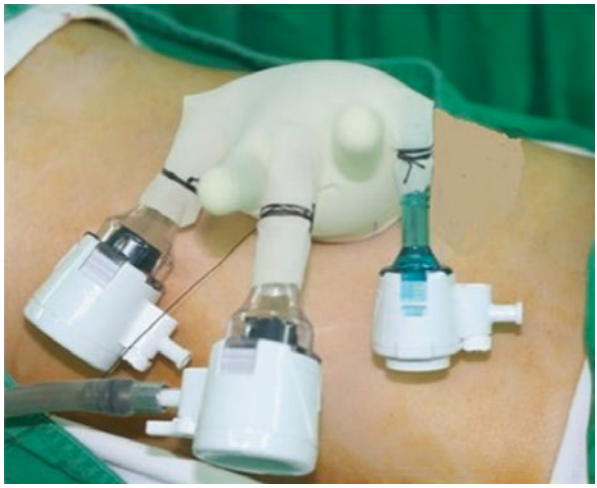

Fig. 8.6 Glove port with ports fixed

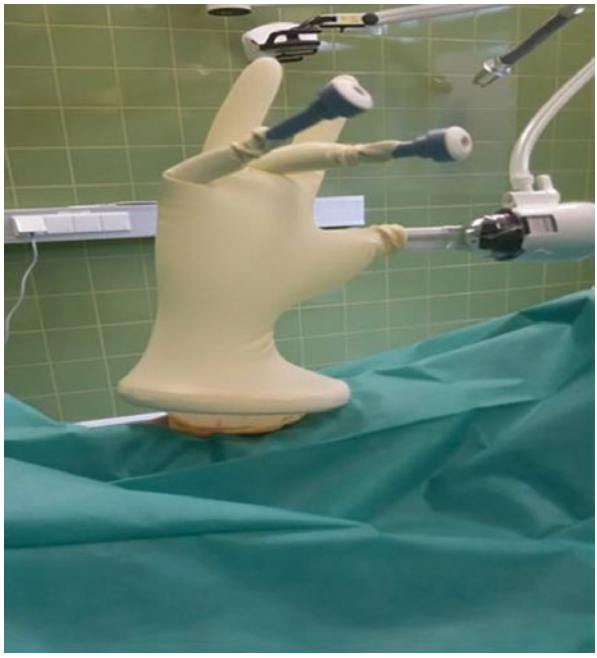

Fig. 8.7 Glove port after insuffulation and instrument insertion

however, have not studied requirements of analgesia in postoperative pain management after SILS (Adair et al. 2010; Waters et al. 2010; Champagne et al. 2011).

However, one of the studies reports that SILS group as compared to SLS showed significantly higher pain scores (3.07 ± 1.14 vs. 2.41 ± 0.63, respectively, $P < 0.001$ (Lu et al. 2012)).

8.3.2 Disadvantages

Poor exposure, triangulation principle compromise, crowding of instruments, compromise of surgeon maneuver, and difficult dissection.

Various types of ports used in SILS are:

(a) Glove port.
(b) Octo port.
(c) SILS port.

SILS/SPLS can be performed safely in slim patients with a small tumor and the surgeons can use various methods for specimen extraction like

- TUSE (trans-umbilical specimen extraction).
- NOSE (natural orifice specimen extraction) which may be TASE (trans-anal specimen extraction) or TVSE (transvaginal specimen extraction).

8.3.2.1 Conclusion

SILS/SPLS can be an alternative option in minimal access surgery for selected patients with skilled laparoscopic surgeons (Bulut 2011).

8.4 Combined CO_2 Colonoscopy and Laparoscopy

This concept is based on the principle to supplement the craft of laparoscopy with an aid from CO_2 colonoscopy and it is a very useful method to locate small malignant or benign lesions comfortably which otherwise may be missed and difficult to localize on standard laparoscopy. This is a suitable alternative for the lesions which may not be amenable to endoscopic mucosal resection (EMR).

The biggest advantages of this combined method are that we can localize the lesion with better precision and can excise the lesion with wide excision under vision (wedge resection) with endostaplers and an impression on the margin negativity can be confirmed by a frozen section. This technique also keeps the colon inflated so surrounding viscera fall off. It also helps to avoid a major resection for a benign disease or a small lesion and decreases the chances of unwanted morbidity like surgical site infections, bleeding, and paralytic ileus. Patients planned for such procedures can be put on enhanced recovery after surgery (ERAS) protocol and their hospital stay can be markedly reduced (Fig. 8.8).

However, this type of surgery cannot be offered to every patient but only to a selected group as mentioned earlier. We can also offer this surgery to complex benign lesions of right colon but same needs to be evaluated in larger series (Yan et al. 2011). The said technique can be of immense importance to confirm the margins of resection in early malignant and benign lesions which, because of lack of tactile sensation at times pose difficulty in laparoscopic surgery.

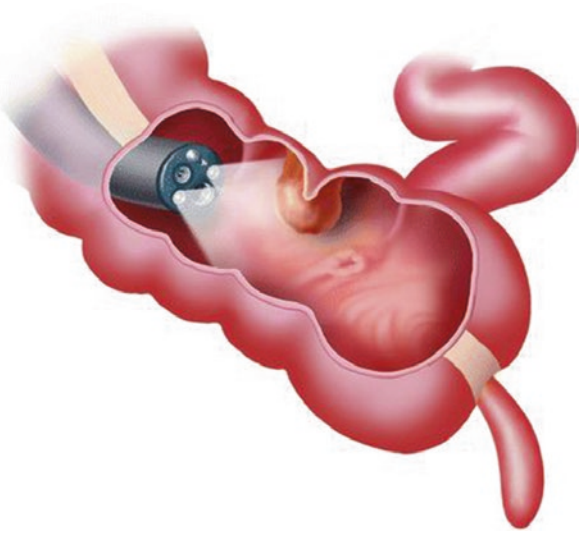

Fig. 8.8 View of combined CO_2 colonoscopy with laparoscopy (helpful in smaller lesions)

8.5 Hybrid Technique

It is a blend of laparoscopy and robotic surgery to ensure faster mobilization and fewer conversions for performing TME. Some studies have definitely shown the advantage in laparoscopic surgery with robotic assistance. Larger RCTS are needed to ascertain whether really a robot has an advantage over SLS in rectal cancer to decrease the number of conversions (Ashwin et al. 2010).

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Extralevator Abdominoperineal Excision (ELAPE) in Rectal Cancer

9

Fazl Q. Parray, Natasha Thakur, and Munir A. Wani

Abbreviations

APE	Abdominoperineal excision
APR	Abdominoperineal resection
CAPE	Cylindrical abdomino-perineal excision
CECT	Contrast-enhanced computerized tomography
CRM	Circumferential resection margin
ELAPE	Extralevator abdominoperineal excision
IOP	Intraoperative perforation
QOL	Quality of life
RCT	Randomized controlled trial
TME	Total mesorectal excision

The gold standard for low rectal cancer with sphincter involvement continues to be APE/APR. This surgery has stood the test of time for so many decades but the chances of recurrence still remain there. These chances further increase when CRM of the excised specimen is positive or if intraoperatively while dissecting there occurs a perforation known as intraoperative perforation (IOP). In order to minimize the chances of recurrence, the specimens of APE/APR were studied in detail and almost all specimens show a narrowing or neck effect near pelvic floor levators and most of the recurrences were found to occur there. Hence, a new concept of

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cylindrical specimen was born in which the levators up to bony edges of perineum were included with the specimen hence the name extralevator abdominoperineal excision (ELAPE) came into limelight which was found to be oncologically a correct procedure and was found to decrease the recurrences over a period of time.

APE/APR is performed in supine lithotomy position while as ELAPE in prone position which facilitates a better perineal dissection by better visualization. Better visualization obviously decreases the chances of perforation and allows the dissection of wider resection margins including levator muscles to decrease the chances of CRM positivity, thus decreasing the chances of local recurrence. One of the studies conducted to assess the efficacy of APE in prone position did show a reduced incidence of IOP and incomplete resection but failed to establish any statistically significant advantage of this position in decreasing the local recurrence rates (Anderin et al. 2013).

The ELAPE also named as cylindrical abdomino-perineal excision (CAPE) is used as a standard protocol surgery for any low locally advanced rectal cancer in some global centers. In Karolinska, the procedure is being used as a standard for the said indication since year 2000. The audited results showed a significant reduction in CRM positivity and IOP. The said center follows a standard protocol of downstaging all locally advanced low rectal cancers followed by CAPE /ELAPE. Since this surgery decreases the rates of IOP and CRM positivity, it decreases the local recurrence rates. This approach has helped the center to bring down the local recurrence to 6% on patients operated before year 2005 with a follow-up of at least 22 months (West et al. 2008). Recent descriptions of modifications to standard APE, now known as the ELAPE/CAPE aim to improve oncological appropriateness of the procedure by decreasing the risk of intraoperative tumor perforation and positive circumferential resection margins (Holm et al. 2007). Even though the expression "extralevator" may not be entirely appropriate since the levator muscles are eventually transected (and not entirely resected), the term has gained widespread recognition (under "ELAPE"). In this setting, perhaps the name "Cylindrical APE" (CAPE) may be more appropriate (Lynn et al. 2013).

9.1 Surgical Technique

The patient is properly evaluated, staged, and selected for the procedure. Patients with locally advanced disease with sphincter involvement after downstaging are the most appropriate candidates for this procedure. The procedure is performed under general anesthesia supplemented with epidural analgesia. The abdominal part of surgery is completed in supine position by open or laparoscopically following all the principles of TME and dissection is continued up to the level of pelvic floor muscles. Posteriorly, we dissect up to the level of upper third of coccyx, laterally up to the level of hypogastric plexus and anteriorly up to seminal vesicles or uterine cervix. At the completion of abdominal dissection, put a sponge/gauze posteriorly behind rectum. This sponge will be of great help to show you plane in perineal dissection. The recto-sigmoid junction is divided and the cut end of sigmoid colon is brought out as a colostomy and fixed to skin. A drain can also be put in pelvis and brought out through the abdomen and fixed. The abdominal wall is formally closed.

For the perineal part of surgery, the patient is turned prone and placed in jack-knife position (Fig. 9.1). Both the legs are positioned wide apart. The operative area is nicely cleaned with antiseptic solutions and draped with steri drapes. A pear-shaped incision is made around the anal opening with the upper end of incision at the tip of coccyx (Fig. 9.2). Continue the dissection till you cut the subcutaneous

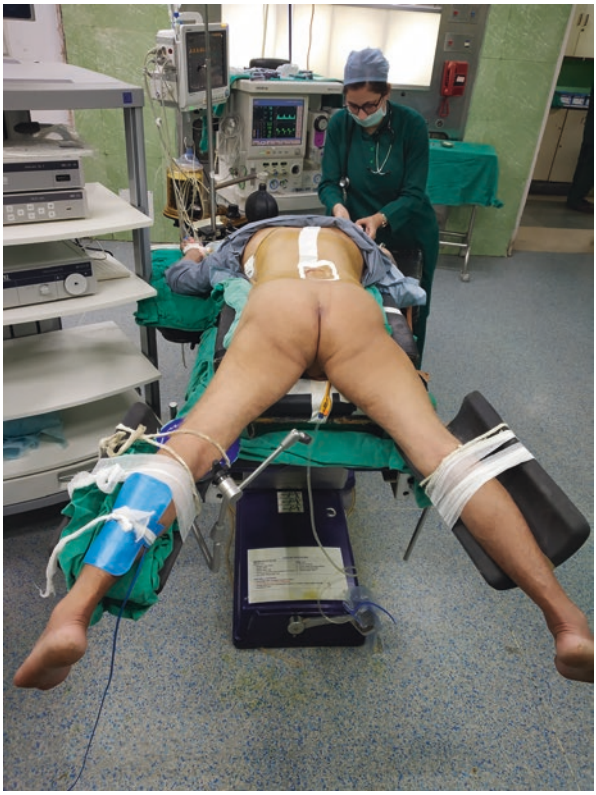


Fig. 9.1 Patient placed in prone position

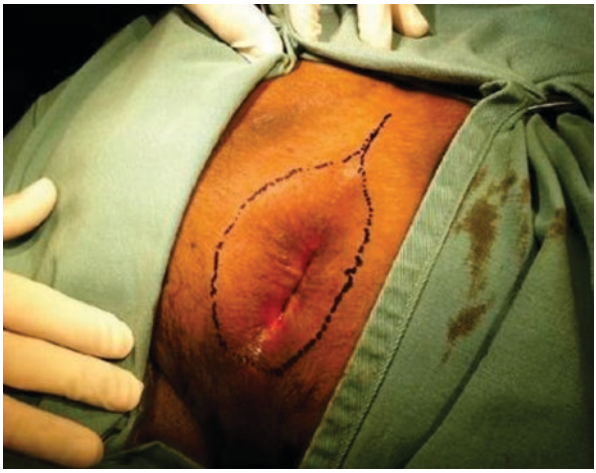


Fig. 9.2 The incision site marked

part of external sphincter (Fig. 9.3). Disarticulate the coccyx which gives a better working space posteriorly and keep on dissecting till you see the sponge/gauze which was placed abdominally (Fig. 9.4). Remove the sponge/gauze and keep on dissecting till you reach the level of levators, go laterally to their attachments and cut them with a diathermy from the attachments. Disengage the specimen from all its attachments. You can appreciate the muscle cuff of levators around the resected specimen (Fig. 9.5). The anterior dissection should be deferred till you evert the specimen through perineum and you have a bimanual hold on the everted specimen and you can see the vagina, seminal vesicles, and anterior wall comfortably under direct vision during dissection. This is the greatest advantage of the prone position (Fig. 9.6). In the end, after you dissect pelvic diaphragm muscles, you will deliver the specimen, and the perineal wound is closed (Fig. 9.7). It is not always easy to close the perineal defect after this procedure. Many a times, you may need to close it with an omental flap, a muscle graft, or biological meshes. Once the skin is closed, the final wound length is not significantly different from APR wounds (Shihab et al. 2012). In the end, you will appreciate that there is no "waisting" rather you will see a cylindrical specimen has been delivered along with a cuff of extralevator muscles (Figs. 9.8 and 9.9).

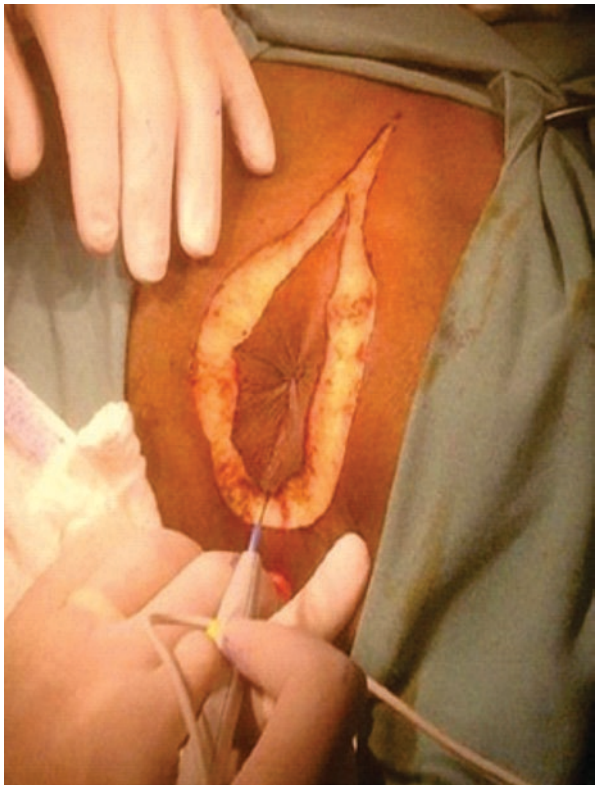


Fig. 9.3 Superficial dissection

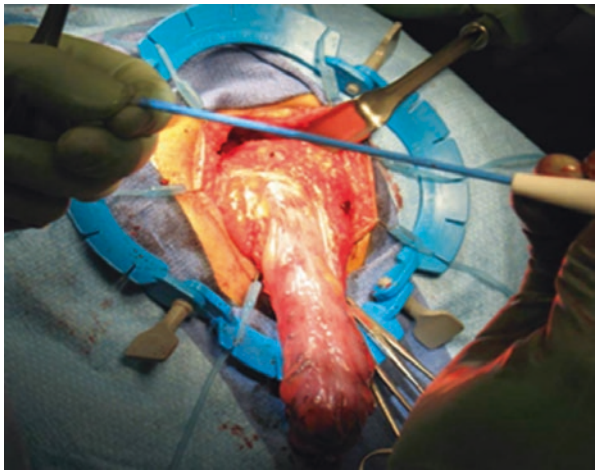


Fig. 9.4 Deeper dissection

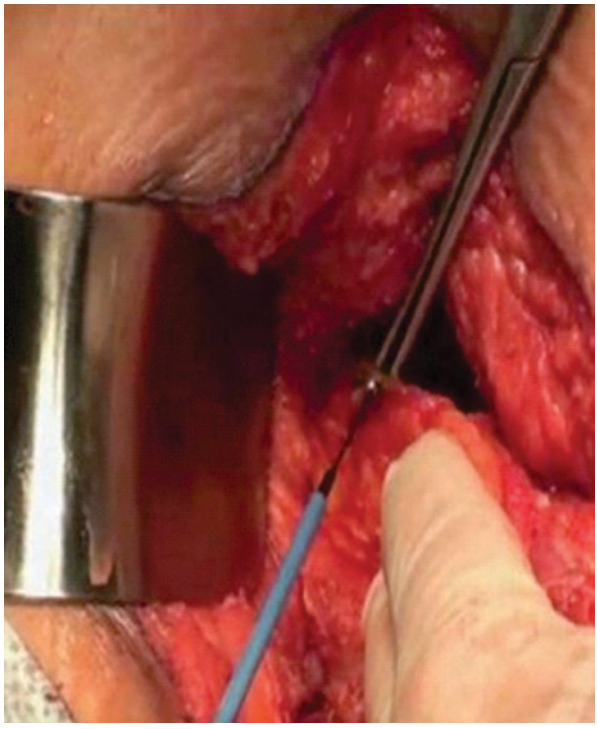


Fig. 9.5 Achieving hemostasis

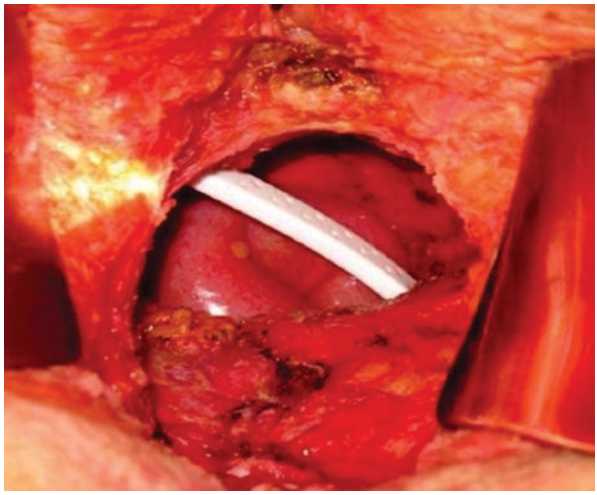


Fig. 9.6 Completed dissection

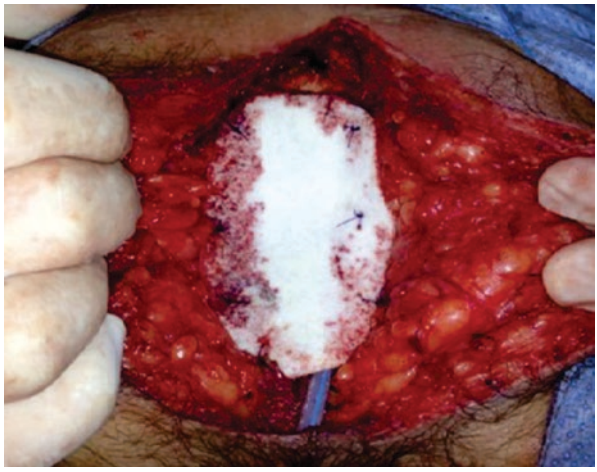
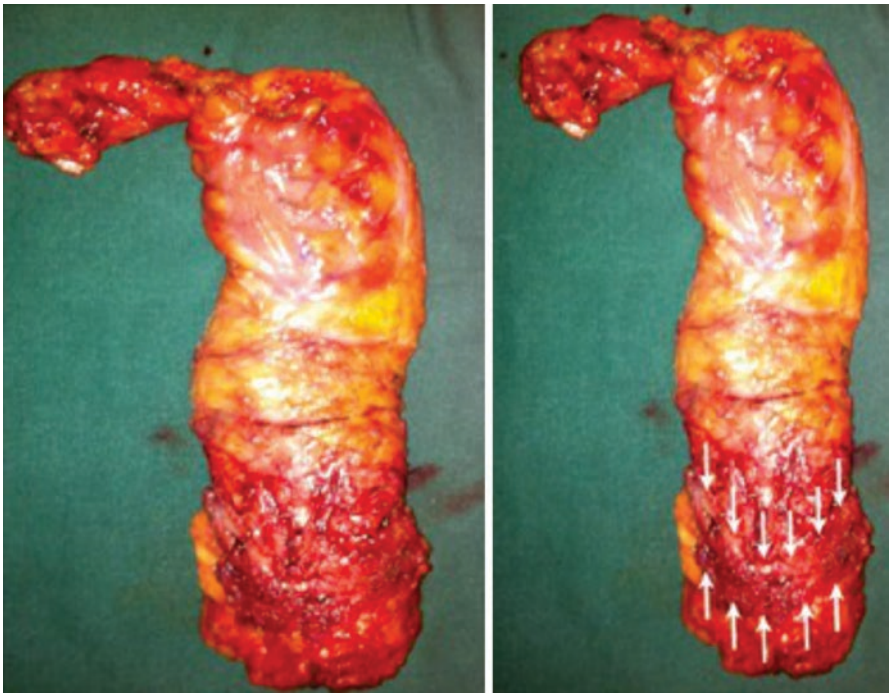


Fig. 9.7 Use of a mesh for the defect

9.1.1 Controversies and Results

The biggest controversy at present is whether ELAPE/CAPE should completely take up the place of standard APR/APE or should continue as an alternative for selected patients. At present, the indications would be almost same for both the surgeries like a low rectal cancer with involvement of sphincters, incontinence, or where you can't achieve a safe resection margin.

Nowadays, it is very important to stage the patients of rectal cancer preoperatively by imaging modalities like CECT abdomen, chest, and pelvic MRI. Pelvic MRI will be one of the most important modalities to decide at the time of performing ELAPE/CAPE whether to operate in a TME plane or in an extralevator plane (Shihab et al. 2012).



Figs. 9.8 and 9.9 Excised specimen

A comparative multicentric study on ELAPE/CAPE vs. APR/APE (176 vs. 124 patients) proved that CRM positivity and IOP rate is significantly less in ELAPE/CAPE, respectively (20% vs. 49%, $p = 0.001$; 8% vs. 28%, $p = 0.001$). Even in the excised specimens, the amount of excised tissue was measured in the distal specimens to compare the two types of surgeries, which again proved that ELAPE/CAPE is superior to standard ARR/APE (2120 mm^2 vs. 1259 mm^2; $p < 0.001$) (West et al. 2010). The major drawbacks of this study are that significant differences might be because of the non-randomized type of study and possibly 49% CRM positivity might be because of the inappropriate control group. Recent literature shows that APR/APE performed in specialized centers shows a CRM positivity of <15% which can be favorably compared to 20% of CAPE/ELAPE of the previously mentioned multicentric study (Messenger et al. 2011).

CRM positivity and IOP rates again emerged as significant factors on comparison between the two techniques when a high powered study comprising of more than 5000 patients was published. CRM positivity and IOP rates in ELAPE/CAPE vs. APR/APE were 9.6% vs. 15.4%, $p = 0.022$ and 4.1% vs. 10.4%, $p = 0.004$, respectively. Even the local recurrence rates were lower for ELAPE/CAPE group on a follow-up of 68 months (6.6% vs. 11.9%, $p < 0.001$). One of the most important observation made in the said study was that CRM positivity and IOP are directly related to Lloyd-Davies lithotomy position and in prone position as we use for

ELAPE/CAPE their incidence decreases. Even if the groups are comparable in this study but still CRM positivity rates of <10% in ELAPE/CAPE seem to be favorably comparable to rates of standard APR/APE (Stelzner et al. 2011).

Every new procedure may come with some potential benefits but has its hazards too. Same is true for ELAPE/CAPE even though it offers the oncological advantages but has the hazard of increased perineal wound morbidity when compared to standard APR/APE group (38% vs. 20%, $p = 0.019$) (West et al. 2010). This can be very well explained on the basis of extensive perineal tissue resection in ELAPE/CAPE. Some studies reveal almost similar rates of perineal complications in both the procedures (23.2% vs. 26.1%, $p = 0.183$) (Stelzner et al. 2011). Even QOL questionnaires present similar results for both the procedures (Vaughan-Shaw et al. 2012).

In our scenario of Indian patients, the body mass index of patients is usually low so many a times even after ELAPE one can comfortably close the narrow perineal defect without any muscle flaps and meshes which becomes an encouraging factor in decreasing perineal wound morbidity and adopting to this procedure more and more. In fact at our center, Sher-i-Kashmir Institute of Medical Sciences colorectal division, we are practicing this surgery since 2010 and we till date did not need any help from the plastic surgeon to close the perineum because of low body mass index of patients, and we could not find any significant perineal wound morbidity in our patients.

The definitive conclusions about ELAPE/CAPE can only be drawn after RCTs are available about the efficacy, safety, and potential advantage of these procedures over standard APR/APE. However, at present we can definitely take the advantage of this procedure because of improved visualization, decreased CRM positivity and IOP rates because of prone position and better visualization. At present, this novel approach has a place in the armamentarium of colorectal surgeons and in the near future may replace the standard APR/APE on the basis of evidence.

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Natural Orifice Transluminal Endoscopic Surgery (NOTES) in Rectal Tumors

10

Fazl Q. Parray, Asif Mehraj, and Rauf A. Wani

Abbreviations

APC	Argon plasma coagulation
CSI-EMR	Circumferential submucosal incision-endoscopic mucosal resection
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ETAR	Endoscopic transanal resection
LAC	Laparoscopy-assisted colorectal surgery including lymphadenectomy
LAR	Low anterior resection
LE	Local excision
MITAS	Minimal invasive transanal surgery
NOTES	Natural orifice transluminal endoscopic surgery
TAE	Transanal excision
TAMIS	Transanal minimally invasive surgery
TATA	Transanal abdominal transanal resection
TaTME	Transanal total mesorectal excision
TEMS	Transanal endoscopic microsurgery
TEO	Transanal endoscopic operation
TME	Total mesorectal excision
UEMR	Underwater endoscopic mucosal resection

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10.1 Natural orifice transanal endoscopic surgery (NOTES)

The concept of performing surgery through natural orifice is well known to colorectal surgeons since time immemorial. Anal canal has been used to perform surgeries like hemorrhoidectomy, polypectomy, fissurectomy, and transanal excisions. However, nowadays apart from conventional surgeries some more additions using endoscopic platforms, what is known as natural orifice transluminal endoscopic surgery (NOTES) have been made. This has happened because of advances in technology and better understanding of pathogenesis and mode of spread of many tumors. Various types of NOTES procedures used in colorectal surgery include:

- Endoscopic mucosal resection (EMR)
- Endoscopic submucosal dissection (ESD)
- Transanal endoscopic microsurgery (TEMS)
- Transanal minimally invasive surgery (TAMIS)
- Transanal total mesorectal excision (TaTME)
- Endoscopic transanal resection (ETAR)
- Transanal abdominal transanal resection (Hybrid NOTES)

10.1.1 NOTES

Transanal excision (TAE) is an unaided resection of rectal tumors usually done for benign lesions (villous adenoma), early-stage rectal cancer, or rarely as a palliative measure in advanced lesion in patients with serious comorbidities. For the reason of being an unaided surgery, this surgery even though performed via natural orifice is not included under the heading of NOTES. The use of lone star retractor (Fig. 10.1) has again made it a worthwhile option in the management of rectal tumors. In our center, TAE is quite often performed for the lesions which fit the indications for the said procedure and till now we find it a very useful treatment modality for managing early rectal tumors .We routinely put these patients on a meticulous follow-up to rule out any local or distal recurrences at the earliest.

10.1.2 EMR (Fig. 10.2)

EMR is a minimally invasive, organ-sparing endoscopic method of removing benign and early malignant lesions in the GI tract. This technique is used for the removal of sessile or flat neoplasms that are confined to mucosal and submucosal layers of the GI tract. Before offering EMR to a patient, it is of paramount importance to properly evaluate the patient using endoscopy and/or endo ultrasound. There are various techniques of performing EMR which include injection-, cap-, ligation-assisted EMR, and underwater EMR.

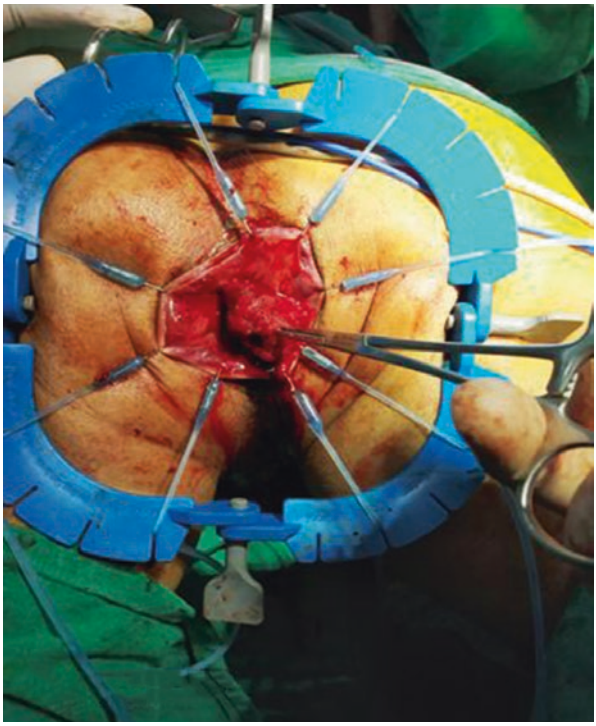

Fig. 10.1 Lone star retractor

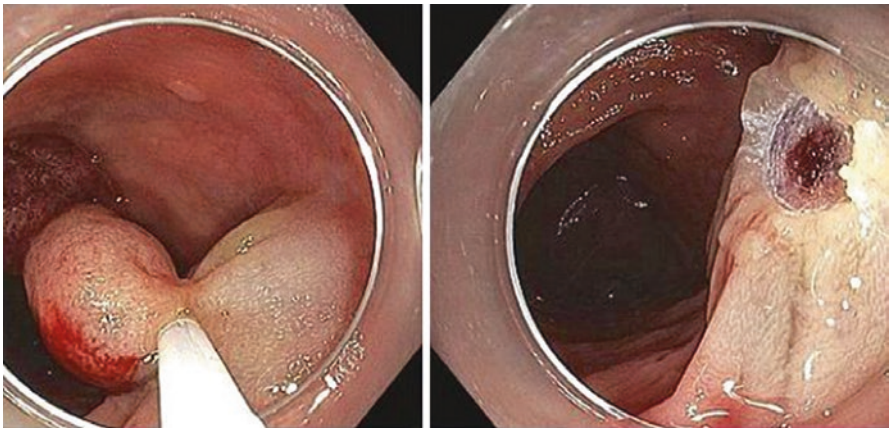

Fig. 10.2 Endoscopic mucosal resection (EMR)

10.1.2.1 Injection-Assisted EMR

Injection-assisted technique is the simplest form of EMR. It's also called saline solution lift-assisted polypectomy. This technique involves injection of saline under the lesion into the submucosal plane, thereby lifting the lesion and minimizing mechanical or electrocautery damage to the deeper layers of the GI wall. The lesion can be captured easily and removed by using a snare.

Various solutions that have been used for submucosal injection include normal saline, glycerol, hyaluronic acid, succinylated gelatin, hydroxypropyl methylcellulose, and a fibrinogen solution. Dilute adrenaline (1:100,000–1:200,000) is usually added to the submucosal injection fluid. It helps in decreased bleeding because and a prolonged submucosal cushion, due to decreased vascular flow resulting in delayed absorption of fluid.

10.1.2.2 Cap-Assisted EMR

Cap-assisted EMR also begins with submucosal injection of saline to lift the target lesion. However, this technique utilizes a specifically designed endoscope that has a cap with a specially designed crescent-shaped electrocautery snare fixed to its tip (EMR Kit; Olympus America Inc., Center Valley, Pa) (Inoue et al. 1992). The endoscope with its tip assembly is positioned over the target lesion, and mucosa is pulled into the cap with the help of suction. The lesion is captured and excised using the snare.

10.1.2.3 Ligation-Assisted EMR

This technique uses a band ligation device (Duette Multi-Band Mucosectomy device, Cook Medical Inc., Winston-Salem, NC) which is attached to the endoscope. Mucosa may or may not be lifted using submucosal saline injection. The banding cap is positioned over the target lesion, and suction is applied to pull the lesion into the banding cap. The lesion is captured within the band. An electrocautery snare is then used to resect the lesion in the band, either proximal or distal to the band (Chaves et al. 1994; Fleischer et al. 1996).

10.1.2.4 Underwater EMR

In the underwater EMR (UEMR) technique, the GI lumen is instilled with water and the target lesion is immersed in it after suctioning luminal air. This technique enables visualization of lesion without over distention of the GI tract wall. It is postulated that mucosa and submucosa "floats" away from the deeper muscularis propria layer and allows resection without submucosal injection (Binmoeller et al. 2012). Therefore, because of avoiding submucosal injection, there is no risk of seeding malignant cells into deeper UEMR has also be used in managing lesions that have recurred following previous EMR, as well as patients who have underwent partial resections and biopsies of lesions (Friedland et al. 2013).

Staining dye (i.e., diluted indigo carmine or methylene blue) is frequently added to the injection solution to facilitate identification of the lateral and deep margins of the target lesion before and during the resection process.

10.1.2.5 Complications

Complications of EMR include:

- Bleeding: most common complication, 11–22% in lesions >20 mm (Burgess et al. 2014; Fahrtash-Bahin et al. 2013).
- Perforation.
- Strictures.

10.1.3 **ESD** (Fig. 10.3)

ESD is an endoscopic modality for the treatment of premalignant and early-stage malignant lesions of the esophagus, stomach, and colorectum. ESD was first reported by from Tokyo by Hosokawa in 1998 for the treatment of early gastric cancer (Hosokawa and Yoshida 1998). With advances in technology, ESD was further applied to esophagus, rectum and, finally, large bowel. In this technique, the endoscopist uses dedicated diathermic knives instead of a snare to make a mucosal incision around the lesion and then progressively dissect the submucosa after injecting various solutions below the neoplasm. Compared with EMR, ESD has several advantages that include:

- Higher rates of en bloc (especially in lesions >20 mm), R0, and curative resections.
- Lower rate of local recurrence.
- Excellent T-staging tool to identify noncurative resections that will require further treatment.

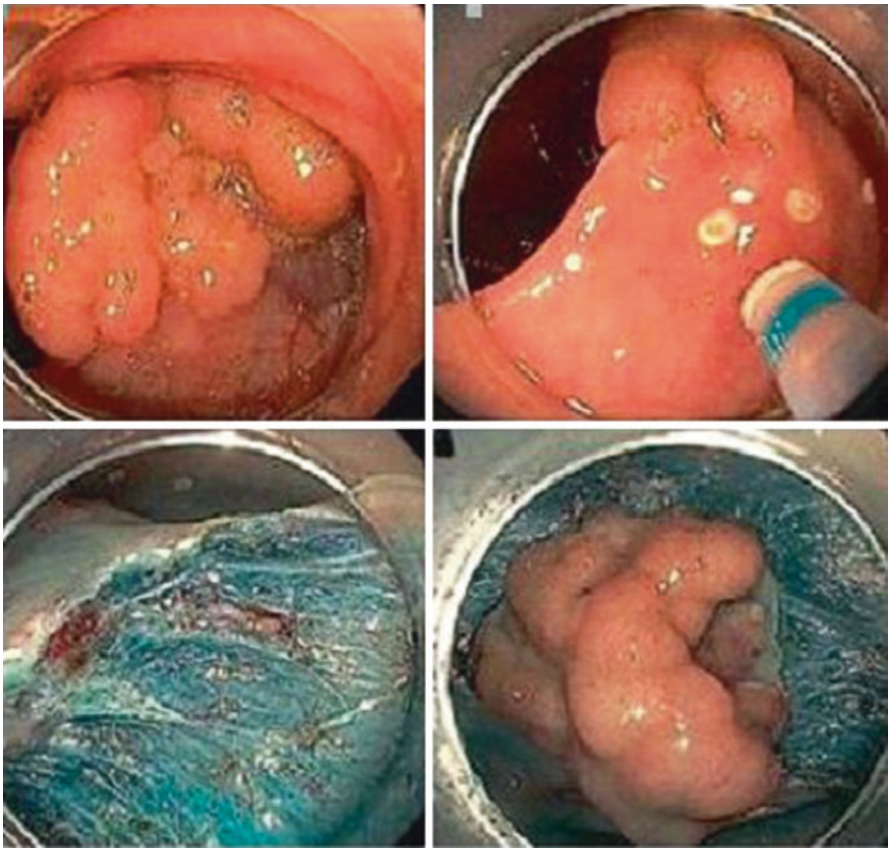

Fig. 10.3 Endoscopic submucosal dissection (ESD)

However, despite so many advantages, ESD has also some disadvantages.

- Complex procedure, with steep learning curve.
- Time consuming (240 min for lesions >50 mm).
- Uncomfortable for the patient and requires general anesthesia or deep sedation.
- Higher complication rates (Saito et al. 2010; Kobayashi et al. 2012).
- Expensive.

Electrosurgical knives are the main devices used in ESD that differentiate it from other types of endoscopic resection.

Various types of electrosurgical knives used in ESD include:

- IT knife
- Hook knife
- Triangle tip knife
- Dual knife
- Flex knife
- Hybrid knife

The other tools used (e.g., endoscope, electrosurgical unit, and other ancillary devices) are similar to those used for standard endoscopy.

Complications

- Bleeding (managed by coagulation current or hemostatic forceps)
- Perforation (managed by clipping or sometimes require urgent surgery)

10.1.4 Circumferential Submucosal Incision-Endoscopic Mucosal Resection (CSI-EMR)

It is a hybrid technique of EMR and ESD. An incision is made in the mucosa and submucosa around the lesional with the knives used for classic ESD thereby creating a groove. En bloc excision of the lesion is carried out using the diathermic snare.

Advantages

- Simpler and time-saving technique
- Adequate specimen for an optimal histopathological examination
- Lower risk of incomplete resection
- Lower recurrence rates
- Lower complication rate

10.1.5 Transanal Endoscopic Microsurgery (TEMS) (Fig. 10.4)

It is a minimal invasive procedure (MIP) through natural (anal) orifice. This technique was reported from Germany in early 1980s.The concept of this technique was devised by collaboration of a German surgeon Gerhard Buess (Fig. 10.5) and a

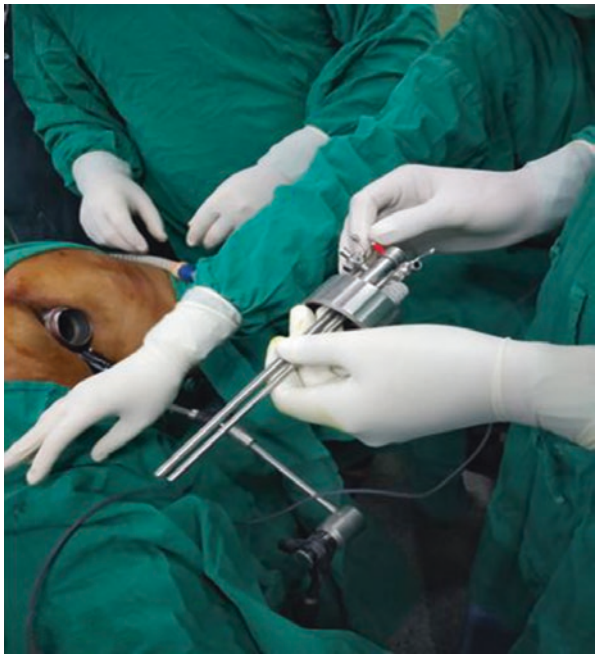

Fig. 10.4 TEMS equipment

Fig. 10.5 G Bues; inventor of TEMS port

renowned medical company Richard Wolf. It was used initially to remove a large rectal polyp which otherwise was beyond the reach of transanal excision. This technique was used for the excision of an early rectal cancer for the first time by E Lezoche in 1996 (Lezoche et al. 1996).

In TEMS, a binocular magnified operating system comprising of an operating proctoscope, insufflation, and magnified stereoscopic vision is used to perform local excision through natural orifice. With the help of light in the rectal lumen, three-dimensional amplification, and a magnified view, the surgeons are able to see better and resect better with lot of precision including a full-thickness excision. It has evolved into a valuable, state-of-the-art technology equaling any other technique in terms of reliably positive patient outcome (Fig. 10.6).

At present, indications for this surgery are:

- Excision of polyps not amenable to colonic resection
- Excision of early rectal cancers
- Treatment of anastomotic strictures
- Repair of complex fistulae
- Resection of carcinoid tumors
- Resection of retro rectal tumors

The greatest advantage of the TEMs is that it allows resecting lesions up to 20 cm from anal verge. The surgeon can reach up to the distal sigmoid colon. There are four ports of access which can be employed for simultaneous use of an illuminated camera, energy source, graspers, and suction. This allows one to perform better dissection and suturing inside the rectal lumen.

TEMS has certain advantages over standard transanal excision of neoplasms like

- Better visualization
- More proximal access
- Less tumor fragmentation and dissemination

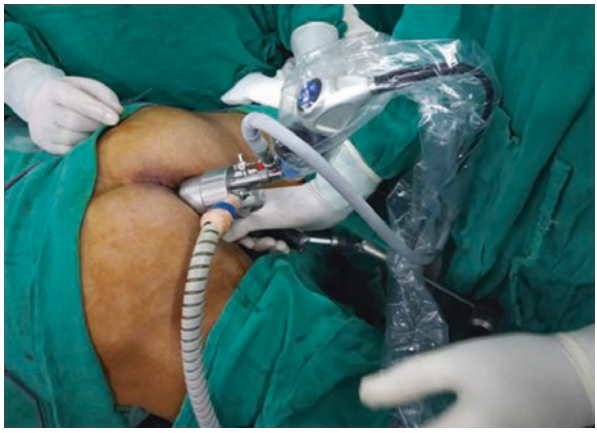

Fig. 10.6 Transanal fixation of TEMS port

- Higher rate of tumor-free margins
- Less trauma to tissues
- Resection of the potentially infiltrated mesorectum

However, there are certain limitations associated with the procedure which include:

- Steep learning curve
- Extraordinary surgical skills
- High initial cost
- Vast experience

Transanal resection for early-stage rectal cancer is associated with a relatively higher risk of local recurrence. Introduction of TEMS in such a scenario has induced a new interest among surgeons because of the inherent advantages of this platform over the conventional transanal excision.

With the evolution of the concept of NOTES, the future of the TEMS seems to be more wider. TEMS can be used to access the peritoneal cavity via the transrectal route to facilitate the removal of larger organs (Palma and Horisberger 2011).

10.1.5.1 Technique

Patient should be given a mechanical bowel preparation. As already discussed in indications, the procedure can be carried out for both benign and malignant lesions.

The following procedures can be performed using TEMS:

- Mucosectomy: In this technique, only the polyp and mucosa are removed sparing the muscle. It is suitable for benign sessile adenomas that are located in the proximal upper rectum.
- Full-thickness excision: In this technique, full-thickness excision of all the layers of the rectal wall is done. This is carried out in a plane located just superficial to the peri-rectal fatty tissue. Most of the times such an excision is performed for early malignant lesions.

In cases of malignancy, it is imperative that the procedure includes not only a full-thickness excision but also a 1 cm safety margin of normal mucosa surrounding the lesion. It is imperative to correctly align the specimen immediately after resection. The proximal and distal resection margins as well as the deep margin should be labeled for the orientation of pathologist. The rectal defect should be closed transversely by a continuous suture to prevent stenosis. Intra-luminal knotting in this limited space is at times quite challenging, and the difficulty can be overcome with the help of application of clips at the suture ends or using an auto lock braided sutures.

Alternatively, recent reports indicate the possibility to leave the defect open for secondary wound repair, especially in cases of partial-thickness excision and those located distally below the peritoneal reflection (Palma and Horisberger 2011).

10.1.5.2 Glove Port Transanal Endoscopic Microsurgery

Abdominopelvic surgery is associated with high risk of complications. In order to overcome some of the side effects of such conventional surgeries, TEMS is a minimally invasive technique which can be used as an alternative for excision of rectal tumors. Although appealing, the initial installation cost and steep learning curve associated with this procedure has limited its acceptance as a routine procedure by majority of colorectal surgeons. In order to overcome the difficulty of using specialized equipment, the glove port TEMS has been introduced. It is a safe, inexpensive, and readily available access tool for transanal resection of rectal lesions (Hompes et al. 2012).

In this technique, a wound retractor (Alexis) is applied through a disposable circular anal retractor and is fixed by suturing with the skin. A surgical glove is then put, air tight, on the wound retractor, and three to four trocars are inserted via the finger tips. Middle finger port is used for insertion of laparoscopic camera. Standard laparoscopic instruments can be used freely through the glove port without any limitation in maneuverability. The pneumorectum is maintained at 12–15 mmHg. The operation then proceeds exactly like the traditional TEMS. The tumor is resected deep to the level of mesorectal tissue through the rectal wall along the marking and ensuring wide resection margins. The smaller length of the anal retractor, compared to the traditional TEMS, allows easy excision of the distal margin of the specimen even at 1.5–2 cm from the dentate line. The excisional area is then closed with an absorbable continue suture (Alessandro et al. 2012).

Glove TEM is a promising surgical technique, safe, effective, and easy to install and to perform. It is made from commonly used and relatively inexpensive surgical equipment and offers the possibility to use all the conventional laparoscopic instruments with an amazing maneuverability thus avoiding long and complex learning curves for a laparoscopic surgeon.

10.1.6 Transanal Minimally Invasive Surgery (TAMIS) (Fig. 10.7)

Since its inception in 2009 by Sam Atallah and team (Fig. 10.8), TAMIS is witnessing convincing growth as an alternative to the more expensive and complex system of TEMS. One of the most important factors that has led to more acceptability of TAMIS procedure among majority of surgeons is the familiarity with the minimal invasive procedure and the instruments used are same as those used in conventional laparoscopy. TAMIS utilizes common laparoscopic instruments like graspers, cautery, hook, suction irrigation catheters, etc. (Fig. 10.9). A 5–10 mm, 30° or 45° camera is used for the procedure. Only a specific item to be used in TAMIS is the platform for gaining access into the rectal lumen. SILS™ port was the first such platform used to gain access. This is a multiple access advanced surgical device actually designed to perform laparoscopic surgery

Fig. 10.7 SILS port for transanal minimal invasive surgery (TAMIS)

Fig. 10.8 Sam (Osama) Atallah, father of TAMIS surgery

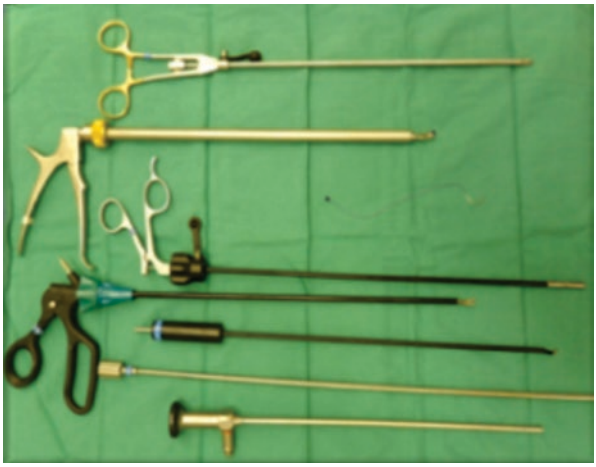

Fig. 10.9 Common laparoscopic instruments used for TAMIS

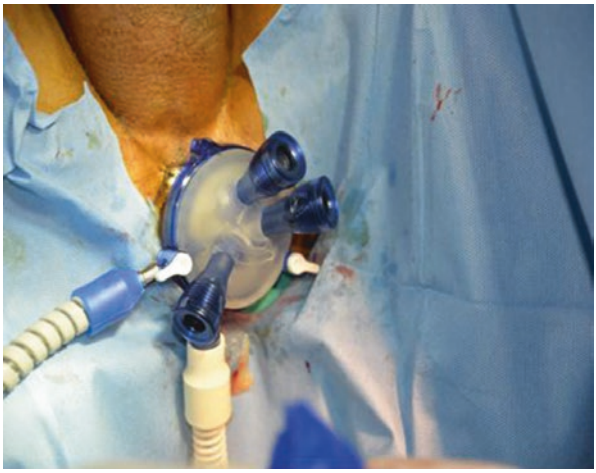

Fig. 10.10 Gelport for TAMIS

through a single incision, but over the years has gained popularity as an access port for rectal procedures in TAMIS. Its design and malleability allows the surgeon to use multiple instruments through adjustable cannulas with a lot of maneuverability. The other device used is GelPOINT® Path Transanal Access Platform (Fig. 10.10). Its gel base provides utmost versatility and accessibility for surgeons to perform TAMIS. It consists of GelSeal cap, access channel, and self-retaining sleeves with obturators. General or spinal anesthesia is used and the patient is placed in the dorsal lithotomy position. At our center, we prefer giving general anesthesia, as the patients feel some discomfort as a result of prolonged pneumorectum. An access port (SILS or GelPOINT) is first lubricated and introduced into the anal canal and pneumorectum is established with a standard laparoscopic CO_2 insufflator up to a pressure of 12–15 mm of Hg. Laparoscopic camera lens and instruments are introduced through the access port to assist the operator in performing a full-thickness resection of the neoplasm

with 1 cm margins. The remaining rectal defect is either closed or left open (below peritoneal reflection). Postoperatively, patients are expected to have an overnight hospital stay and quick recovery with early resumption of normal diet and activities. Martin-Perez et al. (2014) performed a systemic review and reported that complications following the TAMIS procedure were infrequent with an overall rate of 7.4%. The conversion rate in 390 cases performed for both benign and malignant lesions was 2.3%. Inadvertent peritoneal entry during the procedure was reported in 1% of cases and in some cases, the closure of the rectum was successful transanally. In malignant polyps, the rate of positive margins was 4.4%, and the rate of tumor fragmentation was 4.1%.

The advantages of TAMIS are:

- Less expensive.
- Setup time is significantly lower.
- Can use conventional laparoscopic instruments.
- Access platforms are pliable and allow well-fitted positioning at the anal canal, possibly leading to less impairment of sphincter function than the 40 mm rigid scope used for TEM.
- Learning curve is not that steep.
- Suture with Endo Stitch (V-loc™) to avoid tying knots.

TAMIS has been used successfully for excision of benign rectal lesions. For carefully selected patients, TAMIS is a valid option for local excision of rectal neoplasia. It has the advantage of organ preservation and is associated with low morbidity (Lee et al. 2017).

Besides benign lesions, TAMIS can be used for resection of early as well as advanced rectal cancers. TAMIS seems to be a safe and feasible option for treating patients with locally advanced rectal cancer who show good response to preoperative CRT (Lee et al. 2017).

We have been performing TAMIS at our center from last 4 years now. We have operated upon 48 patients who had a preoperative diagnosis of tubulovillous adenoma or early-stage adenocarcinoma (T1, N0, M0) within 4–12 cm from anal verge. Out of 48 patients 36 were having benign lesions and 12 had adenocarcinomas, which were located at an average distance of 6.2 (Burgess et al. 2014; Lee et al. 2017; Casadesus 2009; Deijen et al. 2016; Chaves et al. 1994; Fahrtash-Bahin et al. 2013; Fleischer et al. 1996; Friedland et al. 2013; Hompes et al. 2012) cm from anal verge. The mean operating time was 72 (46–110) min. There were no intraoperative complications; however, 1 (2.08%) patient suffered postoperative bleeding, which was managed conservatively. 2 (4.16%) patients developed acute urinary retention who required indwelling catheterization. Resection margin was positive in 3 (6.25%) benign cases. Average hospital stay was 2.7 (Ma et al. 2016; Binmoeller et al. 2012; Burgess et al. 2014; Lee et al. 2017; Casadesus 2009; Deijen et al. 2016; Chaves et al. 1994; Fahrtash-Bahin et al. 2013) days. Follow-up period ranged from 2 to 36 months. Local recurrence occurred in 2 (4.16%) villous adenoma patients (after 11 and 13 months), in whom local excision was done. We have found TAMIS to be a safe and feasible procedure for benign tumors and early rectal cancers, located in low and middle rectum.

10.1.7 Transanal TME

Low anterior resection (LAR) with total mesorectal excision (TME) is considered to be the ideal procedure at present to achieve low recurrence rate for rectal cancer surgery. However, performing LAR with TME by either open or laparoscopic technique is technically challenging operation due to reduced working space in the pelvis, especially in male patients with narrow pelvis and obese individuals and because of inadequate retraction capabilities and poor visibility. These challenges have led to increased interest towards robotic rectal surgery. However, even with robotic surgery, there still remain several technical difficulties in the minimally invasive approach to rectal cancer. The division of the distal rectum remains to be one of the most technically difficult steps due to the limited space in the pelvis, even after utilizing modern stapling devices. To perform TME for rectal cancer, whether by open laparotomy, laparoscopy, or robotic surgery, access to peritoneal cavity is gained through incision(s) in the abdomen. To overcome these challenges, a new approach to the surgical excision of rectal cancer is transanal total mesorectal excision (TaTME), in which the rectum is mobilized per-anally using endoscopic instruments. TaTME can be performed using different platforms like TEMS, TEO, (Transanal endoscopic Operation), or TAMIS, depending on the availability and experience of the surgeon. The surgical procedure for the TaTME is same as that for abdominal TME, except that the dissection starts from below.

Transanal TME for rectal cancer has many potential advantages compared to the transabdominal TME:

- A safe distal resection margin can be obtained under direct vision into the lumen of the rectum, which is not possible in either open laparoscopic or robotic surgery.
- CO_2 pneumorectum facilitates proper dissection through the avascular embryologic tissue plane surrounding the rectum. This pneumatic pressure dissection does not occur when using a transabdominal approach to rectal surgery
- The low coloanal anastomosis can be performed using a double circular stapler technique or hand sewn technique, thereby avoiding the multiple staple line and staple cross over lines which are associated with an increased rate of anastomotic leak
- The retraction of the rectum is technically less difficult from the transanal approach as rectal retraction is a "forward pushing motion" for transanal rectal surgery compared to a "pulling up and out of the pelvis motion" required for transabdominal rectal surgery.

Since the first TaTME resection assisted by laparoscopy was reported in 2010 (Sylla et al. 2010), TaTME performed on patients with rectal cancer has shown promising results with regard to pathologic quality and short- and mid-term outcomes (Lacy et al. 2015; Veltcamp Helbach et al. 2016; Muratore et al. 2015). However, Lacy popularized it by performing it in live operative workshops and displaying the correct planes and control of distal resection margin better

transanally (Fig. 10.11) and delivering the whole rectal specimen through natural orifice and avoiding any abdominal incision for specimen delivery which is the biggest advantage of this procedure (Fig. 10.12).

A meta-analysis carried out by Bin Ma et al. included seven studies consisting of 573 patients (TaTME group = 270, LaTME group = 303). On oncological front, there was no difference observed in the number of harvested lymph nodes and positive distal resection margin between the two groups. However, the TaTME group showed a better quality of TME specimen as compared to LaTME. A longer circumferential resection margin and less involvement of positive circumferential resection margin were also observed. As far as perioperative outcomes are concerned, intraoperative complications, hospital stay, and readmission rates did not show any significant difference between the two groups. Operation time was shorter and conversion rate was lower in TaTME. However, more patients in the TaTME group were subjected to higher rates of splenic flexure mobilization. Although as per the incidence there was no difference in the rate of anastomotic leakage, ileus and urinary morbidity between the groups. Overall, there was a significantly lower rate of postoperative complications observed in the TaTME group (Ma et al. 2016).

Charlotte et al. designed an international, multicenter, phase 3, randomized study (COLORIII Trial) in May 2016, comparing short- and long-term outcomes of laparoscopic TME and TaTME for mid- and low rectal carcinomas. The primary endpoint of the study is to determine rate of positive CRM. Secondary outcome measures include morbidity and mortality, completeness of TME, residual mesorectum, functional outcome and quality of life, percentage of sphincter-saving procedures, local recurrence rate, disease-free, and overall survival. The quality of the study will be assured by following a standard protocol including centralized MRI review, standardization of surgical techniques, monitoring and assessment of surgical quality, and review of histopathology. Patients who have histologically proven single cancer within 0–10 cm from anal verge on MRI will be included in the study. Patients with T4 tumors, T3 tumors with mesorectal fascial involvement following neoadjuvant chemo radiotherapy,

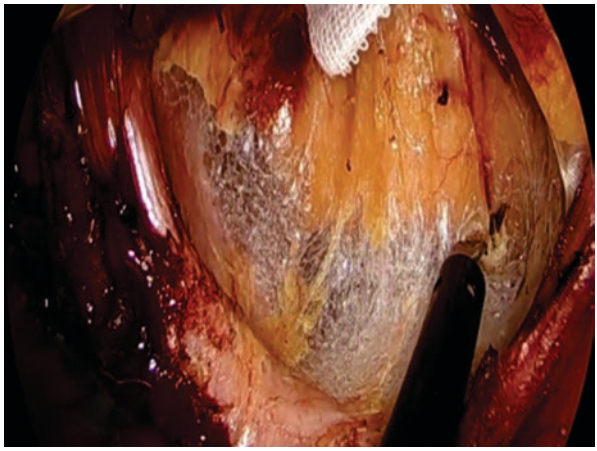

Fig. 10.11 Transanal view of avascular plane

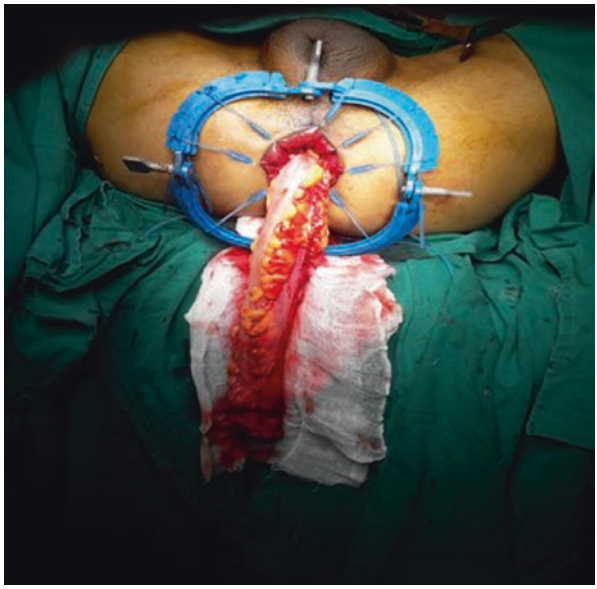

Fig. 10.12 Delivery of rectal specimen by transanal route

metastatic disease, and concomitant other malignancy are to be excluded from the study. The hypothesis that has been put forward for evaluation is that TaTME will result in a better quality of mesorectal resection with lower rate of CRM involvement and hence lead to lower rate of local recurrence. TaTME is therefore expected to be superior to laparoscopic TME in terms of oncological outcomes in case of mid- and low rectal carcinomas (Deijen et al. 2016). Study is expected to be completed by May 2025.

10.1.8 Transanal Abdominal Transanal Resection (TATA)

This procedure is not a pure NOTES operation; however, it is referred to as hybrid NOTES. This involves access both through anal orifice to complete the transanal TME and through abdomen for left colonic as well as splenic flexure mobilization and inferior mesenteric vessel ligation. The TATA procedure is transanal transabdominal radical proctosigmoidectomy with coloanal anastomosis. This was first developed in 1984 in the cadaver lab at Thomas Jefferson University by Dr. Gerald Marks. The hallmark of the operation is that it starts transanally followed by an abdominal phase, and then again transanal phase to complete the anastomosis. There are multiple advantages of this approach. First, the distal resection margin is selected well in advance and under direct vision which facilitates a precise distal dissection. In patients who have shown good response to neoadjuvant treatment present with impalpable lesion if procedure is done through abdominal route; however, using the transanal access first, the lesion can be marked well under direct vision. Lastly, it allows the surgeon to save the sphincter in case of very low rectal cancers which were otherwise candidates for APR and also that it can be predicted well in advance. In developing countries like ours where medical insurance is not common, it saves patients the cost of stapling devices because of the ability to perform a direct hand sewn coloanal anastomosis (Fig. 10.13).

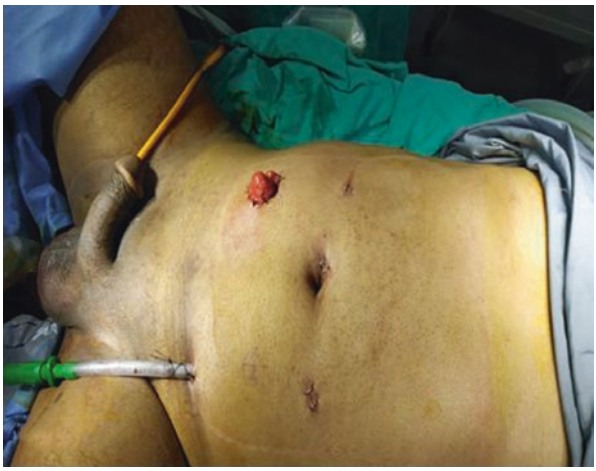

Fig. 10.13 Transanal transabdominal (TATA) surgery

Marks J et al. from Lankenau Medical Center, USA, published their study which reports the short- and long-term results from a prospective rectal cancer management program using laparoscopic radical TATA procedure after subjecting the patients to neoadjuvant therapy. The study included 102 rectal cancer patients treated with laparoscopic TATA from 1998 to 2008. The results of the study showed a local recurrence rate of 2.7% and improved 5-year survival rates without the need for permanent colostomy in patients with cancers in the distal one-third of the rectum. From their study they concluded that laparoscopic total mesorectal excision (TME) with the TATA approach is safe and can be performed laparoscopically. However, to establish the reproducibility of this promising approach, they suggest that more and more multi-institutional studies must be carried out (Marks et al. 2010). We have been performing this procedure from last 2 years at our center and have found excellent results in terms of short-term oncological outcomes as well as improved sphincter preservation rates.

10.1.9 MITAS (Minimal Invasive Transanal Surgery)

In 1993, Koutarou Maeda from Fujita Health University Hospital, Nagoya, devised the technique of MITAS in which he combined E-type retractor and Endo-GIA.

Local excision is often fully justified for rectal carcinoid tumors. However, insufficient surgical field and difficult access to proximal tumors have been drawbacks in performing local excision procedures. A novel local excision technique called MITAS has been experimented for local removal of carcinoid tumors in the rectum. A specially designed anal retractor connected to the octopus retractor holder was used and an endo-stapler allowed the simultaneous excision and anastomosis to be performed (Maeda et al. 2002).

10.1.10 Endoscopic Transanal Resection (ETAR)

Linden Schmidt et al. first described the technique of ETAR for a rectal adenoma. The technique involves the use of urologic resectoscope with angled resectoscope. Resection is carried out using the diathermy loop electrode using glycine 1.5% as irrigation fluid. A review of 464 procedures suggests that ETAR is an acceptable procedure with low morbidity and mortality in patients of rectal adenoma. The advantages of this procedure include no requirement for surgical assistance, anesthesia, extreme positioning, new technology, or special training. The biggest drawback associated with this procedure is that since the tumor is removed piecemeal, so it becomes difficult to comment on the resection margins. Also, this technique provides limited resection of mesorectal fat and lymph nodes, limited histopathological information regarding extent of resection, and poor local disease control. Hence, it is not widely used these days (Casadesus 2009).

10.1.11 Rootic Transanal Excision and Minimal Invasive Transanal Surgery

Rootic Transanal excision and minimal invasive transanal surgery are the new evolving techniques but still with limited support from case numbers and evidence (Fig. 10.14).

Fig. 10.14 Robotic transanal surgery (RTAS)

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Enhanced Recovery After Surgery (ERAS) in Colorectal Surgery

11

Nisar Ahmad Chowdri, Asif Mehraj, and Iqra Nisar

Abbreviations

ASA score	American society of anesthesia score
ERAS	Enhanced recovery after surgery
ERP	Enhanced recovery protocol
MBP	Mechanical bowel preparation
PCA	Patient controlled analgesia
SSI	Surgical site infection

11.1 Introduction

Hospital services are the most expensive component of health care systems and hospitals are under increasing pressure to enhance the efficiency of hospital care. Length of stay for inpatient care is quoted as an important index of efficiency. Hospital stay of 8 days after open and 5 days after laparoscopic surgery, high treatment cost, up to 80% of postoperative nausea and vomiting, and up to 20% surgical site infection rates have been reported following colorectal surgery in the literature (Thiele et al. 2015, Eberhart et al. 2002). Nagle et al. reported readmission rates of

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as high as 35.4% after discharge from the hospital (Nagle et al. 2012). End result of any surgery is not only a meticulously performed procedure but a functionally, physiologically, and psychologically well-recovered patient.

Enhanced recovery after surgery (ERAS) protocol is a collection of strategies combined in a structured pathway to decrease the physical insult and aid fast recovery after surgery thereby reducing the length of hospital stay in several ways. In fact, it is a multidisciplinary treatment protocol achieved with fewer complications. This concept was pioneered by Professor Henrik Kehlet, a surgeon from Hvidovre University Hospital in Denmark. Kehlet developed a multimodal rehabilitation program in 2001 in collaboration with university and specialized departments of surgery from northern European centers like Royal Infirmary of Edinburgh; Karolinska Institute at Ersta Hospital, Stockholm, Sweden; University Hospital of North Norway, and Maastricht University Medical Centre, Maastricht, The Netherlands (ERAS Group). They analyzed the colorectal surgery patients in these centers with respect to their clinical management and outcomes. From their study, it was shown that the length of stay in fast track centers was significantly shorter (2 days vs. 7–9 days). However, there was no influence on overall morbidity and 30-day mortality. The group considered the evidence base for individual components of perioperative care which ultimately led to the development of ERAS protocol (ERP). With the introduction of this multimodality program, the traditional perioperative care principles such as immobilization, fasting, nasogastric tube insertion, and placement of drains were abandoned. Various innovative techniques were introduced in this protocol that included consumption of a carbohydrate-rich drink before surgery, techniques of regional anesthesia, minimally invasive open or laparoscopic surgical techniques, maintenance of normothermia during surgery, optimal pain management following surgery, and prophylaxis for nausea and vomiting [Kehlet and Wilmore 2002, Kehlet et al. 2003]. As a result of implementation of this fast protocol, the surgical stress associated with surgical procedures decreased substantially.

The outcomes of surgical patients have improved as a result of incorporation of evidence-based techniques into perioperative management (White et al. 2007). For colorectal surgery, many of these are targeted at maintaining normal gut physiology. There has been a significant decrease in postoperative recovery time as a result of use of minimally invasive techniques, better analgesia using regional anesthetic techniques, use of ultra-short-acting anesthetic drugs, latest efficient energy sources, blend of new drugs, and technology. As a consequence of faster recovery time from anesthesia, patients can be directly transferred to day care surgery unit. The duration of hospital stay of patients got reduced. The introduction of ERAS concept reduced morbidity and improved quality of care by getting patients back to their preoperative status as quickly as possible (Teeuwen et al. 2010).

The concept of fast track surgery became popular since Henrik Kehlet reported a 2 days median postoperative hospital stay in colectomy patients (Basse et al. 2000). As a routine, patients subjected to colonic surgery usually require a postoperative hospital stay of around 1 week. The application of such fast track multimodal perioperative care programs in colorectal surgery patients results in a reduced length of hospital stay, less morbidity, reduced postoperative ileus, less pain, improved

pulmonary function, and less fatigue (Gatt et al. 2005). Median postoperative hospital stay of 2 days in 60 consecutive colectomy patients was reported by Basse et al. in 2000 (Basse et al. 2000).

Implementation of fast track protocol requires a multidisciplinary approach, mainly consisting of a surgeon, anesthesiologist, medical oncologist, physiotherapist, psychotherapist, stoma therapist, and other members of the nursing team. It is important to designate a task force group before implementing the ERAS protocol, which will assess the current practices in the hospital, review the literature, and suggest evidence-based recommendations for implementing the program. Clinicians' inputs are incorporated before the program is finalized and the protocol is framed. The task force should standardize the collected data. The data should include patient outcome and satisfaction, administrative compliance, and financial issues. After confirming the safety and benefits of new program, it is shared with the involved team members. As per the standard protocol, appropriate forms, patient education material, etc. are framed and ordered. After finalizing the protocol, it is handed over to concerned clinicians for implementation. Selected patients are enrolled for the fast track protocol and assessed for patient satisfaction, compliance, and outcomes. The outcomes of interest to patient and the ERAS team include relief from pain and nausea, early return of bowel functions, better wound healing, shorter hospital stay, and early return to work. Subsequent studies showed that it was also associated with reduced health care cost and improved patient satisfaction (Thiele et al. 2015; Hughes et al. 2015). Enhanced recovery protocols (ERPs) were associated with less complication rates and shorter length of hospital stay when compared to conventional perioperative patient management protocols (Spanjersberg et al. 2011). The type of approach whether open or laparoscopy did not influence the outcomes after implementing ERP (Currie et al. 2016). Regular auditing of ERP must be done to check for compliance and further suggest measures to improve the quality and outcome of protocol (Bakker et al. 2015; Day et al. 2015).

11.2 Enhanced Recovery Protocols (ERPs)

ERPs include many preoperative, intraoperative, and postoperative components. Although many surgeons currently apply some of the fast track elements which are not incorporated in a complete fast track perioperative care program, such as the omission of oral bowel preparation and drains, and early removal of the nasogastric tube, considerable variation still exists throughout Europe in the degree into which these elements are applied into daily practice (Nygren et al. 2005; Fearon et al. 2005). However, most beneficial and strongest components of the program were identified in a retrospective review of 8 years by Bakker N et al. in 2015 (Bakker et al. 2015). These include short midline or transverse incisions (laparoscopic preferred), mid-thoracic epidural or spinal anesthesia, paracetamol as baseline analgesic, avoidance of long-acting opioids and fluid overload, avoiding hypothermia, no drains, no nasogastric decompression tubes, removal of indwelling urinary

catheters, prevention of postoperative nausea and vomiting in high-risk patients, early mobilization, standard laxatives, early oral nutrition and nutritional supplements, and shorter length of hospital stay.

Patients should be followed according to protocol and following discharge should be contacted within 2 days, and then reviewed after 7–10 days and later at 30 days. Results and patient compliance should be audited and analyzed.

A protocol is not enough (Maessen et al. 2007). The importance of such collaboration has previously been described by others (Basse et al. 2000, Kehlet and Wilmore 2002, Maessen et al. 2007, Kehlet and Holte 2001, MacKay et al. 2006, Anderson et al. 2003, Kehlet and Wilmore 2008). Oral nutrition until 6 h prior to surgery and early postoperative feeding is safe as reported by various authors (Basse et al. 2000, Kehlet and Wilmore 2002, Fearon et al. 2005). This may even decrease morbidity, particularly in patients with poor nutritional status (Maessen et al. 2007).

11.2.1 Preoperative Elements

There are various components of ERAS protocol recommended in the preoperative setting. These include preoperative patient information and counseling, no oral bowel preparation, no preoperative fasting, preoperative carbohydrate loading with clear fluids up to 2 h and solids up to 6 h before induction, no pre-anesthetic medication, prophylaxis against thromboembolism (well-fitting compression stockings, intermittent pneumatic compression, low molecular weight heparin (started 2 h after insertion of epidural catheter) till patient is mobilized fully, single dose antibiotic prophylaxis half an hour before surgery with additional dose for prolonged surgery.

11.2.2 Preoperative Counseling

11.2.2.1 Milestones and Discharge Criteria

Milestones and discharge criteria per ERP should be discussed with the patient before surgery. Criteria for discharge include adequate pain control with oral analgesics, able to tolerate solid food, passage of flatus or stools, no intravenous fluid dependence, ambulatory, ability to perform self-care, no evidence of complications or untreated medical problems, adequate post discharge support and willingness to go home.

Preadmission counseling regarding milestones and defined discharge criteria are well-established aspects of ERPs (Gustafsson et al. 2012; Gustafsson et al. 2013; Adamina et al. 2011; Fearon et al. 2005; Kehlet and Wilmore 2002; Kehlet and Wilmore 2008; Delaney et al. 2003). Further in prospective trials and national audits, compliance with preoperative counseling and defined admission criteria has been shown to be inversely associated with the length of stay and complication rates (Wolk et al. 2016; Nelson et al. 2016).

11.2.2.2 Stoma Education

Educating the patient regarding various aspects of stoma care and complications is of paramount importance. This is supported by strong recommendation based on moderate quality evidence, 1B (Carmichael et al. 2017). Preoperative counseling done by a trained stoma therapist is associated with significantly improved quality of life and lesser postoperative complications with improved patient independence regardless of type of stoma (Danielsen and Rosenberg 2014, McKenna et al. 2016, Millan et al. 2010). In fact, stoma creation is one of the independent risk factors for a prolonged length of hospital stay after colorectal surgery (Delaney et al. 2003; Cartmell et al. 2008). Many studies have shown that structured stoma education significantly helps in improving the quality of life, reducing length of hospital stay and hospital cost and improving psychological state of the patient (Danielsen et al. 2013; Altuntas et al. 2012).

11.2.2.3 Hydration

Patient should be counseled to avoid dehydration. This is supported by strong recommendation based on moderate quality evidence, 1B (Carmichael et al. 2017). Dehydration has been found to be one of the most common causes of hospital readmission after stoma creation, ranging from 40 to 43% (Messaris et al. 2012; Hayden et al. 2013). Patients must be counseled preoperatively regarding the possibility of dehydration and the means to prevent it. Nagle et al. reported reduced readmission rate for dehydration from 15.5 to 0% following preoperative counseling (Nagle et al. 2012).

11.2.2.4 Bowel Preparation

There is no benefit of mechanical bowel preparation (MBP) alone in colonic surgery as stated in 2013 guidelines for perioperative care in elective colonic surgery and a 2011 Cochrane review. MBP causes distress to the patient (Gustafsson et al. 2013; Guenaga et al. 2011). However combining MBP with oral antibiotic preparation (OBP), significant reduction in surgical site infection rate has been reported after colorectal surgery (Chen et al. 2016; Mik et al. 2016; Kim et al. 2014).

11.2.2.5 Nutrition

Contrary to the traditional practice of overnight fast, consumption of clear fluids and carbohydrate-rich beverages <2 h before surgery has been found safe. It improves patient's sense of well-being as well (American Society of Anesthesiologists Committee 2011). The concept is fully supported by ASA and European Society of Anesthesiologists (Smith et al. 2011). Studies including multiple randomized controlled trials have supported and shown that ingestion of clear fluids within 2–4 h of surgery is associated with smaller gastric volume and higher gastric pH at the time of surgery as compared to allowing taking fluids >4 h before induction of anesthesia (Sutherland et al. 1987; Agarwal et al. 1989; Yagci et al. 2008).

In a cochrane review of 2014 which included 27 trials and 21 randomized studies including 1685 patients, no significant increase in complication rate or hospital stay was found (Smith et al. 2014; Awad et al. 2013). However, a meta-analysis

of 43 trials showed improved length of hospital stay compared to fasting group (Amer et al. 2017). Therefore, it is recommended to encourage use of carbohydrate-rich drink in nondiabetic patients to attenuate insulin resistance induced by surgical stress and starvation.

11.2.2.6 Optimization

Postoperative morbidity can be reduced by improving the functional capacity of the patient by proper preoperative optimization. It can also help in faster postoperative recovery (Le Roy et al. 2016, Carli and Zavorsky 2005). Optimization may be considered in patients with comorbidities undergoing elective surgery. However, this is supported by a weak recommendation with moderate quality evidence (Carmichael et al. 2017).

11.2.2.7 Proforma

Proforma should be framed as per the standard ERP for preoperative, intraoperative, and postoperative management and compliance with such order forms has been shown to be associated with reduced hospital stay (ERAS compliance group 2015). Complete compliance with the protocol is better than in piece meals (Carter and Kennedy 2012).

11.2.3 Intraoperative Measures

11.2.3.1 Bundle Measures

Colon care bundle is a set of measures to be implemented in the perioperative period to reduce the surgical site infection (SSI) and improve patient outcome (Tanner et al. 2015). The SSI prevention bundle includes: chlorhexidine shower, mechanical bowel preparation with oral antibiotics, intravenous antibiotic within 1 h of incision, and preparation of surgical field with chlorhexidine in the preoperative period. During the operation, theater room traffic should be limited, a wound protector should be used, separate tray for wound closure should be used, and glove and gown should be changed before fascial closure. Normothermia and blood sugars should be maintained in the perioperative period. In the postoperative period, dressings should be removed within 48 h followed by daily cleansing with chlorhexidine.

Other measures of SSI bundle include cessation of smoking, appropriate hair removal, limited use of intravenous fluids, use of double gloves, lavage of subcutaneous tissue, and use of Penrose drains for obese patients supplementary oxygen.

11.2.3.2 Fluid Management

During major abdominal surgery, a maintenance infusion rate of 1.5–2 mL/kg/h of balanced crystalloid solution is recommended (Brandstrup et al. 2003). Excessive fluid administration and fluid overload should be avoided as it can significantly impair organ function and increase postoperative morbidity and hospital stay. Goal-directed fluid therapy based on objective indices of hypovolemia and fluid

responsiveness is recommended in patients undergoing major colorectal surgery and high-risk patients (severe cardiopulmonary illness or age >70 years, limited physiological reserve, or prolonged surgery of >8 h). It has been found to reduce postoperative morbidity and hospital stay and guide physicians about fluid administration (Hamilton et al. 2011; Benes et al. 2014). Use of normal saline is associated with increased postoperative morbidity and mortality and renal dysfunction. However, chloride restricted crystalloid solution is preferred to normal saline as it decreases the risk of hyperchloremic metabolic acidosis (Burdett et al. 2012; McCluskey et al. 2013). In patients with preexisting renal dysfunction or those at risk should be managed with crystalloids rather than colloid solutions as increased risk of acute kidney injury has been reported with use of colloids (Gillies et al. 2014; Qureshi et al. 2016).

Fluid restriction is thought to enhance mobilization and recovery and reduce the complication rates (Brandstrup et al. 2003). The level of fluid restriction, however, is not yet settled. Mackay et al. did not find any effect and Holte et al. described increased morbidity after strict fluid restriction (MacKay et al. 2006; Holte et al. 2007). Behrns et al. reduced the hospital stay to 4.4 days, but the patients were discharged on liquid diet regardless of bowel function (Behrns et al. 2000).

11.2.3.3 Nausea and Vomiting

Nausea and vomiting are one of the most common postoperative complications, leading many a times to prolong the length of hospital stay. Control of these complaints has been found to significantly reduce hospital stay, overall cost, and patient satisfaction (Hill et al. 2000; Habib et al. 2004). The incidence of postoperative nausea and vomiting of 30% in all patients to 80% patients at high risk has been reported (Franck et al. 2010; Eberhart et al. 2002). Considering the high incidence of this complications, it is recommended to use multimodal antiemetic prophylaxis for all patients irrespective of risk. Besides, antiemetics are generally safe, cost-effective, and carry low risk (Eberhart and Morin 2011).

11.2.3.4 Anesthesia and Pain Management

Open laparotomy wounds are usually associated with significant postoperative pain. In patients undergoing open colorectal surgery, thoracic epidural analgesia as compared to parental analgesia is considered to be the gold standard for controlling pain (Block et al. 2003). Stress hormone release is blocked and insulin resistance is inhibited by epidural analgesia with opiate-restriction before surgery. This may reduce the surgical stress response, decrease postoperative pain, reduce postoperative ileus and pulmonary complications (Basse et al. 2000; Kehlet and Wilmore 2002; Kehlet and Holte 2001; White et al. 2007). Apart from epidural anesthesia, patient controlled analgesia (PCA) is another alternative for pain relief (Delaney et al. 2003).

However, in laparoscopic surgery the same does not hold true. For parental analgesia, multimodal therapy is recommended. Minimizing the use of opioids is associated with early return of bowel function and reduced hospital stay (Thiele

et al. 2015; Bakker et al. 2015). Postoperative analgesia can be achieved by the use of nonselective or selective nonsteroidal anti-inflammatory drugs (NSAIDs) if not contraindicated, acetaminophen, gabapentinoids, ketamine, and even steroids. These drugs help in surgical recovery and reduce systemic opioid consumption (Eipe et al. 2015; Vignali et al. 2009). Other measures like infiltration of wounds by local anesthetic agent has also shown promising results in terms of postoperative pain control (Fiore et al. 2013).

11.2.3.5 Surgical Technique

Minimally invasive approach should be used whenever appropriate and necessary expertise is available. This is supported by a strong grade of recommendation based on high quality evidence, 1A (Carmichael et al. 2017). Minimally invasive approach has been found to be beneficial in terms of less blood loss, less pain, early return of bowel function, shorter hospital stay, and reduced overall surgical and nonsurgical complications for management of colorectal diseases as compared to open approach (Hewett et al. 2008; Veldkamp et al. 2005). Multiple studies have shown advantage of minimally invasive surgery with respect to short-term outcomes and equivalent better and long-term outcome as equivalent to open approach for colorectal cancers (Bonjer et al. 2015; Van der Pas et al. 2013; Jeong et al. 2014; Kang et al. 2014).

11.2.3.6 Tubes and Drains

There is enough evidence in the literature that there is no benefit of putting naso-gastric tubes and intra-abdominal drains in colorectal surgery to prevent or decrease postoperative complications like nausea and vomiting, return of bowel function, anastomotic leaks, and hospital stay (Feo et al. 2004; Brown et al. 2001; Merad et al. 1999).

11.2.3.7 Postoperative Measures

Fluid Therapy

Resumption of oral feeding in postoperative period with clear liquids should be encouraged as early as possible in patients undergoing any type of surgery. Intravenous fluids should be discontinued to avoid negative impact of excess fluid on clinical outcome (Varadhan and Lobo 2010, Brandstrup et al. 2003).

Feeding

According to ERPs, regular diet should be started immediately following elective colorectal surgery. Early resumption of diet has been shown to accelerate gastrointestinal recovery, reduce risk of ileus, reduce rate of postoperative complications and mortality, and decrease hospital stay (Dag et al. 2011; Lobato Dias Consoli et al. 2010; da Fonseca et al. 2011; El Nakeeb et al. 2009).

Also chewing sugar-free gums many times a day may be associated with small improvement in gastrointestinal recovery and reduced hospital stay (Chan and Law 2007, Ho et al. 2014, Li et al. 2013).

Catheters

Urinary catheters should usually be removed after 24 h for uncomplicated colonic and upper rectal resections and after 48–72 h following mid and lower rectal resections. Early removal of urinary catheters has been shown to have many beneficial effects in terms of urinary tract infection and urinary retention (Emori et al. 1991; Lee et al. 2015; Yoo et al. 2015).

Mobilization

Immobilization for a prolonged period is associated with various complications like thromboembolism, insulin resistance, skeletal muscle loss, atelectasis, and reduced exercise capacity (Brower 2009, Convertino et al. 1997). Mobilization reduces insulin resistance, risk of thrombo-embolic complications undesired muscle loss and fatigue and improves pulmonary function and tissue oxygenation (Kehlet and Wilmore 2002; Fearon et al. 2005).

Early and progressive mobilization is associated with reduced hospital stay (Carmichael et al. 2017). In ERPs, early mobilization refers to any mobilization started within 24–48 h (Feroci et al. 2013).

11.2.4 Conclusion

Treatment of colorectal surgery patients according to ERP leads to faster recovery and shorter hospital stay without affecting mortality and morbidity. Additionally, the implementation of this fast track protocol after proper analysis and standardization is associated with significant improvements of perioperative parameters. Principles of ERAS program are applicable and beneficial in view of the dearth of hospitals and expertise available in most parts of the world.

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Neoadjuvant and Adjuvant Therapy for Rectal Cancer

12

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Abbreviations

ACOSOG	American College of Surgeons Oncology Group institutions
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FOLFOX	5-Fluorouracil, Leucovorin, and Oxaliplatin
FU	Fluorouracil
Gy	gray (symbol: Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI)
IMPACT	International Multicenter Pooled Analyses of Colon Cancer Trials
K-ras	a gene that acts as an on/off switch in cell signaling
LV	Leucovorin
MOSAIC	Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer
pCR	pathologic complete response
SRCT	Swedish Rectal Cancer Trial
TNM	Tumor, Node, Metastasis

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12.1 Colon Cancer

The stage of disease at presentation is the most important predictor of outcome for colon cancer patients. Stage I disease (T1-2N0M0) has a 5-year survival rate of 95% after resection, and surgical treatment alone is considered sufficient.

Stage II disease (T3-4N0M0) has a 5-year survival, averages 70–80%, but a subset of high-risk patients with poor prognostic factors like lymphovascular invasion or poor histological tumor grade have poorer prognosis and may benefit from adjuvant therapy.

Stage III (TanyN1-2M0) disease has improved survival with adjuvant treatment, with 5-year survival of approximately 40–60%.

12.1.1 Adjuvant Chemotherapy for Stages II and III Colon Cancer

One of the most important single prognostic factors in colon cancer is nodal status. Recurrences are often systemic.

5-Fluorouracil (5-FU)/leucovorin (LV)-based adjuvant chemotherapy is now considered to be the standard of care for stage III disease.

In 1990 while establishing 5-FU plus levamisole as the standard adjuvant therapy for stage III colon cancer, the usefulness of 5-FU/levamisole in stage III disease was being confirmed; leucovorin emerged as a beneficial agent for the treatment of metastatic disease. Its applicability to stage II and stage III disease was confirmed by the IMPACT (International Multicenter Pooled Analyses of Colon Cancer Trials) study in 1995; 3-year disease-free survival increased from 62 to 71% ($p = 0.0001$), while overall survival increased from 78 to 83% ($p = 0.029$) in the 5-FU/leucovorin group.

While the efficacy and benefits of adjuvant chemotherapy for stage III node-positive disease are unequivocal, the role of adjuvant chemotherapy for stage II node-negative disease remains controversial.

Irinotecan and oxaliplatin are effective in treating stage IV (metastatic) colorectal cancer but no survival advantage was achieved by adding irinotecan to 5-FU (5-year survival was 74% vs. 71%) and toxicity (gastrointestinal and hematologic) was increased for stage III disease.

The multicenter international randomized MOSAIC trial confirmed that the addition of oxaliplatin to 5-FU/leucovorin (FOLFOX) further decreases the risk of recurrence in stage II and stage III disease by 23%, resulting in a significant improvement in 3-year disease-free survival.

Overall survival benefits have proven durable in stage III disease. In the FOLFOX group, 6-year overall survival was 73% vis a vis 69% in the 5-FU group. Toxicity also proved to be acceptable, with less than 1.5% of patients experiencing grade 3 peripheral sensory neuropathy.

For stage II patients, the addition of oxaliplatin offered no survival advantage over 5-FU alone.

With result of these studies, FOLFOX is now recommended for adjuvant therapy in stage III colon cancer.

In select stage II patients, especially those with high-risk features such as T4 tumors, vascular invasion, or poor differentiation, FOLFOX may have a role.

12.1.2 Targeted Biologic Therapy

Monoclonal antibodies targeting specific tumor proteins have proven useful in treating selected patients with metastatic colorectal cancer. In the adjuvant setting, antibodies against epidermal growth factor receptor (cetuximab) and vascular endothelial growth factor (bevacizumab) failed to show benefit even when K-ras wild-type tumors were looked at separately.

12.1.3 Radiotherapy

Combined chemoradiotherapy has been shown to increase both local control and survival for patients with locally advanced and node-positive rectal cancer.

- The most important risk factors for local recurrence are
  - Pathological staging: Higher the stage of disease, the greater are the chances of recurrence.
  - Primary tumor localization in a fixed, nonperitonealized segment of the colon, with the highest failure rates in the cecum, descending colon, hepatic or splenic flexures, and sigmoid colon.
  - Colon carcinoma complicated by perforation or obstruction, with a two- to threefold increase in local recurrence for any given pathological stage.
- At this time, the precise role of adjuvant radiotherapy in the treatment of colon cancer remains undefined. The potential risks of adjuvant radiotherapy for colon cancer, particularly radiation damage to surrounding organs (e.g., small bowel), are significant. Treatment for individuals deemed at high risk for local recurrence after curative surgery for colon cancer should be individualized.

12.2 Rectal Cancer

Single most important factor that dictates the decision for talking a patient for radiotherapy and/or chemotherapy in adjuvant and/or neoadjuvant setting is the local and distant stage of the disease. This factor also dictates the choice among the various available surgical options such as local excision or an abdominal procedure.

12.2.1 Adjuvant/Neoadjuvant Therapy for Stage I Rectal Cancer

Like stage I colon cancer, 5-year survival after curative intent surgery (radical resection) for stage I rectal cancer exceeds 90% and adjuvant/neoadjuvant therapy is not recommended for patients who undergo radical resection of T1 or T2N0 tumors.

The morbidity resulting thereof from complications of radical surgery has paved the way for some surgeons to consider local (transanal) excision for early lesions. Recurrence after local resection of T1 tumors ranges from 4 to 18%; for T2 tumors, recurrence ranges from 27 to 67%.

Adjuvant radiation and/or chemoradiation therapy after local (transanal) excision have been suggested as an adjunct to surgery to improve local control and prolong survival. Studies suggest that the addition of adjuvant therapy improves outcome.

ACOSOG Z6041 is evaluating patients with T2 N0 rectal cancers in an attempt to determine if preoperative chemoradiation followed by transanal excision will result in disease-free survival equivalent to that seen after radical surgery. Preliminary results have shown considerable morbidity for patients in whom medical comorbidities preclude an abdominal procedure; adjuvant or neoadjuvant chemoradiation therapy may be appropriate to improve local control. Adjuvant/Neoadjuvant Therapy for Stages II and III Rectal Cancer.

Combined modality chemotherapy and radiation have long been used as adjuvant therapy for locally advanced (stages II and III) rectal cancer. Studies have demonstrated both improved local control and prolonged survival.

There is little controversy regarding adjuvant or neoadjuvant therapy for stage III (TanyN1M0) disease. However, advances in surgical technique, such as total mesorectal excision (TME), for locally advanced node-negative cancers (T3-4, N0, M0; stage II) have improved local control with surgery alone, prompting some surgeons to abandon adjuvant therapy in these patients. Although the data from these studies are intriguing, other reports have shown that chemoradiation improves local control and survival even in patients who undergo TME. Adjuvant or neoadjuvant therapy is still recommended for all patients with stage III disease and the majority of patients with stage II disease. In well-selected patients with T3 tumors, favorable histology, and negative radial margins, chemoradiation may not be necessary, but larger prospective studies are required before this approach can be recommended.

12.2.2 Radiation Therapy

Initial neoadjuvant radiation has long been considered an important adjunct in the treatment of rectal cancer. A short preoperative course, 20–30 Gy given over 1 week (most commonly used), is biologically equivalent to the traditional postoperative course of 45–55 Gy given over 5–6 weeks. In 1993, the randomized Swedish Rectal Cancer Trial (SRCT) demonstrated that a biologically equivalent short course

(25 Gy) of preoperative radiotherapy with surgery within the next week significantly reduced local recurrence from 27 to 12% and improved 5-year survival rates from 48 to 58% when compared to surgery alone.

- The undisputed major benefits of preoperative radiotherapy remain locoregional tumor control and decreased local recurrence.
- In the randomized multicenter study (Dutch trial) of 1861 patients with rectal cancer, 2-year local recurrence rates were significantly improved from 8.2 to 2.4% when preoperative radiation was given prior to TME. Five-year figures confirm a reduction in local recurrence rates from 11.4% after TME alone vs. 5.6% for preoperative radiotherapy followed by TME, but this does not translate into an improvement in 5-year survival rates.
- Neoadjuvant radiotherapy still has a place in the treatment of rectal cancer, even when surgical technique is optimized.
- A recent update of the EORTC 22921 trial confirmed that chemotherapy in addition to radiation therapy is beneficial for patients who respond well (ypT0-2) vs. those who respond poorly (ypT3-4). Because it is difficult, if not impossible, to predict tumor response to neoadjuvant therapy, most oncologists currently recommend combination chemoradiation therapy.

12.2.3 Adjuvant vs. Neoadjuvant Therapy

Although combination chemotherapy and radiation have been shown to decrease local recurrence and improve survival for patients with stage III rectal cancer and many with stage II rectal cancer, the optimal timing of therapy has been controversial. According to three recently published meta-analyses, there is no doubt that neoadjuvant treatment is superior to adjuvant treatment with regard to reduction in local failure rates and cancer-specific survival. As such, preoperative chemoradiation is now recommended for all patients with clinical stage III disease and most with clinical stage II disease.

12.2.4 Chemotherapeutic Agents

Like colon cancer, adjuvant and neoadjuvant therapy for rectal cancer have long utilized 5-FU-based regimens. Infusional 5-FU and, increasingly, oral 5-FU (capecitabine) have used as radiosensitizing agents.

Because additional agents such as oxaliplatin have shown synergistic efficacy in the metastatic setting, the addition of this agent to neoadjuvant regimens has been suggested. Two recent phase II studies of oxaliplatin in combination with capecitabine and radiation demonstrated good complete pathologic responses (16 and 24%) with acceptable toxicity (grade 3–4 toxicity in only 12 and 20% of patients).

12.2.5 Radiation Dose and Timing of Surgery After Completion of Treatment

Controversy also exists as to the optimal radiation dose and timing of post-treatment surgery. Current regimens in the USA typically give a total of 45–54 Gy of radiation over 4–6 weeks. Surgery is then performed 6 weeks later. Many European centers, in contrast, favor a short course of radiation consisting of five fractions of 5 GY (total dose = 25 Gy) without chemotherapy followed by surgery within 1–2 weeks. Advocates of the short course of radiotherapy suggest that the lower dose of pelvic radiation will result in fewer complications while maintaining efficacy in tumor control. Earlier surgery theoretically may prevent tumor progression. Detractors counter that the lower dose may not be as efficacious and that immediate surgery does not allow enough time for maximal tumor shrinkage. • The Swedish Rectal Cancer Trial has shown that short-course radiotherapy improves local control and long-term survival compared to surgery alone. Similarly, the Dutch Colorectal Cancer Group has shown that short-course preoperative radiotherapy decreases local recurrence and increases survival compared to total mesorectal excision alone. • However, there are no studies to date that compare short-course vs. long-course chemoradiation and the majority of radiation oncologists in the USA continue to offer standard 45–54 Gy treatment.

Delaying resection may improve the clinical response to chemoradiation and lead to a larger proportion of patients having a pathologic complete response (pCR).

12.2.6 Chemotherapy Alone

In contrast to colon cancer, chemotherapy alone as adjuvant treatment in rectal cancer remains questionable. Many trials have concluded that chemotherapy improved survival compared to surgery alone. Adjuvant chemotherapy alone for stage III rectal cancer is not acceptable unless the patient cannot receive radiotherapy (history of previous pelvic radiation).

12.2.7 Neoadjuvant Therapy in Unresectable Rectal Cancer

In this section, we define a non-resectable rectal cancer as a tumor which cannot be resected without a very high risk of local recurrence. These tumors are clinically tethered or fixed (due to cancer overgrowth or fibrosis). Such tumors probably involve the rectal fascia, and resection carries a high likelihood of involvement of the circumferential resection margin. Based on available data, patients with such large tumors benefit from long-course preoperative radiotherapy (45–55 Gy over 5–6 weeks) with the aim of downsizing the tumor.

12.2.8 Neoadjuvant Therapy and Sphincter Preservation

Several series claim that preoperative radiotherapy (and preferably chemoradiotherapy) downsizes tumors to the extent that it is possible to increase the number of patients in whom the sphincters can be preserved. An important consequence of increased sphincter preservation is poor function. Poor quality of life may be the price to pay for intact sphincters: up to 20% of all patients who undergo a low anterior resection are incontinent of solid stool. This contrasts with reports that patients with a stoma had a better quality of life compared to those with an anterior resection. This must be considered when selecting surgical options for individual patients.

Another important thing that is to be kept in mind while treating patients following neoadjuvant chemoradiotherapy with an intent to spear sphincter is that, in patients with tumor downstaging, such patients are to be managed as per stage of their disease prior to neoadjuvant chemoradiotherapy and not as per the disease stage post-neoadjuvant chemoradiotherapy. In this context, the advantage of neoadjuvant chemoradiotherapy is that the chances of R0 resection increase as a result of tumor shrinkage post-neoadjuvant chemoradiotherapy and thus having higher chances of sphincter preservation.

12.2.9 Molecular Profiling and Chemoresistance

Increasingly, tumor characteristics are found to influence response to chemotherapy and "personalized" treatment based upon molecular profiling shows increasing promise for increasing response to therapy while decreasing toxicity. Microsatellite instability (MSI) and rates of phenotypic expression of DNA synthesis-associated enzymes recently have been found to predict chemoresistance to 5-FU and irinotecan. For example, microsatellite instability not only appears to confer better prognosis but may also predict poor response to chemotherapy, suggesting that patients with MSI-high tumors may not benefit from adjuvant therapy. Similarly, polymorphisms in the enzymes that synthesize and metabolize folate may affect both efficacy and toxicity of 5-FU-based therapy. Finally, the observation that K-ras status predicts response to EGFR-targeted therapy in metastatic colorectal cancer has implications for adjuvant therapy. This is an area of research, which is evolving rapidly, and our increasing knowledge on the impact of molecular characteristics will certainly change the recommendations for adjuvant treatment in the future.

Non-operative Management for Rectal Cancer

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Abbreviations

APE	Abdominoperineal excision
cCR	Complete clinical response
CR	Complete response
CRT	Chemoradiotherapy
CT	Computerized tomogram
ELAPE	Extralevator abdominoperineal excision
MRI	Magnetic resonance imaging
nCRT	Neoadjuvant chemoradiotherapy
OS	Overall survival
pCR	Pathological complete response
TME	Total mesorectal excision

13.1 Non Surgical Management

Wait-and-watch policy is one of the evolving concepts of the recent times to opt for non-operative management in patients who have a complete pathological response (pCR) after neoadjuvant chemoradiotherapy (nCRT). The proponents of this concept believe that all radical rectal cancer surgeries like total mesorectal excision (TME), abdominoperineal excision (APE), and extralevator abdominoperineal excision (ELAPE)

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continue to have their procedure-related morbidity and mortality. This concept popularized avoidance of radical surgery in a subset of patients who show a complete clinical response to nCRT. The proponents believe that at times the complications associated with radical surgeries might be at times too big a price you may pay in this subset of patients just to confirm pathological complete response (pCR). The non-operative approach, known as "watch and wait," has been used by Habr-Gama et al. for many years (Habr-Gama et al. 1998, 2009, 2004). Even though good long-term results have been reported, but still this approach has received a cold shoulder at other institutions and remains highly controversial, principally because of concerns about the inaccuracies of post-treatment clinical staging and uncertainty regarding the potential oncologic benefit of resection even when there is pCR (Habr-Gama et al. 2009; Hiotis et al. 2002; Glynne-Jones et al. 2008).

The biggest difficulty in these patients a clinician can face is the interpretation of radiology of complete response (CR) which is more elusive than the pathological determination due to limitations of imaging, particularly after CRT. Besides, there stays an iota of suspicion always on the minds of treating physician as well as the patient on follow-up under wait-and-watch protocol. Lack of any strict guidelines about the timing of assessment on follow-up is other area of concern. As per the literature evidence from Habr-Gama et al. that a clinical assessment of carcinoma rectum patients at less than 8 weeks post-neoadjuvant treatment might be deceptive as many of them who show a partial response at this time might become complete responders after 8 weeks (Habr-Gama et al. 1998, 2009, 2004). Likewise, inaccuracies of clinical detection of CR (typically demonstrating clinical under identification of pCR) may be the consequence of a short (6 weeks) waiting period. Also the lack of uniform guidelines and expertise for the clinical assessment of tumor response leads to differences and variations (Habr-Gama et al. 2010). These concerns could limit the usefulness of "wait-and-watch" policy even if other issues were resolved.

The "watch-and-wait" policy is in fact a conservative approach that is suitable for highly selected tumors under strict surveillance which anytime may change to operative approach on follow-up. The follow-up needs to be meticulous by an experienced colorectal surgeon using digital rectal and endoscopic examinations at 4- to 6-week intervals for the first year after completing nCRT (Habr-Gama et al. 2008). A very important word of caution is that strict criteria are used to identify potential complete responders, but the final designation of complete clinical response (cCR) is not made until a full 12 months after nCRT. The best thing in potential responders is to be completely sure by a full excisional rather than endoscopic biopsy. As per the devised policy, patients are counseled that disease detection during the first 12 months (i.e., failure to meet cCR criteria) or recurrence after 12 months requires surgical intervention. As per the retrospective review, patients who were initially having a cCR but are required salvage radical resection on follow-up showed no oncologic compromise compared with radical resection group (Habr-Gama et al. 2008). In their study group, salvage surgery was possible all the time in the first year on follow-up. The comparison in the two study groups did not show any oncologic benefits in terms of overall survival (OS) or disease-free, cancer-specific survival between patients (Habr-Gama et al. 2004).

More and more literature came to limelight in support or against this concept of wait and watch in subsequent years. In a recent report by Smith et al. to address the uncertainties of this policy, certain strict criteria for patients on wait and watch need to be followed selecting them after complete clinical response.

Years 1–2

- The most intensive monitoring period after neoadjuvant.
- Patients need follow-p with an organ preservation surveillance specialist every 3 months and undergo a digital rectal examination and flexible sigmoidoscopy. This should aim to incorporate narrow band imaging.
- **MRI (Magnetic resonance imaging)** of pelvis every 4–6 months.
- Carcinoembryonic antigen (CEA) blood test every 4 months.
- Computed tomography (CT) of thorax, abdomen, and pelvis every 6 months.
- Colonoscopy carried out as per NICE surveillance guidelines.

Years 3–5

- If cCR is maintained, the frequency of flexible sigmoidoscopy and DRE to be reduced to every 6 months in third year and yearly thereafter up to 5 years.
- CEA blood test every 6 months.
- Patient's last MRI at 36 months.
- One further CT of thorax, abdomen, and pelvis at 36 months.

After 5 years

- Annual digital rectal examination, flexible sigmoidoscopy, and CEA blood test.
- MRI or CT based on clinical suspicion
  - Suspicion or confirmation of tumor regrowth at any stage in surveillance program.
- Patient should be referred to colorectal surgeon immediately for further management (Smith et al. 2018).

A recent study was conducted to review the risk of local recurrence and impact of salvage therapy after watch and wait for rectal cancer with complete clinical response (cCR) after chemoradiation therapy (CRT).

Patients with cT2-4N0-2M0 distal rectal cancer treated with CRT (50.4–54 Gy + 5-fluorouracil-based chemotherapy) and cCR at 8 weeks were included. Forty-nine percent patients experienced a cCR% whereas 31% experienced local recurrence on a median follow-up of 60 months. Twenty-six patients out of these 28 (31%) underwent salvage therapy. Out of these, four patients developed local re-recurrence. The 5-year cancer-specific overall survival and disease-free survival for all patients (including all recurrences) were 91% and 68%, respectively (Habr-Gama et al. 2014).

Current evidence suggests that patients on watch and wait have similar overall and disease-free survival compared with patients who undergo surgical resection.

Regrowth on follow-up was seen in approximately 30% in first 2 years and 85% of these patients with recurrence were suitable for surgical resection without any oncological disadvantage. In most of the studies, the long-term outcome is still lacking. The International Watch and Wait Database (IWWD), 19th largest series of patients with rectal cancer managed by watch and wait (880 patients), noted that 5-year overall survival was 85% (95% confidence interval 80.9–87.7%) and 5-year disease-specific survival was 94% (91–96%) (Smith et al. 2018).

There are several limitations of the evidence at present available in literature. The biggest concern is raised on the absence of randomized controlled trials which puts a question mark on treatment selection bias and propensity score matching (Renehan et al. 2016). In addition between study heterogeneity in age, performance status, and cancer stage which is illustrated in meta-analysis of individual participant data in T stage in particular (Chadi et al. 2018). Locally advanced cancer definition still lacks international uniformity, thus leading to selection bias in patient selection for wait and watch and the final outcome. Also, one more bias can be encountered by expertise level, treatment, and follow-up protocols (Chadi et al. 2018).

13.2 Prediction of Tumor Response: Genetic Studies

Molecular studies hold a great hope for future on the issue of prediction of response to nCRT in patients with rectal cancer. Few studies have attempted to identify gene expression signatures by microarray platforms capable of predicting "good" versus "bad" responses to CRT. Unfortunately, these studies lack standardization to define good response, pCR, near-complete pathological response, or even any T-category downshift. In addition, all studies assessed tumor response at the relatively short interval of 4 weeks to 6 weeks from CRT completion (Rimkus et al. 2008; Kim et al. 2007). On basis of these studies, some retrospective studies have suggested that longer intervals may increase complete response rates and short interval assessment may have influenced the results of all studies. Also, there were absolutely no overlaps with respect to genes included in the gene signatures that might predict survival in each of the studies. Perhaps newer protocols using high-output sequencing for gene expression analysis may provide additional molecular and genetic information about the prediction of tumor response to nCRT.

13.3 Conclusion

With the level of evidence at present available; wait and watch cannot be considered as standard of care. It is a must to take patient and his attendants on board in a patient of cCR and explain the chances of failures and recurrences associated with wait and watch and also the importance of a meticulous follow-up.

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