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Impact of Neoadjuvant Chemoradiotherapy on Surgical Outcome of Rectal Cancer

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Background

Multimodality treatment is the most important component of potential for curative resection of Rectal cancer. Local recurrence and metastatic disease in locally advanced Rectal cancer are due to positive circumferential resection margin and lymph node involvement. Overall survival and local recurrence control are improved by Postoperative chemo Radiotherapy, Preoperative Chemo Radiotherapy has increased local control rates, tumor down staging, sphincter saving procedures and enhancing resectability a fact shown by several studies. This study on Neoadjuvant Chemoradiotherapy for carcinoma Rectum evaluates presentation, potential benefits and outcome following multimodality treatment for locally advanced operable Rectal cancer.

Aim

Trials comparing different treatment modalities for carcinoma Rectum have arrived at different conclusions. The aim of the study is to analyze the surgical outcome following neondjuvant Chemo Radiotherapy in patients with locally advanced operable rectal cancer (T3, T4 and Node positive tumor).

The main aim is to analyze whether preoperative Chemo Radiotherapy is

1. Beneficial to the patient or not.
2. Analyzing the primary end points- are downsizing of tumor, down staging of the tumor, sphincter preserving rates. Radiotherapy regimen and compliance for the regimen
3. Analyzing Secondary endpoints- which are analyzed in other rials are the incidence of local recurrence, distant metastases. The incidence of peroperative complications and postoperative complications also analyzed.

Material and Methods

This study was conducted in the Department of Surgical Gastroenterology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai from March 2012 to February 2014.All patients with lower and mid rectal locally advanced T3, T4 node positive tumors without distant metastasis, histologically confirmed adenocarcinoma within 12 cm from anal verge with upper Anal canal involvement and Radiological evidence of mesorectal invasion were included in this study. Patients who had received radiotherapy or chemotherapy, Contraindications of chemoradiotherapy, Tumor involoving pelvic side walls, upper sacral vertebra, involving upper rectum, Distant metastasis, Patients with poor performance status were excluded. Medical ethics committee of the hospital approved the study

Preoperative Evaluation

After obtaining informed written consent from patients, Colonoscopy was done to confirm diagnosis and to rule out synchronous lesions. Loco regional staging done with contrast enhanced CT of abdomen and pelvis, Endorectal ultrasound and cystoscopy in cases suspected of bladder invasion. A lymph node metastatsis of four or greater than four as detected by imaging was staged as N2 disease. Distant metastasis was excluded by contrast enhanced CT of abdomen and Pelvis, chest X-Ray and if necessary a CT chest. basic work up including complete hemogram, Renal function tests, Liver function tests, Tumor markers –CEA, Pulmonary function tests and Cardiac tests –ECG & Echocardigram was done to rule out any major illness and to confirm the patients fitness for surgery.

Treatment

Preoperative external beam radiotherapy was given for a total does of 50.4 in 28 fractions of 180 cGy each, five times per week for total duration of five and a half weeks. It was given as anterior and posterior opposed portals using Telcobalt machine of 1.33 meV. The radiotherapy was given to include the tumor area and its drainage lymph nodes (pelvic-internal, external iliac, obturator). The upper margin of radiotherapy field was L5-S1. The lower margin was obsturator foramen, 1.5 cm below lower border of public symphysis. The lateral margin was 1 cm lateal to true pelvis at leval of mid inguinal point. If the tumor extended to anal canal, inguinal nodes were included in the field. Laterally the radiotherapy field was extended to anterior superior iliac spine. The chemotherapeutic agent used was 5 Fluroracil, used as a bolus of 350mg/m2/d for 5 days, during the first and fifth weeks of radiotherapy along with 20mg/m2 of leucovorin. Postoperatively 5 Flurouracil was given for four cycles (350mg/m/d, once in four weeks five times weekly) started postoperatively for weeks after surgery. Patients were assessed five weeks after surgery regarding the response to treatment CT abdomen and pelvis

Decision for abdominoperineal excision of rectum, an anterior resection or pelvic exenteration was made preoperatively and modified according to the preoperative findings. According to the standardized technique Total mesorectal excision was done. All patients who underwent anterior resection had a protective ileostomy. Patients with unresectable growth due to locally advanced disease had colostomy only. During therapy, for sings of acute toxic effects requiring change in dosage or regimen patients were monitored weekly. According to the Radiation Therapy Oncology Group criteria – Acute and long term toxic effects were graded with respect to acute and late adverse effect of radiotherapy. Patients were observed for Peroperative and postoperative complications which included bleeding, ileus, intestinal fistulas, intra – abdominal abscess, perineal wound complications, urinary retention and death.

Follow up

Patients were followed at three monthly intervals for two years. Evaluations consisted of History and physical examination, a Complete blood count and Liver function tests and Renal function tests, Tumor marker –CEA, Proctoscopy, Abdominal ultrasonography, CT of Abdomen and Chest radiography (annual) .Local recurrence was to be confirmed hisotpathologically or by sequential radiological studies to detect mass lesion. Distal recurrence was confirmed histopathlogically.

All resected specimens were examine for histological grade, degree of fibrosis, resected margin status and nodal status. The primary end poins analyzed were downsizing of tumor, down staging of the tumor, sphincter saving rates, toxicity of chemoradiotherapy, and patients compliance for the regimen. Secondary end points analyzed were the incidence of local recurrence, distal metastasis. Downsizing was defined a reduction in the size of tumor after chemoradiotherapy as determined by physical

examination. Down staging was defined as decreases in TNM stage, as assessed after chemo-raditherapy in the surgically resected specimen.

Results

From March 2012 to February 2014, fifteen patients were enrolled with mean age of 58.4 years (37 – 73) and includes 11 males and 4 females. All patients underwent surgery after neoadjuvant chemoradiotherapy. Part of the tumors extended into anal canal from lower third of rectum into upper anal canal (20%) Nine patients had tumors involving lower rectum and Three had tumor involving middle third of Rectum.14 patients were well or moderately differentiated and one poorly differentiated. Among 15 patients 60% were stage 3B (T3/T4N1M0), 20% of cases stage 2A (T3N0M0), 13%stage 3C (N2M0) and 7% stage 2B (T 3N0M0).

Fourteen patients underwent surgery at six weeks after chemoradiotherapy; one patients had surgery after seven weeks in post chemoradiotherapy period. Five patients underwent anterior resection (33%), none of the female patients had uterine or bladder involvement which was noticed in preoperative imaging as well as intra operative assessment. Ten patients (67%) underwent abdominoperineal resection. Patient with growth extension up to pelvic side wall which were inoperable were not included in the study and the patients were offered palliative sigmoid colostomy and they were not included in the study.

Complications

Peraperative complications Bleeding	1
Post operative complications	
Abdominal wound infection	4
Perineal wound infection	3
Intra abdominal abscess	0
Urinary retention	2
Chemoraditheray toxicity	3 (20%)
Mild –Skin irritation & Discoloration	2 (13.32%)
Vomitting	2(13.32%)
Diarrahoea	1 (6.66%)
Severe – Anaemia	1 (6.66%)

One patient developed intraoperative bleeding due to injury to sacral plexus. It was controlled by packing. Minor complications occurred in four patients, developed abdominal would infection which was treated conservatively by Antibiotics after confirming the sensitivity by culture Fourteen patients in the series are treated by open approach; one patient underwent laparoscopic abdominoperineal excision of rectum. One patient developed anemia requiring blood transfusion after the second dose of chemotherapy in the fifth week. Minor complications like wound infection ,skin irritation occurred in two patients, vomiting in two, diarrhea in one which was self – limiting.

Results of Surgery

Down sizing of tumor seen in fourteen of fifteen patients who had responded well to neoadjuvent chemoradiotherapy. In twelve of fifteen (12/15) patients down staging occurred. The follow up period ranged from six months to twelve months, with median follow up period being nine months. No patients developed local recurrence. Distant metastases in the form of Liver Metastasis not noted in any of the patients who had disease. Of the twelve patients who had been treated for locally advanced carcinom Rectum for whom APER was planned, a sphincter conservation surgery was possible in two of them after neoadjuvant chemoradiotherapy and those patients underwent anterior resection. Before neoadjuvant chemoradiotherapy only three anterior resections were planned. After it, five anterior resections were done with covering ileostomy done to protect the anastomosis as well as to reduce leak related complications. Neoadjuvant chemoradiotherapy increased sphincter conservation in 2/15 patients in our study. Fifteen of the fifteen patients had completed the full course of chemoradiotherapy followed by surgery (100%) with minimal toxicities to chemoradiotherapy treatment.

Postoperative TNM staging

(T1, T2, NO, MO) Stage I	3 (20%)
(T3, NO, MO) Stage 2 A	6 (20%)
(T4, NO, MO) Stage 2 B	0
(T1, T2, N1, MO) Stage 3 A	2(13.2%)
(T3, T4, N1, MO) Stage 3B	4(26.64%)
(any T, N2, MO) Stage 3C	0
(any T, any N, M1) Stage 4	0

Discussion

The rational for giving preoperative chemoradiotherapy is to improve the survival and the advantage of delivering both the agents preoperatively. These advantages include improved compliance given before a major surgery in well vascularized setting to assist in down staging to enhance the rate of curative surgery, prevents tumor tract seeding at surgery by sterilizing the tumor field and permit sphincter preservation in low lying rectal tumors. Irradiation is more effective is better if given preoperatively due to better tumor oxygenation. The sphincter conservation rate also doubled after preoperative chemo radiotherapy. Postponing the surgery to Six weeks help in shrinkage of tumor and recovery of tissues after treatment before fibrosis sets in. Higher pathological complete response produced by addition of 5 FU to preperative radiotherapy over radio therapy alone[13]

No improvement in disease – free survival (DFS) or overall survival but Better loco regional control. About 30% patients develop distant metastases. Due to Better pCR and loco regional control rates, 5-FU-based preoperative chemo radiotherapy followed by total mesorectal excision has become the standard of care in patients with locally advanced rectal cancer.

High levels of normal tissue damage, including small bowel injury, nerve dysfunction rectal bleeding, impaired Sphincter function, vaginal stenosis, and sacral fractures with Radical pelvic RT at doses of 55-60 Gy.40-50 Gy in 1.8 to 2.0 Gy fractions lower radiotherapy doses have become established as a standard, because it is associated with a good tumor response and with more acceptable levels of late morbidity.

Downsizing tumor

Study	Downsizing	p value
Polish Trial [13] 2004	Present	p<0.001
German Rectal Cancer study group [12] 2004	Present	p<0.001.
EORTC trial 22921 [17] 2005	Present	p<0.001
This study	Present	

Neoadjuvent chemo radiotherapy helps significant downsizing of tumor as it causes tumor shrinkage. In this study downsizing occurred. This is almost in accordance with other studies which have shown similar significant regression of the tumor after chemoradiotherepy.

Downsizing is indicator of good response to preoperative chemo radio therapy. This is concurrence with the results of Polish trial the tumor was 1.9 cm smaller in patients after chemo radiotherapy.

Study	Down Staging	Percentage of patients down staged
Rich et al [20] 1995	Present	64% p<0.001
German Rectal Cancer Trial [12] 2004	Present	62 % p<0.001.
EORTC trial 22921 [17] 2005	Present	52% p<0.01%
This study	Present	

After preoperative chemoradiotherapy, postoperative histopathology shows downgrading of the tumor. In this study of showed down staging (p<0.0001). A good pathological response is good prognostic indicator, with patients having a good response having fewer incidences of improved overall survival and local recurrence 1. Chung Wah Lam et al[4] in 2005 has shown that 69 % of his patients had decreased tumor stages after chemo radio therapy.

Preoperative TNM Staging Vs Post –Operative TNM Staging This Study

Stage	Preoperative TNM	Postoperative TNM
Stage I (T1, T2, NO, MO)	0	3
Stage 2 A (T3, NO, MO)	3	6
Stage 2 B (T4, NO, MO)	1	0
Stage 3 A (T1, T2, N1, MO)	0	2
Stage 3B (T3, T4, N1, MO)	9	4
Stage 3C (any T, N2, MO)	2	0
Stage 4 (any T, any N, M1)	0	0

In this study preoperatively around 60% of the tumors were in stage 3 B. Post –Operative, histopathology showed a significant shift towards lower stages stage.

2A in 20% and 20% in stage 1. Due to the tumoricidal effect of chemoradio therapy the lymph node positively was reduced.

Effect of time interval on surgery and down staging.

Long time interval between radiotherapy and surgery led to sphincter preservation because of tumor down staging when the optimum time interval between radiotherapy and surgery was analyzed.

In 1999 Francois et al, conducted a randomized trial to compare short interval outcome with along interval of 6-8 weeks. A long interval between preoperative radiotherapy and surgery was associated with pathologic down staging (10.3% in the SI group v 26% in the LI group, P.005) and a significantly better clinical tumor relapse, and short-term survival noted between the two groups at median follow-up of 33 months.

Sphincter – preserving surgery was performed in 76% of cases in the cases in the LI group versus 68 in the SI group ($p<0.27$). He concluded that a long interval between preoperative irradiation and surgery provides increased tumor down staging. In questionable sphincter preservation, a long interval may increase the chance of a successful sphincter – saving surgery.

The ideal time interval is 6 weeks (56, 21,28) for surgery after radiotherapy when there is an optimal tumor response and further delay does not enhance the effect of radiotherapy. When fibrosis sets in, dissection also becomes technically difficult with increased incidence of complications like intra –abdominal sepsis, increased bleeding. In this study, the interval ranged from 6 to seven weeks, median being six weeks.

Sphincter Saving Procedures after neoadjuvant chemo radiotherapy

Study	Sphincter Saving	Percentage
Rich et al [20] 1995	Present	66.6%
NSABP Trial[14] 1997	Present	50%
Polish Trial[13] 2004	Present	58%
German Rectal Cancer Group Trial [12] 2004	Present	39%
Chung Wah Lam et al [4] 2005	Present	82%
This study	Present	13.12%

One of the advantages of prooperative chemoradiotherapy is that tumor downsizing helps sphincter saving procedures. The incidence of sphincter saving procedures range from 39% up to 82%. In this study, preoperatively only three patients were planned for an anterior resection.

After neoadjuvant therapy, anterior resection was possible in five patients, sphincter conservation rate were increased. The lower number of sphincter saving procedures is due to the fact that most of the tumors (66.6%) had already extended into the anal canal, necessitating adbodminoperineal excision of rectum.

Distal Resection Margin after Neoadjuvant Chemoradiotherapy

Nearly 50% of patients undergo Abdominoperineal excision of rectum despite the increasing use of sphincter preservation for rectal cancers. In may circumstances, for adequate distal margins, Abdominoperineal excision of rectus is performed.

More limited distal margins may be appropriate as per evidence. For low lying rectal tumors doing an abdominoperineal excision does not increase the radicality of the procedure or improve survival. Study by Party et al found that no increase in pelvic recurrence when the distal margin was <2 cm compared with >2cm. 1 cm distal margins are adequate as per recent evidence'22. in the past, distal margins as great as 5 cm were advocated.

Smaller distal margins, even 1 cm, may be adequate, supported by pathological evidence that distal intramural spread rarely exceeds 1 cm. A number of clinical pathological studies22 that examined distal intramural Spread suggest that. When significant distal spread does occur, long term survival is affected adversely, despite abodminoperineal excision of rectum. The presence of distal spread is associated with decreased survival due to recurrence (mainly in lung). The use of centimeter and sub centimeter margins is controversial.

Jose G Guillem et al[25] one prospective pathological analysis of whole mount sections of

rectal cancer following combined modality therapy in 109 patients has shown that intramural extension occurred only in 1.8% patients (<0.95cm). Hence he concluded 1 cm margins are sufficient after preoperative chemo radiotherapy and this increases the chances of sphincter preservation without increasing the chances of local recurrence.

Preoperative chemo radiotherapy also reduces circumferential resection margin positively. Circumferential resection margin positively is as high as 25% if no preoperative chemo radiotherapy is used. In this study a distal margin of one cm did not result in margin positively in any of the postoperatively examined specimens.

Local Recurrence

Study	Duration of follow up	Local Recurrence	Percentage
EORTC Trial ^984	7 Years	Present	15%
Rich et al [20] 1995	2 Years, 3 Months	Present	4%
Polish Trial[13] 2004	4 Years	Present	14.2%
German Rectal Cancer Group Trial [12] 2004	4 Yeas	Present	6%
EORTC Trial 22921 [17] 2005	5.4 Years	Present	8%
Jean Pierre Gerard et al [19] FFCD 9203, 2006	81 Months	Present	8.1%
This study		Present	13.12%

Local recurrence

Tumors in the distal rectum

Locally extensive tumors are far more likely to recur than mobile tumors, which type of procedure is performed does not matter. Local recurrence is significantly higher in patients who have circumferential involvement than those without involvement. Recurrence is also influenced by site of lesion in rectum, lower one third tumors have higher incidence than upper third tumors. Incomplete removal of tumor is a very important cause for local recurrence.

Local recurrence ranges from 5.8% as reported by Kapitijein et al 24 to 15% TME considered as a contributing factor in reducing pelvic recurrence to as low as 5% to 8% in high – risk patients.

Follow up of this study during a ranging from 6 months to 9 months and no evidence of local recurrence is noted. This correalates well with the response of chemo radiotherapy and an adequate TME as evidence by downsizing and down staging.

Quirke et al. demonstrated that radial spread into the mesorectum is a common occurrence. Sharp dissection along the parietal pelvic fascia ensures resection of (5mm) occult nodal metastases which may be left behind and causing local recurrence.

Radial margins are a more important predictor of disease recurrence and survival than distal margins.

There is an increased risk of recurrence for patients who undergo have abdominoperineal excision of rectum and reflects the worse prognosis attributed to tumors of the low rectum. The location of the tumor may be a more important prognostic factor.

Toxicity of Chemo radio therapy

Study	Mild Toxicity	Severe Toxicity (%)
German Rectal Cancer Group Trial [12] 2004	*l*2	27
EORTC Trial 22921 [17] 2005	38.4	13.9
This study	26.66	6.66

About 26.6 % of patients developed toxicity of chemo radiotherapy, Skin irritation and discoloration was the most common toxicity encountered. It was totally reversed after few weeks. This is comparable with other studies showing a range of 11% to 15%. the EORTC 22921 trial showed a very high toxicity of 38.4%. In this study no patient had a change in the chemo radiotherapy schedule due to toxicity.

Postoperative complications

Study	Complications (%)
German Rectal Cancer Group Trial [12] 2004	*36*
EORTC Trial 22921 [17] 2005	22.8
Jean Pierre Gerard et al[19] FFCD 9203, 2006	20.9
This study	26.7

There is always a fear that neoadjuvant chemo radiotherapy increases preoperative complica-

tions, delays would healing, and patients may need perineal flap cover to prevent post-operative would disruption. the postoperative complications in this study were 26.7% only. Often patients who underwent only on abdominoperinial excision of rectum only one developed perineal would complication which was successfully treated conservatively. So preoperative chemo radiotherapy can be given safely with good patient compliance, minimal side effects and less postoperative complications.

Effect on Survival

With preoperative readiotherapy alone Randomized controlled studies have not shown any significant survival benefit.

Jose G.Guilem et al[23] "analyzed the long term outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer, estimated 10-years overall survival was 58% and 10 year recurrence – free survival (RFS) was 62%. With a median follows-up of 44 months.

Lymph vascular invasion and /or pareneural invasion (PNI), pathologic response of greater than 95%, and positive lymph nodes were significantly with disease free survival and overall survival.

There is always a fear that neoadjuvant chemo radiotherapy increases preoperative complications, delays would healing, and patients may need perineal flap cover to prevent post-operative would disruption. The postoperative complications in this study were 26.7% only. Often patients who underwent only on abdominoperineal excision of rectum only one developed perineal wound complication which was successfully treated conservatively. So preoperative chemoradiotherapy can be given safely with good patient compliance, minimal side effects and less postoperative complications.

Conclusion

Neoadjuvant chemoradiotherapy given in stage 2 / middle and low rectal cancers causes significant downsizing, down staging of the tumor, increases the rate of sphincter conservation surgeries. The toxicity of chemoradiotherapy is minimal, patient compliance is good. The postoperative complications are not increased and it helps decrease the incidence of local recurrence. The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with stage 2 /3 middle and low rectal cancers.

References

1. S. Boulis Wassif, Gerard MD, J Loygue, Final Results of a Randomized Trial on the Treatment of Rectal Cancer with Preoperative Radiotherapy Alone or in Combination with 5-Fluorouracil, Followed by Radical Surgery, Trial of the European Organization on Research and Treatment of Cancer Gastroinstestinal Tract Cancer Cooperative Group, Cancer 1984; 53:1811-1818.
2. Heald RJ, Moran BJ, Ryall RD et al. Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998; 133; 894-899.
3. N.Arbman G, NilssonE, Local recurrence following TME for rectal cancer; BJS 83: 375-79.
4. Chung-Wah Lam, William Tzu-Liang Chen, Effect of preoperative concurrent chemoradiotherapy in locally advanced low rectal cancer after radical resection surgery. Int Surg 2005:9053-59.
5. Jin C Kim, Keiichi Takahashi et al, Comparative outcome Between Chemoradiotherapy and Lateral Pelvic Lymph Node Dissection Following Total Mesorectal Excision in Rectal Cancer, Ann Surg 2007 ; 246 ; 754 – 762.
6. Masato Kusunoki et al, Current Surgical management of Rectal Cancer, Dig Surg 2007 : 24 : 115 – 119.

7. Steams MW jr, Learning RJ et al Irradiation in inoperable rectal cancer. JAMA 1975 ; 231 : 1388.
8. Swedish Rectal Cancer Trial Group. Improved survival with preoperative radiotherapy in respectable rectal cancer.NEngl J Med 1997; 336; 980-987.
9. Frykholm GJ, Pahlman L, Glimelius B. Combined chemo and radiotherapy vs. Radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 2001; 50 : 433-440.
10. Ruo L, Tikoo S, Klimstra D. Long term prognostic significance of extended rectal cancer response to preoperative radiation and chemotherapy. Am J Surg 2002; 236 : 75-81.
11. Roh M, Petrelli N, Wieand H. Phase III randomised trial of preoperative versus postoperative multimodality therapy in patients with carcinoma of the rectum (NSABP R-03). J Clin Oncol 2001; 20(suppl 1): 123a
12. Sauer R, Becker H. Hohenberger W et al. German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351 : 1731 – 1740.
13. Bujko.K, Nowacki MP, Nasierowska – Guttmejer A et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004: 72 : 15-24.
14. Hyams DM, Mamounas EP, Petrelli N et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum : A progress report of National Surgical breast and Bowel project protocol R-03. Dis Colon Rectum 1997 : 40 : 131-139.
15. RobGlynne _ Jones, mark Harrison. Locally Advanced Rectal Cancer : What Is the Evidence for Induction, Oncologist 2007; 12; 1309-1318.
16. Gerard JP, chapet O, Nemoz C et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: The Lyon R96-02 randomized trial. J Clin Oncol 2004; 22 : 2404-2409.
17. Jean-Frangois Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D., Laurent Mineur, M.D., and Jean-Claude Oilier, M.D., for EORTC Radiotherapy Group Trial 22921 Chemotherapy with Preoperative Radiotherapy in Rectal Cancer N Engl J Med 2006; 355 : 1114-23.
18. Bosset JF, Calais G, Mineur L et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer : Preliminary results – EORTC 22921. J Clin Oncol 2005; 23 : 5620-5627.
19. Jean-Pierre Gerard, Thierry Conroy, Franck bonnetain, Seitz, Bruno Buecher, Remy Mackiewicz, Michel Ducreux, and Laurent Bedenne. Preoperative Radiotherapy with or without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers : Results of FFCD 9203. J Clin Oncol 24 : 4620-4625.
20. Rich TA, Skibber JM, Ajani JA, et al. Preoperative infusionl chemoradiation therapy for stage T3 rectal cancer. Int J Radiat Oncol Biol Phys 1995 ; 32 : 1025-9.
21. Yves Francois et al, Influence of the time interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter sparing surgery : The Lyon R 90-01 randomized trial; J of Clinical Oncology, Voll7, No8, 1999, 2396-2402.
22. Boris Kuvshinoff, Irfan Maghfoor, Brent Miedema, David Ota

23. Distal Margins requirements after preoperative Chemoradiotherapy for distal rectal carcinomas : Are <=1 cim margin sufficient? : Annals 9of Surgical Oncology : 8 (2) : 163-169.
24. Jose G. Guillem, David B Chessin, JinruShia, A Prospective pathologic Analysis Using Whole Mount Sections of Rectal Cancer Following Preoperative Combined Modality Therapy, Implications For Shincter Preservation; Ann Surg 2007; 245; 88 – 93.
25. Kapitjein E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345; 638-646.
26. Jose G. Guillem et al. Long-term Oncologic Outcome Following Preoperative Combined Modality Therapy and Total Mesorectal Excision of Locally Advanced Rectal Caner, Ann Surg 2005; 241 : 0829-838).
27. Karanjia ND, Shache DJ, North WRS Heald RJ. “Close shave” in anterior resection. Br J Surg 1990; 77 : 510-2.
28. Moore HG, Riedel E, Minsky BD et al. Adequacy of 1 cm distal margin after restorative rectal cancer excision with sharp mesorectal excision and preoperative combined modality therapy. Ann Surg oncology 2003 : 10 : 80-85.
29. Cam-Ly Tran, SejalUdani, Aliucia Holt, Tracey Amell. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer; American Journal of Surgery; 2006; 192; 873-877.
30. ClaudusRodel, Peter Martus, prognostic significance of Tumour Regression after Chemoradiotherapy for rectal cancer : J of Clinical Oncology, 2005 : 23, 8688 – 8696.
31. Bujko K, Nowacki MP, Long term results of randomized trial comparing preoperative short course radiotherapy with preoperative conventionally fractionacted chemoradiation for rectal cancer. BJS 2006, Oct : 93 (10) : 1215-23.
32. Morita T, Murata A, Koyama M :CuiTent status of autonomic nerve preserving surgery for mid and low rectal cancers: Japanese experience with lateral node dissection. Dis of Colon Rectum 2003; 46; S 78-S87.
33. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer; Lancet 1996; 348; 1605-1610.
34. Rullier E, Goffre B, Bonell C. Preoperative radio-chemotherapy and sphincter saving resection in T3 carcionmas of lower third of rectum. Am surg 2001; 234; 633-640.
35. Ruo L, Tikoo s, klimstra D. Long term prognostic significance of extended rectal cancer response to preoperative radiation and chemotherapy. Am J Surg 2002; 236; 75-81.
36. Bujko J, kepka L. Michalski et al. Does rectal cancer shrinkage induced by preopertive chemoradiotherapy increase the likelihood of anteror resection? A systematic review of randomized trails. Radiotherapy Oncology 2006; 80; 4-12.
37. RohMs, colangelo L, Wieand S et al. Response to preoperative multimodality therapy predicts survival in patients wirh carcinoma of rectum.J Clinical oncology 2004; 22; 246s.
38. Enker WE, Thaler Ht, CranorMl et al. Total Memorectal excision in the operative treatment of carcinoma rectum. J Am coll Surg. 1995; 181; 335-346.
39. de Haas-Kock DF, Baeten, Jager JJ et al. Prognostic significance of radial margins of clearance in rectal cancer. Br J Surg.1996; 83; 781-785.

40. Wibe A, Syese A, Andersen E et al. Oncological outcomes after total mesorectal excision for cancer of lower rectum: anterior vs abdominoperineal excision. Dis Colon rectum 2004; 47; 45-58.
41. Williams NS, Durdley P, Johnston D : The outcome following Sphincter saving resection and abdominoperineal resection of rectum for low rectal cancer; Br J Surg 1985; 72; 595-598.
42. Law WL, Chu KW. Abdominoperineal excision is assosciatecl with poor Oncological outcome. Br J Surg 2004; 91; 1493-1499.
43. Tviet KM. guldvog 1, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short term time scheduled 5-FU against surgeryalone in treatment of Dukes B and C rectal cancer, Norwegian Adjuvant Rectal Cancer Group. Br J Surg 1997; 84; 1130-1135.
44. Bouzourence H, Bosnian FT, et al. Importance of tumour regression assessment in predicting outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002; 94; 1121-1130.
45. Moore HG, Gittleman AE, Minsky BD, et al: Rate of pathological response with increased time interval between preoperative combined modality therapy and rectal cancer excision. Dis Colon Rectum 2004; 47; 279-286, 46.
46. Heimann TM, Szporn A, Bolnick K et al. Local recurrence following surgical treatment of rectal cancer. Dis Colon Rectum; 1986; 29; 862-864.
47. Holm T, Rutquvist LE, Johansspon H et al. Postoperative mortality in rectal cancer treated with and without radiotherapy; causes and risk factors, Br J Surg 1996; 83; 964-968; 48
48. Bokey EL, Chapuis PH, Dent OF. Factors affecting survival after excision of the rectum for cancer. dis Colon Rectum 1997; 40; 3-40.
49. Grann A, Minsky BD, Cohen AM, et al. Preliminary results of preoperative 5 fluorouracil, low dose leucovorin and concurrent radiation therapy for respectable T rectal cancer. Dis Colony Rectum 1997; 40; 515-522.
50. Wichmann MW, Muuller C Meyer G, Strauss T, Homung HM et al. Effect of preoperative chemoradiotherapy on lymphnode retrieval after resection of rectal cancer. Arch Surg 2002; 137; 206-210.
51. Lavery IC, Lopez-Kostner F, Fazio VW, Fernandez Martin M et al. Chances of cure are not compromised with sphincter saving procedures for cancer of the lower third of rectum. Surgery 2002; 122; 779-785.
52. Emami B, PilepichM,Willett C et al. Effect of preoperative irradiationonresectability of colorectal carcinomas. Int J Radiat Oncol Biol Phys. 1982; 8: 1295-1299.
53. Aschele, Carlo, et al., Primary Tumor response to preoperative chemoradiation with our without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Onc. Published online before print. Dio : 10. 1200/JCO.2010.34.4911.
54. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil along in locally advaned rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial – The Lancet Oncology, Volume 13, Issue 7, Pages 679-687, July 2012.
55. 2010 by American Society of Clinical Oncology Comparison of Two neoad-juvant Chemoradiotherapy Regimens for Locally Advanced Rectal Cancer: Results

of the Phase III Trial ACCORD 12/0405-prodige 2.

56. ARISTOTLE Trial – ARISTOTLE: a phase III trial comparing standard versus novel chemoradiation treatment (CRT) a pre-operative treatment for magnetic resonance imaging (MRI)-defined locally advanced rectal cancer.
57. Dis Colon Rectum.2013 Jul; 56(7):921-30. timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Foster JD1, Jones EL, Falk S, Cooper EJ, Francis NK.