CORRELATION OF RADIATION DOSE TO ANAL SPHINCTER AND ANAL MANOMETRY CHANGES IN LOCALLY ADVANCED RECTAL CANCER PATIENTS UNDERGOING PREOPERATIVE LONG COURSE CHEMORADIATION THERAPY

Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfilment of the requirement

for the award of the degree of

DOCTOR OF MEDICINE

in

RADIOThERAPY

by

KANMANI VELARASAN . S

DEPARTMENT OF RADIOThERAPY

CHRISTIAN MEDICAL COLLEGE

VELLORE - 632004

APRIL – 2016

CHRISTIAN MEDICAL COLLEGE, VELLORE
DEPARTMENT OF RADIOThERAPY
This is to certify that the dissertation entitled ‘CORRELATION OF RADIATION DOSE TO ANAL SPHINCTER AND ANAL MANOMETRY CHANGES IN LOCALLY ADVANCED RECTAL CANCER PATIENTS UNDERGOING PREOPERATIVE LONG COURSE CHEMORADIATION THERAPY’ is an original work by Dr. Kanmani Velaranas in partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2016.

GUIDE
Prof. Thomas Samuel Ram
Department of Radiotherapy
Christian Medical College, Vellore

HEAD OF THE DEPARTMENT
Prof. Selvamani B
Department of Radiotherapy
Christian Medical College Vellore
I Kanmani Velarasan , S, PG Registrar , Department of Radiation therapy , Christian Medical College Vellore hereby declare that the dissertation titled ‘CORRELATION OF RADIATION DOSE TO ANAL SPHINCTER AND ANAL MANOMETRY CHANGES IN LOCALLY ADVANCED RECTAL CANCER PATIENTS UNDERGOING PREOPERATIVE LONG COURSE CHEMORADIATION THERAPY’ is a bonafide work done by me for partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2016.

DR. KANMANI VELARASAN. S

PG REGISTRAR ,

DEPARTMENT OF RADIOTHERAPY,

CHRISTIAN MEDICAL COLLEGE,

VELLORE
February 24, 2015

Dr. Kanmani Velarasan, S
Department of Radiation Therapy Unit 1
Christian Medical College, Vellore 632 004

Sub: Fluid Research Grant Project:
Co-relation of radiation dose to anal sphincter and anal manometry changes in locally advanced rectal cancer patients undergoing preoperative long course chemoradiation therapy.
Dr. Kanmani Velarasan, S, Dr. Thomas Samuel Ram, Dr. Selvamani. B, Mr. Sathish Radiation Therapy Unit 1, Dr. Mark Raman, J, Colorectal Surgery, Dr. Anu Eapen, Radiodiagnosis, Mrs. Visalakshi, Biostatistics, CMC, Vellore.


Dear Dr. Kanmani Velarasan, S,

I enclose the following documents:

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. Nihal Thomas
MD, MAMS, DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Secretary - (Ethics Committee)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Thomas Samuel Ram, Radiation Therapy Unit 1, CMC, Vellore.
February 24, 2015

Dr. Kanmani Velarasans. S
Department of Radiation Therapy Unit 1
Christian Medical College, Vellore 632 004

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Dear Dr. Kanmani Velarasans. S,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled “Co-relation of radiation dose to anal sphincter and anal manometry changes in locally advanced rectal cancer patients undergoing preoperative long course chemoradiation therapy.” on November 12th 2014.

The Committees reviewed the following documents:

1. IRB Application format
3. Informed Consent form (English, Tamil, Hindi & Bengali)
4. Information Sheet(English, Tamil, Hindi & Bengali)
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 12th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.
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<tbody>
<tr>
<td>Dr. Chandra Singh</td>
<td>MS, MCH, DMB</td>
<td>Professor, Urology, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. Ranjith K Moorthy</td>
<td>MBBS M Ch</td>
<td>Professor, Neurological Sciences, CMC, Vellore</td>
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</tr>
<tr>
<td>Dr. Bobby John</td>
<td>MBBS, MD, DM, Ph.D, MAMS</td>
<td>Professor, Cardiology, CMC, Vellore</td>
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</tr>
<tr>
<td>Dr. Benjamin Perakath</td>
<td>MBBS, MS, FRCS</td>
<td>Professor, Colorectal Surgery, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. Rajesh Kannangai</td>
<td>MD, Ph.D</td>
<td>Professor &amp; In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. Anup Ramachandran</td>
<td>Ph. D</td>
<td>The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC</td>
<td>Internal, Basic Medical Scientist</td>
</tr>
<tr>
<td>Dr. Anand Zachariah</td>
<td>MBBS, PhD</td>
<td>Professor, Medicine, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. Simon Pavamani</td>
<td>MBBS, MD</td>
<td>Professor, Radiotherapy, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. Visalakshi. J</td>
<td>MPH, PhD</td>
<td>Lecturer, Dept of Biostatistics, CMC, Vellore</td>
<td>Internal, Statistician</td>
</tr>
<tr>
<td>Dr. T. Balamugesh</td>
<td>MBBS, MD(Int Med), DM, FCCP (USA)</td>
<td>Professor, Pulmonary Medicine, CMC, Vellore</td>
<td>Internal, Clinician</td>
</tr>
<tr>
<td>Dr. B. J. Prashantham</td>
<td>MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)</td>
<td>Chairperson, Ethics Committee, IRB, Director, Christian Counseling Centre, Vellore</td>
<td>External, Social Scientist</td>
</tr>
</tbody>
</table>


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*Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.*  
*Tel : 0416 - 2284294, 2284202  
Fax : 0416 - 2262788, 2284481  
E-mail : research@cmcvellore.ac.in*
We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any adverse events, occurring in the course of the project, annual report, any amendments in the protocol and the patient information / informed consent. On completion of the study you are expected to submit a copy of the final report. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Policies.html in the CMC Intranet and in the CMC website link address; http://www.cmcv-vellore.edu/static/research/Index.html.

Grant Allocation:

A sum of 50,000/- INR (Rupees Fifty Thousand only) will be granted for 2 years.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

C: Dr. Thomas Samuel Ram, Radiation Therapy Unit 1, CMC, Vellore.
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correlation of anal manometry changes with me...
By 20149052, Md Radiotherapy
Dr. Kannam Valavan S

INTRODUCTION: Though the incidence of rectal cancer in the world and in India is low it is gradually increasing. Outcomes of rectal cancer has improved significantly since the evolution of TME and Concurrent Chemoradiation. We have seen a local control rates decreased from 20% to less than 5% and 5 year overall survival of 22.3% to 99.2%([1]) while increasing number of patients are long term survivors their quality of life specifically related to anal dysfunction is of great concern. Organ preservation and organ sparing techniques of managing cancers is of utmost importance for such long term survivors. Some anatomical sites like head and neck cancers and prostate cancers have shown promising outcomes in quality of life with such techniques. Anal sphincter sparing attempts have been made by surgeons in some low rectal cancer patients. However a proactive approach by radiation oncologists towards anal sphincter sparing radiation techniques has been lacking. Few authors have reported the dose to anal sphincter and correlated with anal dysfunction in patients undergoing radiation therapy for prostate cancer which is usually given upto a mean dose of 70 Gy[1]). However there is currently very little information on anal dysfunction in high or mid rectal cancer patient undergoing chemoradiation followed by low anterior resection. Hence this study was undertaken to develop a contouring method, evaluate the dosimetric characteristics of anal sphincter and correlate the anal manometric changes with the anal sphincter dose. AIM: AND OBJECTIVES: AIM 1: To assess the relation of anal manometry changes and radiation dose to anal sphincter. OBJECTIVES 1: To generate dose volume histograms for anal sphincter 2: To study the effect of low anterior resection on anal sphincter function and correlate the dose distribution.
INTRODUCTION:

Though the incidence of rectal cancer in the world and in India is low it is gradually increasing. Outcomes of rectal cancer has improved significantly since the evolution of IMRT and Concomitant Chemoradiation. We now see a local control rates decreased from 20% to less than 5% and 5-year overall survival of 62.3% to 69.2% (1). While increasing number of patients are long time survivors their quality of life specifically related to anal dysfunction is of great concern. Organ preservation and organ sparing techniques of managing cancers is of utmost importance for such long term survivors. Some anatomical sites like head and neck cancers and prostate cancer have shown promising outcomes in quality of life with such techniques.

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ACKNOWLEDGEMENT

This work would have never been accomplished without an outstanding support system and is a fruit of efforts of many and I am grateful to my teachers, grandparents, parents and God and all who have directly or indirectly helped me.

Mere words are not enough to thank Dr. Thomas Samuel Ram, Dr. Selvamani and Dr. Visali, led me from initiation to culmination of this dissertation.

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At last, I would like to thank my friends and other consultants in my department for their constant inputs towards my study.
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AIMS AND OBJECTIVES
AIMS:

To assess the relation of anal manometry changes and radiation dose to anal sphincter.

OBJECTIVES:

1. To generate dose volume histogram for anal sphincter
2. To study the relation of anal manometry gradient changes and radiation dose to anal sphincter
REVIEW OF LITERATURE
REVIEW OF LITERATURE

EPIDEMIOLOGY

Cancer is one of the major non communicable disease worldwide (2). Cancer is one of the leading cause of morbidity and mortality with approximately 14 million new patients and 8.2 million deaths in 2012(3). Colorectal cancers are one of the most common cancers in the world. World Health Organisation estimates 9,45,000 new cases and 492 000 deaths annually. Rectal cancer is more common in the developed countries (4). 70% arise in the colon and 30% occur in the rectum(5).

FIGURE 1 SHOWS THE DISTRIBUTION OF MOST COMMONLY DIAGNOSED CANCERS

Most of the studies consider colon and rectal cancer as a single entity. Rectal cancer follows a different natural disease course compared to carcinoma colon(6). Physical inactivity, obesity, diet low in fruits and vegetables and smoking are considered risk factors (7). Rectal cancer has male preponderance(7). Biological
and gender linked factors may play a role (8). Colorectal cancer has a disease-specific mortality rate of approximately 33% in developed countries(9). There is increased incidence of rectal cancer in Asian countries probably due to adoption of Western lifestyle(10).

SCENARIO IN INDIA

In India, incidence of the colorectal cancer is low. According to the registries, rectal cancer is higher in the rural region(11). India has diversity in cultural and diet practices. Incidence varies among the regions (3). Chennai registry showed the highest while Ahmedabad showed the lowest(7). The incidence of rectal cancer was 5.5 to 1.6/100,000 among men while women ranges 2.8 to 0/100,000 among women. One interesting observation was that there were many younger with rectal cancer(12). High rates in young Indians suggests different etiopathogenesis. The absolute number of cancer patients in India rising because of increasing population and improved life expectancy.

Initiation of screening programmes may bring change in trends (13). Bringing such programme is big challenge. Effort has to be made to bring health awareness among the public. According to one study, physician recommendation plays a role in screening behavior in all countries. Before implementing mass screening programs, awareness has to be raised and promoting the physicians' participationis necessary(10). Problems faced by India are affordability, adequate healthpersonnel, and sociocultural barriers to cancer control(2)
ETIOLOGY - RISK AND GENETIC FACTORS

Obesity is considered as a risk factor and increase the risk of CRC by 19%. (7). Cereals, fruits, vegetables are considered to have chemopreventive properties while good and routine physical activity reduces this risk by 24% (14). Role of lifestyle remains an area of research.

Fish consumption leads to reduced risk (9). Benefit is attributed to omega3 and omega 6 polyunsaturated fatty acids. Risk is reduced upto 12%. Effect is more on rectal cancer than colon cancer.

One study from Tata Memorial hospital showed no significant risk for chewers, smokers and alcohol drinkers compared to those without the habits.

Cabbage-eaters had 50% reduction in risk compared to those who did not eat cabbage. Fresh fish eaters has a 40–70% reduction in risk is seen when compared to those who did not eat fresh-fish. Dark-green-leafy-vegetables did not have protective effect (15). Some nondietary risk factors are genetic predisposition, tobacco smoking and ulcerative colitis.

ANATOMY OF RECTUM

The terminal portion of digestive tract is rectum. It originates from cloaca (16) and starts at the rectosigmoid junction ending at the level of levator ani (17). This formed by pelvic rectum measuring around 12-15 cm length, formed from the
primary intestine, covered by mesorectum and the anal canal, 3–4 cm length. These corresponds to the sphincters. They are formed from the ectoderm (18).

Rectum is classified into upper one third (12–16 cm), middle one third (6–12 cm), and lower third (within 6 cm) from the anal verge.

Rectum supports the fecal matter and initiates the urge to defecate (19). Anterolaterally upper third of the rectum is covered by the visceral peritoneum. Middle third is covered by the peritoneum in front while the lower third of the rectum is extraperitoneal. It is bordered anteriorly by the Denonvilliers fascia and the presacral fascia is continuous with Waldeyer fascia posteriorly (19).

Rectum is supplied by superior hemorrhoidal artery. It is a branch of inferior mesenteric artery and supplies upper two thirds. The distal 1/3 of the rectum is supplied by middle hemorrhoidal artery which is a branch of internal iliac artery.

Superior rectal vein drains into inferior mesenteric vein and from there into the portal circulation. Middle rectal vein drains to the internal iliac vein and thereafter into inferior vena cava. Upper two-thirds of the rectum drains along the superior hemorrhoidal artery then inferior mesenteric nodes followed by para-aortic nodes. Lower one-third of rectum supplies the nodal basin along the internal iliac artery.
ANATOMY OF ANAL SPHINCTER

Anal sphincter surrounds anal canal, is bent forward, and averages around 5 cm. Anal canal consists of dentate line and is covered by the internal anal sphincter and external anal sphincter. Anal sphincter consists of multiple layers. It is made up of anal lining (innermost), internal sphincter and outer striated muscle layer. External sphincter consists of three parts: subcutaneous, superficial and deep part.

Functioning of the anal sphincter is carried out by rich supply of sensory endings near the dentate line and proprioceptive fibres. Anal lining consists of colonic mucosa on top and lowest part made by (keratinized) squamous epithelium.

INTERNAL ANAL SPHINCTER:

This smooth muscle sphincter is continuation of muscularis propria. The important role is maintaining the anal sphincter rest pressure. It does not extend till lower part of anal sphincter. Muscular part is made up of external anal sphincter.

Internal sphincter is supplied by sympathetic fibres and parasympathetic fibres. It is carried through the inferior pelvic plexus and splanchnic nerves (S2–S4). The afferent impulses pass through the parasympathetic nerves and the pain impulses are carried through sympathetic and parasympathetic nerves. Space between internal and external anal sphincter is called as inter sphincteric space. It consists
Of longitudinal muscle of rectum which is nothing but part of puborectalis (puboanalis) and part of levator ani.

Internal anal sphincter is a ring like structure surrounding approximately 2.5–4.0 cm of the anal canal. The inferior border is in touch with but separated from external anal sphincter.

Its action is entirely involuntary. It is in a state of continuous maximal contraction. It helps the external anal sphincter to close the anal opening and helps in the defecation.

Sympathetic fibers from the superior rectal and hypogastric plexuses initiate and control internal anal sphincter contraction. Its contraction is prevented by parasympathetic fibers. Sphincter is tonically contracted for most of the time to avoid leakage of gas or fluid. It is relaxed upon distention of the rectal ampulla which requires voluntary contraction of the puborectalis and external anal sphincter.

The internal anal sphincter is not innervated by the pudendal nerve. Pudendal nerve supplies motor and sensory supplying external anal sphincter.

Internal anal sphincter does contribute 55% of the resting pressure of the anal canal, important for bowel continence (mainly liquid and gas).

When the rectum fills beyond a certain amount, rectal walls are distended, initiates defecation cycle. It begins with the rectoanal inhibitory reflex, where the internal
anal sphincter relaxes. It allows a small amount of rectal contents to descend into the anal canal. Anal mucosa checks whether it is gas, liquid or solid. Any interference with the internal anal sphincter present as varying degrees of fecal incontinence (mainly incontinence to liquid) or mucous discharge.

**EXTERNAL ANAL SPHINCTER:**

This is an striated muscle which controls tones voluntarily. They are made up of slow twitch fibres which are capable of prolonged contraction. They are flat plane of muscular fibers, elliptical, and tightly attached to the covering surrounding anus. They measure about 8 to 10 cm in length, in anterior to its posteriorextremity. They measure about 2.5 cm opposite the anus at the time of defecation occurs as sphincter muscle pulls back. 

They are supplied by a nerve from inferior rectal branch of pudendal nerve and perineal branch of the fourth sacral nerve.

External sphincter consists of three segments.

1. **Subcutaneous:** Surrounding the lowermost portion of canal.

2. **Superficial part** is situated above the subcutaneous part. It is attached to perineal body and coccyx. Superficial part consists of main portion of the muscle, arising from anococcygeal raphe. It stretches from the tip of coccyx to the posterior margin of the anus.
3. Deep part is continuous with the superficial division, surrounding the uppermost portion of the canal and they are associated with the puborectalis posteriorly. Deeper portion forming a complete sphincter to the anal canal. Their fibres closely surrounds to internal anal sphincter.

They are supplied by inferior rectal nerves and by perineal branch of the fourth sacral nerve. This muscle is in variable tonic contraction during waking hours, and it can be contracted voluntarily. Main function is to postpone defecation and contributing to anal resting tone

The action of this muscle is characteristic..

(1) They are always in a state of tonic contraction. They have no opposite acting muscle to keeps the anal canal and orifice closed.

(2) They can be put into a condition of greater contraction voluntarily to close the anal opening., (3) They help in fixing the central point of the perineum.
FIGURE 2 a & 2b SHOWS THE RELATION OF ANAL SPHINCTER WITH OTHER SURROUNDING STRUCTURES IN LATERAL VIEW AND ANTEROPosterior VIEW
PHYSIOLOGY OF DEFECATION:

MECHANISM OF CONTINENCE:

Functional and compliant rectum or neorectum is essential for the continence. Maintenance of compliant rectum depends on competent anal sphincter mechanism. During filling of rectum, sensation of rectal contents are felt. Filling further produces temporary defaecatory sensation, followed by constant urge, and then pelvic discomfort. This is called as maximal tolerable volume.

There are variations among the individuals in the maximal tolerable and sensation volumes. Maximal tolerable volume ranges between 130 to 500 ml, being no difference between males and females. But rectal pressures during filling tend to be lesser in females(23).

Rectal motility is periodic, segmental, occurs as either solitary contractions or as chain of periodic pressure waves. Span of those cycles can range from one minute to several minutes.

The main function of puborectalis muscle is contributing to maintenance of the anorectal angle producing a —flap valve effect.

Resting pressure is contributed by external anal sphincter and responsible for most of the pressure during squeeze. In normal subjects, maximal squeeze pressure ranging between 90 to 360 cm H2O(24). Maximal squeeze pressure in normal females was found to be decreased after the fourth decade. They may be
due to decreased function of the pudendal nerves, partial atrophy of external anal sphincter muscle due to estrogen depletion(25). Mass movements through peristalsis pushes the fecal materials from sigmoid colon to rectum. This results in distension of rectal wall stimulating stretch receptors, thereby initiating defecation reflex, thus rectum is emptied. Stretch receptors are present in the puborectalis muscle. Stretch receptors sends sensory impulses to sacral spinal cord. Motor impulses travels through parasympathetic nerves to the sigmoid colon and rectum, finally into anus. If defaecation is socially convenient, relaxation of levator ani, external anal sphincter and puborectalis occurs. (25)

Relaxation of these muscles and sinking of pelvic floor during straining raises the anorectal angle. Voluntary contractions of the abdominal muscles and diaphragm helps in defecation by enhancing the pressure inside abdomen, thereby pushing the wall of sigmoid colon and rectum inward. The rigidity of opening anal sphincter is at least thrice greater in the starting phase of opening in comparison to opening of the anal canal to 1 to 2cm in diameter(25)
### TABLE 1 SHOWS THE TNM STAGING

#### T – PRIMARY

**TUMOR**

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularispropria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades subserosa or into non – peritonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>T4a – Tumor perforates visceral peritoneum</td>
</tr>
<tr>
<td></td>
<td>T4b- tumor directly invades other organs or structures</td>
</tr>
</tbody>
</table>

#### N – REGIONAL LYMPH NODES

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
</tbody>
</table>
N1  
N1a- Metastasis in 1 regional lymph node  
N1b- Metastasis in 2-3 regional lymph node  
N1c- Tumor deposits i.e satellites, in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastasis  

N2  
N2a- Metastasis in 4-6 regional lymph nodes  
N2b- Metastasis in 7 or more regional lymph nodes  

M – DISTANT METASTASIS  

M0  
No distant metastasis  

M1  
M1a – metastasis confined to one organ (liver, lung, ovary, non regional lymph nodes)  
M1b – Metastasis to more than one organ or the peritoneum
MANAGEMENT OF RECTAL CANCER

Management of rectal cancer depends on disease stage at diagnosis based on which patients are classified into high, intermediate, or low risk. Prognostic and predictive markers can be applied for optimal risk stratification and subsequent treatment. These markers can be histopathological, determined with imaging and have biomolecular background. Till now, none of the markers has been found to be of significance and independent value. Recent advances in imaging techniques and biomolecular research promises considerable potential. Over the past years, advances in multimodality treatment strategies have added significance to outcome in rectal cancer patients. Treatment decisions are based on tumor-node-metastasis classification and circumferential resection margin at time of diagnosis. Rectal cancers are divided into: Good, Bad, and Ugly. Every group requires different approach based on the risk of disease metastasis. Implementation of group-specific prognostic markers and predictive markers besides the TNM staging may simplify the treatment decision process. The introduction of the total mesorectal excision technique decreased local recurrence rates in rectal cancer patients from more than 20 per cent to around 10 per cent.

Addition of preoperative radiotherapy (RT) with or without chemotherapy has a beneficial effect on local control and, sphincter preservation is possible in some
19 % of cases (33)(34)(35)(36). True survival benefit of the addition of chemotherapy in the preoperative setting remains unproven. (26). But the treatment is associated with significant acute and long-term toxicity and even mortality (37)(38)(39). Besides decrease in local recurrences, distant metastases predominate with incidences around 30% for locally advanced rectal cancers (40). Thus optimal treatment of rectal cancer is aimed at prevention of both local and distant tumor recurrence and in addition minimizing the risk of side effects due to overtreatment.

Rectal cancer acts different course unlike colonic tumors(5). Surgical approach, local recurrence rates and associated complications of early stage rectal tumors are recognizably different from colonic cancer. This paved the way to develop different specific protocols for rectal cancer. Advances in imaging modality like MRI for staging and preoperative chemoirradiation led to clearly defined improvement in outcomes for the patient.

Good rectal cancers are early stage (T1 or T2), negative lymph nodes rectal cancers that, after (TME) surgery, have very low risk of local recurrence rates and high cure rates(29). More controversial treatment options like rectum preservation with or without preoperative chemoradio therapy (CRT) or chemoirradiation followed by a wait-and-see policy are considered for such patients (41).

Lymph node involvement cannot be relied on magnetic resonance imaging (MRI) alone. (42). Unfortunately, the majority of early rectal cancer patients do not meet
these criteria. For patients with relatively small tumors (T1-3) and where risk of lymph node involvement exceeding more than 6%, treatment with preoperative chemo irradiation therapy followed by surgery for the primary tumor might, be an option.

A challenging approach in this type of tumors is the watch-and-wait policy as propounded by Habr-Gama et al(43). After chemoirradiation, patients with a clinically complete response are closely followed up. The first reports looked promising with a 5-year disease-free survival rate of 95% and an overall survival (OS) rate of 100% in the case of a clinical complete remission. The downside is that, only 25% to 50% of the patients achieving a clinically complete response will have a true pathological complete response (pCR) (44).

Bad or intermediate-risk rectal cancer patients consists of large T3N0 tumors or T1-3N1 tumor and will be treated with preoperative radiation therapy followed by total mesorectal excision surgery. In the case of a threatened and/or involved mesorectal fascia, they are treated with preoperative chemo irradiation. The option of choosing between preoperative long course chemo irradiation and short-course radiation therapy is still a debatable topic.

Two randomized studies compared preoperative long course chemo irradiation therapy with short course radiation. The downside of the studies were underpowered to evaluate the effect on local control (45)(46). Early complications were less frequent in the short course radiation group. There were no differences
neither in late complications nor in quality of life between the 2 groups. Ugly tumors have a very high risk of local and distant recurrence rates. They have features like advanced (T4) stage and advanced lymph node involvement.

Survival improvement may be achieved by response-assessed treatment adaptation and the addition of targeted therapies with radio sensitizing potential.

Few strategies use epidermal growth factor receptor inhibitors, such as cetuximab, and inhibitors of the vascular endothelial growth factor, such as bevacizumab (47). The results of phase I-II trials with cetuximab have been not very good with pCR rates of ranging only 5% to 10%, suggesting a below additive interaction between chemoirradiation and cetuximab. The efficacy of bevacizumab has been proven in metastatic colorectal cancer. The first results of the addition of bevacuzimab to chemoirradiation in patients with rectal cancer are encouraging, showing a trend toward improved 5-year overall survival (95% vs 81% in those not receiving bevacuzimab) and disease free survival (69% vs 55%) and pathological complete rates of around 15%. Results of further prospective randomized trials required to be evaluate. Problems such as heterogeneous responses and tumor resistance have to be overcome.

Local recurrence rate of rectal cancer varies 6% to 10%. The number needed to treat with preoperative radiation therapy to prevent one local recurrence does vary around 10 to 18 patients. Only a subgroup of patients with good tumors has an LR risk of less than 4%. Limited treatment in these patients seems justified. The local
recurrence risks of bad and ugly tumors ranges around 8% and 20%, depending on T,N, and circumferential resection margin involvement. Predicting these tumor characteristics will help us to identify the specific patient groups and thereby select them for suitable treatment in the future(26).

Actual distance of the tumor to the mesorectal fascia has consistently shown to be a important factor for local recurrence because T-stage cannot differentiate between tumors that can be safely resected and those with a high chance of circumferential resection margin involvement. MRI has been the imaging modality of choice found useful for the predicting the circumferential resection margin. Studies have shown sensitivity varying from around 60% and 88% and specificity is between 73% and 100%(27).

Lymph node involvement showed no significant difference between the different imaging modalities like EUS, computed tomography scan, or MRI has been shown.(28). Sensitivity was between 55% - 67% with specificities ranging 74% - 78%. Studies suggest that have shown detection of lymph node metastases can be better with use of additional MRI criteria such as extracapsular extension of disease and signal difference..

**HISTOPATHOLOGY EVALUATION:**

Local tumor extent is designated through the pathologic T-staging, with T3 and T4 tumors are shown to have highest risk of local recurrence. Nodal involvement and CRM involvement are well reliable by histopathology. Lympho vascular invasion, poorly differentiation, serosal involvement and extramural venous
invasion, are the factors considered to have increased local recurrence risk.(29).

Depth of extramural disease and extramural venous invasion are found to be good associations with nodal involvement.(30). They can be used to determine the extent of response to chemoirradiation.

**PREDICTIVE MARKERS:**

Tumor stage and grade were not good enough of predicting response to treatment.(31). Prediction of treatment response with imaging techniques nowadays shows encouraging results(32). But staging accuracy is decreased after preoperative treatment compared to untreated cases. This may be secondary to post radiation edema, fibrosis, necrosis or inflammation.(33).

MERCURY trial found the prognostic relevance of MRI after neo adjuvant treatment. MRI-assessed tumor regression grade after preoperative therapy found better overall and disease free survival in responders compared to non responders. Results for ‘T’ stage were consistent, with accuracy of MRI staged T-stage of 79% after treatment(34)(35). This study showed that amount of tumor replacement by fibrosis related better with survival than T-stage after chemoirradiation.(36).

**STAGING PREOPERATIVELY:**

This has two purposes. It helps in surgical planning by defining anatomy and determining prognosis(6). Assessment of features by histopathologists in the resected rectal specimen remains the well defined method of prognostification.
Those features are assessment of depth of spread, nodal disease, extramural vascular invasion (EMVi), circumferential resection margin and perforation of peritoneum.

**PROGNOSTIC FEATURES :**

**1. T STAGE:**

Multiple histopathological studies have found T3 tumors with 5 mm of extramural invasion have a cancer specific 5-year survival rate of around 54% and more than 85% when the depth is 5 mm or lesser(37). Therefore the identification of high risk patients with an extramural tumor spread of 5-mm depth of extramural tumor invasion directs the treatment. Spread of tumor into the perirectal fat causes increase in nodal involvement. Depth of extramural spread is very important factor in determining the prognosis and directing election of patients for preoperative treatment.

**LYMPH NODAL INVOLVEMENT :**

Dukes’ et al showed the best relationship between depth of spread beyond the muscular is propria and the risk of involvement of lymph node(38). Lymph node positivity is an independent worse prognostic factor, and is more pressed when 4 or more lymph nodes are involved. Low burden of nodal involvement (N1) with a total mesorectal excision was not associated with an increased risk of pelvic recurrence(39).
CIRCUMFERENTIAL RESECTION MARGIN:

It is an important prognostic factor in the assessment of rectal cancer. CRM positivity is a poor prognostic factor for survival, with 40% of patients prone to develop distant metastases, and almost double the risk of dying (40). Identification and aggressive treatment of potentially CRM-positive patients is the key in preventing unwanted pelvic recurrence.

EXTRAMURAL VENOUS INVASION:

Tumoral extramural invasion is an predictor of both local and distant failures.

PERITONEAL INVOLVEMENT:

Peritoneal involvement can be defined as tumor present at the peritoneal surface or tumor cells found to be free in peritoneum and proof of adjacent — ulceration.

Local peritoneal involvement points to considerable prognostic implications, predicting for local recurrence. This is an important cause of pelvic failure. But the prevention and treatment of peritoneal perforation by the primary tumor is not specifically addressed in clinical trials.

Staging for all rectal cancer patients should include chest x-ray, computed tomography of the abdomen and pelvis. Complete colonic examination by colonoscopy should be carried out before treatment, if possible. Serum CEA should be checked preoperatively (41).
Those patients should undergo MRI pelvis to assess T and N categories and the circumferential resection margin. Axial, coronal and sagittal T2-weighted images of the pelvis and high-resolution (HR) T2-weighted sequences using phased-array coil are required. Use of the phase-array coil MRI and the development of T2-weighted fast-spin sequences have made thin-section MRI to delineate rectal tumors. This allows accurate determination of prognostic features as well as anatomic assessment of the pelvis. There is overlap in size between normal, reactive nodes and those containing a tumor. Size is not advocated as a reliable way of checking the involvement of lymph nodes. By identifying mixed intranodal signal and/or irregular border, it can assess lymph node involvement with 85% accuracy. A negative MRI scan of lymph nodes is insufficient evidence as imaging techniques cannot identify micro metastases inside lymph nodes. Patients with stage II or III rectal cancer should be offered preoperative therapy. Restaging MRI after preoperative chemo radiation is optional. No recommendation can be made to support or refuse the regular use of restaging MRI after neo adjuvant therapy. Restaging MRI may be appropriate where there is suspected MRF involvement or when a complete response would change management, asper patient basis.
SURGERY:

Goal of surgery is to decrease risk of not to leave behind gross disease and decreasing local recurrence and also preserving the function of sphincter, sexual and urinary functions(6). Varieties of surgical options are available depending on the location of tumor, stage and the possibility of sphincter preservation.

Some local procedures are transanal local excision, endoscopic microsurgery and trans abdominal resection (anterior resection) with colorectal anastomosis, proctectomy with total mesorectal excision and colo-anal anastomosis / abdomino perineal resection with a definitive colostomy(6). Isolated pelvic recurrence was the disadvantage of surgery. In late 1970’s new procedure called total mesorectal excision was developed and the number of recurrences decreased significantly.(43). Removing the mesorectum, eliminated the foci of adenocarcinoma, which was found several centimeters away to lower edge of rectal cancer(43). In anterior resection much of the tissue remains in the pelvis. Total mesorectal excision by itself decreased local relapse to lesser than 5%(44).

Then importance focused on circumferential resection margin (CRM)(45). It was found to be related to survival and delivered a better prognostic representation(45). Larger the distance of the tumor from the CRM, the better the prognosis. When tumor cells are upto the resection margin (0 mm), worst prognosis was observed(46). There were fewer local recurrences when the margin was more than 1 mm (0.4%)(47).
There are six distinct types of margin involvement. Those are

1. Direct tumor spread (29%),

2. Discontinuous tumor spread (14% to 67%),

3. Lymph node metastases (12% to 14%),

4. Venous invasion (14% to 57%),

5. Lymphatic invasion (9%), and

6. Perineural tumor spread (7% to 14%)(48).

In around 30% of patients, it was found that tumor showed more than one method of involvement(46).

Advanced stage, (46), ulcerative and stenosing pattern of growth, (49), infiltrative margin(48), poorly differentiated tumors(50), vascular invasion(49), these factors have more the chance of margin involvement. Studies have shown more positive margins in tumors situated in the lower rectum when compared to upper and middle rectum tumors. This is due to the difference in surgical technique exercised and also a difficult local anatomy to access surgically(51). It is a very strong indicator of local recurrence even in the time of neoadjuvant therapy. They also behave as marker of tumor reduction(45).
Anterior resection is offered for tumors in the upper and middle thirds of the rectum. This can also be done in low rectal tumors without involvement of the sphincter.

From the oncology perspective margin of around 5 cm is required from the distal end of the tumor for higher tumors. After neoadjuvant treatment, even 1-2 cm margins are considered acceptable for very low lying tumors. It allows sphincter-preservation. APR is indicated with definitive colostomy when the distal margins are not safe or it will lead to incontinence.(6).

**ROLE OF RADIATION THERAPY**

Rectal cancer is well known for local recurrence. Role of radiation therapy is strongly proved in the palliative setting of locally relapsing disease (52). The above finding led to the research of its value in preoperative and postoperative conditions. Radiotherapy was added to surgery in management of patients with resectable rectal cancer either before surgery (53)(54)(55)(56)(57)(58) or after surgery(59)(60).

Upto mid-1990s, post operative radiation therapy was practiced as standard of care.(61). Many studies showed that there was decrease in the local recurrence but no improvement in overall survival(62).

Studies in lab and in animals proved the adding fluorouracil as concurrent therapy increased the local efficiency of radiation(63)(64). From there, post operative radiation therapy with or without chemotherapy has been used to
improve outcomes (61). It showed good local control and overall survival as compared with surgery alone or surgery plus irradiation (62)(52). But these regimens used methyl-CCNU, risk factor for acute non lymphocytic leukemia. GITSG and NCCTG showed methyl-CCNU does not produce any benefit to radiation plus 5Fluorouracil (65)(66). Therefore methyl-CCNU became obsolete.

Preoperative irradiation was considered as very dose-effective than postoperative radiotherapy. Higher doses are required if radiation is indicated after surgery to reduce the local recurrence (67).

Enthusiasm arose in preoperative chemo radiotherapy setting for patients with resectable rectal cancer. This was based on the expected survival benefit achieved.

There are many potential advantages like administering both agents preoperatively (68). Benefits are good compliance, down-staging, increase the chance of cure with surgery, allowing sphincter preservation, radio biologically better tumor oxygenation and decreased side effects. No survival benefit seen when compared preoperative with postoperative chemoradiotherapy.

But Preoperative treatment (chemoradiotherapy) is associated with better overall compliance rate, better local control, reduced side effects and more sphincter preservation in patients with distal rectal tumors (68).

Multiple studies have shown lesser rates of local failure with preoperative radiotherapy compared with surgery alone. Swedish Rectal Cancer Trial assessed
a short course of preoperative irradiation (25 Gy delivered in five fractions) and
found there is advantage in overall survival(69). This is the first trial showed that
there is survival advantage after pelvic radiotherapy alone either given
preoperatively or postoperatively(70).

Introduction of total mesorectal excision questioned the benefit of preoperative
therapy to optimal surgery . A study done by Kapite improved that there is
decrease in local recurrence from 8.2% to 2.4% by adding preoperative radiation
to total mesorectal excision .(71). Significant complication was perineal wound
dehiscence.

**PREOPERATIVE RADIATION THERAPY AND LOW ANTERIOR
RESECTION:**

In patients with resectable rectal cancer, enthusiasm arose in sphincter
preservation. Advantage of preoperative therapy is to reduce the volume of
primary tumor. If the tumor is located very close to the dentate line, the decrease
in volume allows the surgeon to do a sphincter preserving procedure. . One harm
of preoperative therapy is that we may over treat patients who may not require
therapy, like very early stages T1-2N0 or distant metastatic disease. When
sphincter preservation is considered, it should be offered to patients in whom
disease can be resected safe from oncological point of view.

Total radiation dose of 45 to 50.4 Gy at 1.80 Gy per fraction, one fraction per day
is offered. Surgery should be scheduled one to one and half month later to allow
down staging of tumor and patient recovers the side effects of radiation and
chemo therapy. Alternative approach is short course radiation therapy consisting of 25 Gy in five fractions followed by surgery next week.

**LATE SIDE EFFECTS AFTER RADIATION THERAPY:**

Late toxicity are those which arises from 3 months after radiation therapy treatment. Better cure rates in the treatment led to understanding of survivorship issues. Radiotherapy dosimetric factors, like dose per fraction irradiation site, total dose, volume irradiated, and dose heterogeneity shown influence on development of late radiation toxicity. So we should know the incidence of radiation morbidity. Surgery and radiation therapy has detrimental effect on the quality of patient.

Late side effects are bowel frequency and urgency, and fecal incontinence. (43). Decrease in the anorectal function has been seen when compared with post operative radiation therapy vs surgery alone.(72). There is very minimal data on the quality of life in rectal cancer survivors(73). radiation therapy had detriment effect on social function and fecal incontinence.

Symptoms which commonly occur after low anterior resection are increased frequency, urgency to defecate, and soiling. These shows loss of the ability of the rectal reservoir and these symptoms constitute anterior resection syndrome.

Approximately 60% of patients experience some degree of incontinence and around 33% feel urgency and frequency regularly.

Anorectal dysfunction after surgery mainly because of capacity intolerance. One study by Nesbakken showed anal resting and squeeze pressure and volume of...
rectal sensibility were not changed after operation. Effect of preserved anal sphincter was seen well in patients who underwent low anterior resection (74). It showed neorectal capacity was reduced.

One study by Lane et al showed that reflexes of anal sphincter preserved after sphincter preserving surgery (75). Frequency of fecal incontinence was 25% after radiotherapy vs. 11% with surgery-only in studies involving short course radiation therapy. One trial from Poland has compared short-course preoperative radiotherapy with long-course chemo-radiotherapy. They found no difference in the frequency of fecal incontinence. These patients experienced poor social function and global quality of life. This study did not comment on dose deposition to normal tissue.

**ANAL SPHINCTER AND RADIATION THERAPY:**
Sphincter without function is more harmful than not having it. Well functioning colostomy is better. Effect on anal sphincter is worse seen with radiation therapy administered after surgery than before surgery. A study by Birnbaum et al, assessed short-term and long-term effect of preoperative radiation therapy on sphincter function. He assessed them objectively with anal manometry with or without transrectal ultrasound. He found radiation therapy had very less effect on sphincter function (76)(77). One study by Marjinen et al showed short course treatment led to more sexual dysfunction, passive improvement of bowel activities, and reduced daily activity after surgery. But they did not affect health
Considerable amount of cecum, ileum, sigmoid colon, rectum and anal sphincter is involved in the treatment. Acute effects are because of death of large number of cells in tissues with rapid multiplication. Late effects occur in those tissues which has slow proliferation. These changes will not manifest till it enters the next cycle of cell division. Once it starts, injury because of radiation will manifest.

**WHY IT IS DIFFICULT TO MEASURE LATE BOWEL DYSFUNCTION:**

Most patients after follow up for five years are discharged. They get treated elsewhere if they develop any further complications. The oncologist may not know about this. Young patients survive long to get this complication while elder patients may not.

We should rule out any existing abnormal bowel function before starting treatment.

When patients who underwent pelvic radiation therapy, presents with the complaints of gastrointestinal symptoms, most of them attribute to radiation. After thorough investigation about one-third have symptoms arising from an unrelated cause.

Radiation oncologist rely on questionnaires to find out the radiation toxicity.
which may be misleading. This is because of either practical difficulties, patient refusing the socially stigmatized words or patients may feel the symptom is not worth the time spending with doctor. When they report, there is no good support system to help them out. There is no much awareness among the patient and oncology community about the late effects. Lack of basic mechanism and studies aids for it. Therefore specific questionnaires are difficult practically.

**FAECAL INCONTINENCE:**

Faecal incontinence affects almost half of patients with normal preoperative functioning sphincters(80). It may range from unintentional gas release to minor soiling or complete escape of rectal contents(81). This leads to avoidance of activities like long-distance travel, avoiding places where bathroom facilities are not available.

It is the result of failure of more than one component of the continence mechanism. The rectum, the anal sphincters, and the pelvic floor muscles are important in this continent mechanism(82). Rectum behaves like reservoir to store stool. Neorectum after low anterior resection has a lesser capacity thereby causing a decrease in maximum tolerance volumes.

Anal sphincters are supplied by neural fibers, branches and bundles, formed by pudendal nerve, pelvic splanchnic nerves and hypogastric nerves, which in turn forms pelvic plexus. They allow voluntary contraction of the sphincter through somatic impulsation. They also control complex autonomic anorectal reflexes.

Anal canal has nerve endings which are sensitive to pain, temperature, and touch,
which differentiates solid or liquid stool from flatus. This allows for selective passage of flatus.

Radiotherapy decreases this amenability of the rectum due to fibrosis. It results in reduced reservoir function. Fibrosis of the myenteric plexus of the internal anal sphincter secondary to radiation therapy can prevent closing of the anal opening in a resting state.

Radiation injury to pelvic floor also causes fecal incontinence by damaging the levator ani and disturbances in the anorectal angle.

Initially improvement in anorectal function seen around six to twelve months. This is because of expansion in the storing capacity of the neorectum. This is evident from from post-operative assessment of function after one year which showed many patients attained continence to solid stool. Only control of minor staining, flatus, and stool frequency is more variable(83). Worsening of faecal incontinence over time is mainly present in patients who underwent pelvic radiotherapy. This is secondary to radiation injury to endovascular cushions. Endovascular cushions aids in continence at rest(84).

Nerve-sparing surgery can be difficult because of the anatomical variations in the nerve patterns and accurate identification of those structures. These nerves are at risk of diathermy secondary to blood loss and hemostasis. nerve-stimulating device may be useful in these conditions. (85). (71).

Earlier having a stoma was considered a negative impact on quality of life. But
those patients who underwent low anterior resection experience anorectal dysfunction fare poorly in the quality of life scores, (86). (87). How et al showed this relation was better associated with all domains of questionnaire(88).

Cultural, social, religious, and socio demographic factors can play a role in decision of having a stoma.

Managing patients with incontinence after rectal cancer treatment are still not known. No good evidence to support the effectiveness any treatment. Conservative measures are aimed at symptomatic control like dietary regiments, absorbent pads, and pharmacotherapy like hormonal manipulation, constipating agents, and enemas. Colonic irrigation in the morning to clean the colon has shown to relieve symptoms(89). Non-surgical procedures available are biofeedback and pelvic floor muscle training.

Biofeedback therapy helping the patients how to use the pelvic floor muscles properly, is recommended. This helps in rectal sensitivity, strength, and coordination training(90). Pelvic floor muscle training improves pelvic floor support. It is considered as standard of care for urinary incontinence. It improves faecal incontinence too. This may not be benefical in patients whose pelvic floor and its nerve supply are damaged by surgery. If conservative management fails, surgical intervention can be considered. Cause has to be identified. Anorectal physiology is assessed with manometry. mechanical damage to the sphincter muscle assessed by endoanal ultrasound.
Sacral nerve stimulation can be done if there is intact sphincter. But the experience with sacral nerve stimulation is not sufficient (91). If there is defective sphincter, artificial bowel has to be constructed. But there is a risk of complications due to previous injury. This is reported in few studies (92). So this should be an last measure (93).

**ANAL MANOMETRY AND FECAL INCONTINENCE :**

Birnbaum et al assessed the acute effect of preoperative radiation on anal function. He found that radiation therapy before surgery has minimal immediate effect over the anal sphincter. It may not be a considerable factor for incontinence after sphincter preservation (76).

Pollack et al assessed late effects of short-course radiotherapy on anorectal function. He assessed the patients their quality-of-life with questionnaires, clinical examination, anorectal manometry, and endoanal ultrasound for a period of 14 years. He found that short-course radiotherapy, interferes in anorectal function and increases bowel symptoms permanently (94).

Canda studied the acute and long term effects of preoperative chemoradiotherapy on anorectal function and quality of life of the patients. He found that considerable decrease in the resting and squeeze pressures immediately after the completion of preoperative chemoradiotherapy This finding was significant to
the patient group who underwent surgery group alone. They were assessed post operatively(95). Much of the studies are done in prostate cancer patients in relating the dose received by anal sphincter and fecal incontinence. Alsadius et al suggested mean dose to anal sphincter more than 40 Gy associated with higher incidence of fecal incontinence(96). In another study Al-Abany et al showed there is increased risk of fecal leakage for a mean absorbed dose of more than 46Gy to the anal-sphincter(97). They also suggested whether more than 35 Gy to less than 60% of volume or more than 40 Gy to less than 40% volume of the anal-sphincter can provide any benefit is not known.

DELINEATION OF CLINICAL TARGET VOLUME IN RECTAL CANCER:
Correct definition and proper delineation of the clinical target volume is required to avoid under dosage of regions that can possibly have cancer cells. There are five subsites for local recurrence:

1. Mesorectal subsite
2. Posterior pelvic subsite,
3. Lateral pelvic subsite,
4. Inferior pelvic subsite, and
5. Anterior pelvic subsite

Mesorectal subsite comprises mesorectum, which is defined as the adipose tissue with lymph, vascular and nerve structures, surrounded by a fascia. Mesorectum
is cylindrical, with cone-shaped in cranial and caudal direction, arising at the level of the sacral promontory where superior rectal artery arises and ends at the level where levatorani muscle inserts into rectal wall.

Posterior pelvic subsite (PPS) comprises of presacral space. It is a triangular region, surrounded behind by the presacral fascia (Waldeyer's fascia) and in front by mesorectal fascia. This structure is well seen on magnetic resonance imaging. It contains median sacral vessels, lateral sacral vessels, lymphatics of presacral chains, anterior branches of sacral nerves, and inferior hypogastric plexus.

Lateral pelvic subsite consists of area on the lateral side of the mesorectal fascia and the lateral pelvic side walls.

Inferior pelvic subsite: It consists of anal triangle of the perineum, consists of the anal sphincter complex with perianal and ischiorectal space.

Anterior pelvic subsite (APS) has all pelvic organs that are located in front of mesorectal subsite.

**Lymph node regions:**

Five lymph node regions were found to be significant with the lymphatic drainage pathway of the rectum.

Mesorectal lymph node group is the mesorectal tissue surrounded by the
mesorectalfascia, contains mesorectal nodes with their vessels and lymph nodes along with superior rectal artery. Lymph nodal group surrounds lymphatic tissue along the inferior mesenteric artery upwards. Lymphatic spread to the lateral lymph nodal regions is involvement of the lymph nodes along the middle rectal, the obturator, and the internal iliac vessels. Clinical target volume: It encompass 1. tumor, 2. mesorectal subsite, and the 3. posterior pelvic subsite in all cases.

Inferior pelvic subsite is considered to be at risk when the tumor is located within 6 cm from the anal margin, or (2) the tumor reaching anal sphincter and an Abdomino perineal resection is planned.

In all patients, mesorectal nodes and lateral lymph node regions have to be considered. Obturator nodes are included if the tumor is located less than 10 cm from the anal margin. External iliac nodes are considered only when there is involvement of anterior organs.

**TECHNICAL ASPECTS OF IMAGE BASED TREATMENT PLANNING:**

Modern radiation treatment planning are very much advanced. We can provide a very high dose to a certain region while sparing the nearby structures. There are not many studies on the sphincter sparing radiation therapy like parotid and constrictor sparing in head and neck tumors.
MATERIALS AND METHODS
MATERIALS AND METHODS

1. STUDY DESIGN

This study was conducted in Department of Radiotherapy, Christian Medical College (CMC). Patients who were diagnosed to have rectal cancer and planned for low anterior resection were included in this study.

Inclusion criteria:

- Locally advanced rectal cancer-clinical or radiological evidence of T3/T4 or N1,N2
- Adenocarcinoma histology
- Being considered for neo adjuvant radiotherapy (conformal Radiation therapy) along with concurrent chemotherapy (Capecitabine)
- No prior pelvic malignancies
- No history of prior radiation to the abdomen/pelvis
- Not a known case of myelodysplastic syndrome/myelofibrosis

Exclusion criteria

- Low rectum tumors, not amenable for low anterior resection
- Metastatic disease

The proposed study was presented in the Institutional Review Board (IRB) which includes Research committee and Ethics Committee and approval was obtained (copy enclosed). The patients were selected based on the inclusion and exclusion criteria.
DETAILED ALGORITHM:

1. **Locally Advanced Carcinoma Rectum Patients Screened**

   **Eligibility**
   1. Adenocarcinoma Rectum (High and Mid)
   2. Non Metastatic
   3. Patients planned for long course chemoradiation therapy followed by low anterior resection in multidisciplinary tumor board

   **Anal Manometry** was done in surgery OPD by a technician before starting radiation therapy.

   **Immobilisation** was carried out with Vacloc and heel lock and knee support (for some) with patients hand above the head and tattooed at suprapubic level.

   **Planning CT Scan** with RT markers slice thickness – 5 mm extent – from diaphragm to mid thigh with IV contrast and without contrast (for few patients).

   CT Scan images were transferred to treatment planning system (TPS)- Eclipse.

   Contouring was done as per standard guidelines- Target – GTV, CTV & PTV Organ at Risks – Bladder, femoral heads.

   Anal sphincter was contoured with the help of radiologist.

   Disease response will be reassessed after 6 weeks as a part of treatment.

   Anal manometry was done before surgery.

   This will be done for all patients who were included prospectively.
ANAL MANOMETRY:

Anal manometry was done as outpatient procedure using Dyno 3000 software (Biomedica) by a trained technician. This procedure requires 5-10 minutes without the need of anesthesia or any premedications. To obtain measurement a tube was inserted in the anal canal approximately 3 cm, 2 cm and 1 cm from anal verge. At each length the resting pressure and squeeze pressure was measured by asking the patient to be in a relaxed position and try to squeeze sphincter respectively.

ANAL SPHINCTER DELINEATION:

Since there are no established guidelines for anal sphincter delineation, it was done with the help of radiologist. Initially the puborectalis sling was identified on the CT scan and then subsequently the whole of puborectalis sling, internal anal sphincter and external anal sphincter was contoured. The cranial extent was from where the puborectalis sling was visualized and the caudal extent was where the external anal muscle became visible.

SAMPLE SIZE:

This study group consisted of 5 patients prospectively and 16 patients retrospectively treated with conformal radiation therapy in radiation therapy department between January 2013 till July 2015.
Only 5 patients were able to recruit prospectively. An amendment was made, requesting IRB board to allow to take retrospective data who underwent low anterior resection. Planning CT images were chosen and the anal sphincter was contoured with the help of radiologist and dose to anal sphincter was calculated using Plato and Eclipse treatment planning systems. 16 patients were taken retrospectively from the year 2013 January –till February 2015.
RESULTS
RESULTS:

21 patients were selected who underwent conformal radiation therapy and planned for low anterior resection between the period of January 2013- July 2015. 14/21 patients were treated with 3D conformal radiation therapy and 7/14 were treated with intensity modulation radiation therapy.

All of them underwent long course chemoirradiation and were administered concurrent chemotherapy with capecitabine(825mg/m2 twice daily). No chemotherapy was administered for patients who underwent short course radiation therapy.

PATIENT CHARACTERISTICS:

There were 11(52.4%) Male and 10(47.6%) female patients. Most of the tumors were in mid rectum 13(62%) followed by upper third 7(33.3%). One patient was found to have growth in low rectum . He was planned for intersphincteric low anterior resection and underwent the same. Most of the patients were locally advanced stage and the commonest histology reported was moderately differentiated adenocarcinoma.

Most commonly received a dose of was 50.4 Gy in 28 fractions. Few patients who underwent intensity modulated radiation therapy received simultaneous integrated boost. 2/21 patients underwent short course radiation therapy and they received 25
Gy in 5 fractions. 7/21 patients underwent intensity modulated radiation therapy and 14/21 underwent 3D conformal radiation therapy. Most of the tumors showed good response as evident by down staging of T and N. Most of the patients tolerated the treatment well and very few had a break in radiation therapy. The commonest reasons was grade 2 radiation enteritis. Two patients had break in chemotherapy. First patient had mild elevation of transaminases which normalized soon and another patient had low counts.

In this study, we found the mean dose of anal sphincter was 28.77 Gy.

**PATIENT CHARACTERISTICS**

Table No: 1 PATIENT CHARACTERISTICS

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<td>95% prescribed dose covered ---of PTV Phase 1</td>
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<td>D95  phase 2</td>
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<td>Mean dose to anal sphincter</td>
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<td>Volume of anal sphincter</td>
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<td>23.25 Gy</td>
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<td>Left femur Dose received by 40% of the volume</td>
<td>23.56 Gy</td>
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<td>Overall treatment time (Days)</td>
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FIGURE 3 DISTRIBUTION OF MALES AND FEMALES PATIENTS

FIGURE 4 DISTRIBUTION OF MARITAL STATUS AMONG PATIENTS
FIGURE 5 DISTRIBUTION OF LOCATION OF THE GROWTH IN OUR STUDY PATIENTS

FIGURE 6 DISTRIBUTION OF T STAGE PREOPERATIVELY
FIGURE 7 DISTRIBUTION OF N STAGE PREOPERATIVELY

FIGURE 8 DISTRIBUTION OF BIOPSY (MOST COMMON BEING MODERATELY DIFFERENTIATED ADENOCARCINOMA)
FIGURE 9. DISTRIBUTION OF PATIENTS WHO EXPERIENCED BREAK IN RADIATION THERAPY

FIGURE 10. DISTRIBUTION OF PATIENTS WHO EXPERIENCED BREAK IN CHEMOTHERAPY
FIGURE 11 BELOW FIGURE SHOWS DIFFERENT DOSE PRESCRIPTION TO PTV

FIGURE 12. DISTRIBUTION OF TECHNIQUE INVOLVED (IMRT AND 3DCRT)
FIGURE 13. DISTRIBUTION OF PATIENTS WITH ypT STAGE

FIGURE 14. DISTRIBUTION OF PATIENTS WITH yp N STAGE
FIGURE 15 COMPARISON OF _T_ STAGE BETWEEN PREOPERATIVELY AND POSTOPERATIVELY
A preliminary anal sphincter delineation method was established in consultation with a senior radiologist with expertise in Pelvic imaging. The subsequent anal sphincter delineations undertaken by the PI were checked and verified by the guide and radiologist.

The mean dose to anal sphincter was 28.77 Gy. The mean volume of anal sphincter was 29.35cc and the mean length of the anal sphincter was 4.36 cm.
There was no correlation between the mean dose of anal sphincter and volume of anal sphincter. There is definite correlation between dose received by the anal sphincter and distance between them from to midpoints of GTV, CTV and PTV. Higher the distances, there is definite decrease in the mean dose to anal sphincter.

Out of the 5 patient recruited to undergo manometric study only 3 patient's preradiation and post radiation manometric readings were documented. Of the two missing reading one patient was lost for follow up and another patient's post radiation measurement was missed. The pre radiation resting and squeeze pressure for patient 1,2,3 was 91.4 mm Hg and 158.8, mmHg, 77.2 and 141.7 mmHg, 67.5 and 147 mmHg and the post radiation pressure was 78 and 140 mmHg, 67 and 125 mmHg, 65 and 140 mmHg respectively.

Since it was a very small sample size for detecting the pressure change and mean dose to anal sphincter, we were unable to document clinically relevant or statistically significant correlation between any result.
Dose to planning target volume achieved good coverage (more than 95 percent of the prescription dose) and the constraints to organ at risks like bowel bag, femoral heads and bladder were achieved as per QUANTEC guidelines.

FIGURE 17 THE RELATION BETWEEN THE MEAN DOSE OF ANAL SPHINCTER(x axis) AND VOLUME OF ANAL SPHINCTER(Y axis)

The correlation between mean dose to anal sphincter and volume of anal was -0.18, however it was not statistically significant (p=0.483).
FIGURE 18 RELATION BETWEEN MEAN DOSE TO ANAL SPHINCTER (x axis) AND DISTANCE OF MID POINT OF ANAL SPHINCTER TO INFERIOR BORDER OF GTV (y axis)

The correlation between mean dose to anal sphincter and GTV was -0.694, which was statistically significant (p=0.001).
The correlation between mean dose to anal canal and ctvph1 was -0.708, which was statistically significant (p=0.001).
The correlation between mean dose to anal sphincter and PTV Phase 2 was -0.792, which was statistically significant (p=0.000).
The correlation between mean dose to anal sphincter and PTV phase 1 was -0.858, which was statistically significant (p=0.000).
The correlation between mean dose to anal sphincter and phase 2 PTV was -0.716, which was statistically significant (p=0.003).
FIGURE 23 THE RELATION BETWEEN INDIVIDUAL PATIENT (X AXIS)) AND MEAN DOSE RECEIVED BY ANAL SPHINCTER in Gy (Y axis)
FIGURE 24 PTV PHASE 1 ANTERO POSTERIOR VIEW
FIGURE 25 PTV PHASE-2 IN ANTEROPOSTERIOR VIEW
FIGURE 26 DIAGRAM SHOWS PUBORECTALIS SLING (CRANIAL CUT WHERE ANAL SPHINCTER WAS CONTOURED)
FIGURE 27 DIAGRAM SHOWS CONTOUR OF ANAL SPHINCTER DELINEATION BY US
FIGURE 28 DIAGRAM SHOWS ANAL SPHINCTER IN AP VIEW
FIGURE 2 SHOWS ANAL SPHINCTER IN LATERAL VIEW
DISCUSSION
DISCUSSION:

While Outcomes of rectal cancer has improved significantly since the evolution of TME and Concurrent Chemoradiation., the quality of life in survivors specifically related to anal dysfunction is of great concern. Few authors have reported the dose to anal sphincter and correlated with anal dysfunction in patients undergoing radiation therapy for prostate cancer which is usually given up to a mean dose of 70 Gy\(^1\). However there is currently very little information on anal dysfunction in high or mid rectal cancer patient undergoing chemoradiation followed by low anterior resection.

This study was undertaken to develop a preliminary delineation guideline for anal sphincter and evaluate the correlation of dose to anal dysfunction. In our study, to evaluate anal manometry, we were able to measure in only 3 patients prospectively owing to time constraint and strict inclusion criteria which was a major limitation of our study. So we were unable to conclude regarding correlation between manometry changes and dose received by anal sphincter.

The injury caused by the radiation to the sphincter muscle appears to be a secondary factor since 10%-60% of patients with anal sphincter dysfunction are accompanied by urinary and sexual disorders (hyperactive bladder, urine incontinence, urine retention, impotence, lack of ejaculation, lack of orgasm),
pointing towards a most probable neurological etiology of the disorder. Isolated fecal incontinence after radiotherapy is rather rare.

Each of the manometric pressures is composed of several elements. Voluntary squeeze pressure, determined mostly by the external sphincter’s ability to contract in response to somatic impulsion, said to be less important in the Anterior Resection pathogenesis. Basal sphincter pressure consists of pressures generated by the internal anal sphincter (approx. 40-60%), external anal sphincter (about 20-50%) , and hemorrhoidal cushions. Three components are involved. They are autonomic and somatic innervation and anatomical structures within the anal canal. Rectal examination and anoscopy can exclude anatomical disturbances of the anal canal as causes of lower basal pressure, but the influence of both neurological systems yet to be explored. There is only little evidence that radiation causes damage to pelvic floor and muscles.

Better understanding of muscle damage and dysfunction following radiation therapy will improve pelvic floor rehabilitation possibly, preventing detrimental impact(98).

Reducing the dose to anal sphincter may be important to reduce the risk of long term fecal leakage. There are lack of standards in reporting adverse events, both patient and clinician, in trials .It raises a number of questions about how future treatment can be optimized on the basis of past results.
We suggest that it may be worthy to consider the anal sphincter region as an organ-at-risk when irradiating tumors in the pelvis. We may be able to use technological advances in imaging and delivery of radiation to avoid fecal leakage in future survivors from cancer in the pelvis who have been cured by radiotherapy.

In this study, we found that the mean dose to anal sphincter was 28.77 Gy which was similar to the doses reported by Chen et al.(2). According to few studies done in prostate cancer survivors, showed that the mean dose to anal sphincter more than 40 Gy is associated with higher incidences of fecal leakage. Doses less than 40 Gy is associated with less chance of fecal leakage(3). This shows that type of surgery and the surgeons skills may play a role in causing the fecal incontinence, probably due to injury during the procedure to the nerve structures supplying sphincter muscles.

There are not enough studies on the dosimetry of anal sphincter, anal sphincter delineation, relation dose received by anal sphincter and risk of developing fecal continence. Since developing fecal incontinence is late effect of pelvic radiation therapy, we suggest all the patients coming to our clinics have to be assessed with a locally validated questionnaire. Questionnaire, contouring anal sphincter as routine organ at risk (OAR), checking the pressure with anal manometry serially needs to be standardized. A neurophysiological study like (EMG) of anal sphincter will be desirable to objectively document the sphincter function. This will help us in evaluating and recommending the radiation dose constraint for anal sphincter.
CONCLUSION
CONCLUSION:

The mean dose to Anal sphincter was 28.77 Gy which was way below the threshold dose implicated in radiation induced anal dysfunction. Hence factors other than radiation needs to be considered towards the reasons for anal dysfunction. Anal sphincter should be contoured as organ at risk (OAR) in all modern radiation techniques for treating pelvic tumors and the dose volume characteristics of anal sphincter to be documented. Symptoms of anal dysfunction should be assessed subjectively and objectively. However further prospective studies are required in this area for developing guidelines for delineating anal sphincter, recommending dose constraint for anal sphincter, and evaluating the benefit of sphincter sparing radiation therapy in decreasing late complications in rectal cancer survivors.
Bibliography
Bibliography


26. Prediction in Rectal Cancer Eliane C.M. Zeestraten, MD , Peter J.K. Kuppen, PhD , Cornelis J.H. van de Velde, MD, PhD , Corrie A.M. Marijnen, MD, PhD Volume 22, Issue 2, April 2012, Pages 175–183.


63. Cancer Res April 1958 18; 305Effects on Transplanted Tumors* Charles Heidelberger, Lois Griesbach, Betty Jo Montag, Dorothy Mooren, and Olivia Cruz.


### Case Record Form – 1
Demographic and Clinical Details

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- **Sex (1=male 2=female)**: 
- **Marital Status (1=unmarried 2=married)**: 
- **Occupation (1=skilled; 2=unskilled)**: 
- **Location of growth 1.Upper 2.Middle 3.Lower**: 
- **T status (1=T1;2=T2; T3=3; T4=4)**: 
- **N Status (1=N1; 2=N2; 3=N3)**: 

**CHRISTIAN MEDICAL COLLEGE, VELLORE**

**COORRELATION OF RADIATION DOSE TO ANAL SPHINCTER AND ANAL DYSFUNCTION IN RECTAL CANCER PATIENTS UNDERGOING PREOPERATIVE LONG COURSE CHEMORADIATION THERAPY**

**Case Record Form – 1**

**Demographic and Clinical Details**

- **ID NO**
- **Date of Birth**
- **Hospital Number**
- **Recruitment date**
- **RT No**
- **Telephone No**
- **Email**

- **NAME**
- **Last**
- **Middle**
- **First**

- **Sex (1=male 2=female)**
- **Marital Status (1=unmarried 2=married)**
- **Occupation (1=skilled; 2=unskilled)**
- **Location of growth 1.Upper 2.Middle 3.Lower**
- **T status (1=T1;2=T2; T3=3; T4=4)**
- **N Status (1=N1; 2=N2; 3=N3)**
**GENERAL EXAMINATION**

ECOG Performance status .................................................................

0 = Fully active, able to carry on all pre-disease performance without restriction
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4= completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5= Dead

Height (in cm) .................................................................................

Weight (in Kg) ..................................................................................

BODY SURFACE AREA (per square metre) ...........................................

**Digital Rectal Examination**

**Colonoscopy**
1. Growth

**Anal manometric pressure**

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**Systemic Examination:**

**Cardiovascular:**

**Respiratory:**

**Gastrointestinal:**

**Neurological:**
DATE OF BIOPSY:

BIOPSY:

DATE OF STARTING RADIATION THERAPY:

DATE OF COMPLETING RADIATION THERAPY:

BREAK IN RADIATION THERAPY:

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CHEMOTHERAPY USED:

OVERALL TREATMENT TIME:

BREAK IN CHEMOTHERAPY:

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DATE OF SURGERY:

DATE OF LAST FOLLOW UP:
ORGAN AT RISKS

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<td>BLADDER</td>
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<tr>
<td>FEMORAL HEADS</td>
<td>D25% &lt; 45 Gy</td>
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TARGETS

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<td>≤ 15% of the PTV receives ≥ 105% of the prescribed dose</td>
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<td>≤ 10% of the PTV receives ≥ 110% of the prescribed dose</td>
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RADIATION TECHNIQUE:

NUMBER OF FIELDS:

PRESCRIBED DOSE TO PTV:

MEAN DOSE TO ANAL SPHINCTER:

LENGTH OF ANAL SPHINCTER

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<th>V10</th>
<th>V20</th>
<th>V30</th>
<th>V40</th>
<th>V50</th>
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Volume of Anal sphincter (cc)

Distance from midpoint of anal sphincter till inferior border of GTV (in mm)

Distance from midpoint of anal sphincter till inferior border of CTV (in mm)

Distance from midpoint of anal sphincter till inferior border of PTV (in mm)

Date: ___/___/_____  Investigator’s Signature: ______________________