Original Article

Indian Journal of Cancer Education and Research
Volume 5 Number 2, July - December 2017
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.5217.5

Pathological Response in Assessment of Neo-Adjuvant Chemo Radiotherapy in Locally Advanced in Carcinoma of Rectum

U. Umamaheswara Reddy[a], Venkatsambasiva Rao[b]

Author's Affiliation: [a]Assistant Professor [b]Senior Resident: Department of Radiotherapy, Government General Hospital, Kurnool, Andhra Pradesh-518002, India.

Corresponding Author: Venkatsambasiva Rao, Senior Resident, Department of Radiotherapy, Government General Hospital, Kurnool -518002, Andhra Pradesh, India.
E-mail: umason2001@yahoo.co.in

Received on 10.04.2017, **Accepted on** 23.06.2017

Abstract

Aim: To assess the toxicity differences between neo adjuvant and adjuvant chemo radiation in carcinoma rectum. *Materials and Methods:* Patients who underwent neoadjuvant or adjuvant chemoradiation for carcinoma rectum were enrolled into study. The total number of patients 30 (neoadjuvant 15+ adjuvant 15). All patients with histopathological diagnosis of carcinoma rectum. Adenocarcinoma of rectum. Patients belonging to M0 (without metastasis. *Results:* Majority of the patients in this study were males in both neoadjuvant (80%) and adjuvant arms (73.3%). Majority of tumours in neoadjuvant arm were in lower rectum and majority of tumours in adjuvant arm were in upper & lower rectum. Both neoadjuvant and adjuvant arm were of moderately differentiated adenocarcinoma histology. Majority of patients (except four patients) had pathological node positive disease. The difference in yield of lymphnodes between the groups were statistically significant as assessed by two tailed t test P = 0.023. Similarly number of positive lymphnodes were more in patients who underwent surgery first (mean ± SEM = 6.33 ± 2.12) compared those who underwent neoadjuvant concurrent chemo radiotherapy and then underwent surgery (mean ± SEM = 0.28± 0.28), the difference is statistically significant P <0.0001. In neoadjuvant arm one patient had perineural invasion & one patient had lymphovascular invasion, where as in adjuvant arm none of the patients had perineural invasion but one patient had lymphovascular invasion. in neoadjuvant arm majority of patients had pathological T1 status, where as in adjuvant arm majority of patients had pathological T3 status. In neoadjuvant arm most of the patients had pathologically node negative status, where as in adjuvant arm 5 patients had pN2b, 4 patients had pN0, 2 patients had pN1a and 2 patients had pN2a. In the neoadjuvant arm only one patient had pathological positive lymphnodes. In neoadjuvant arm majority of patients had pathological T2 status, where as in adjuvant arm majority of patients had pathological T3 status. In neoadjuvant arm most of the patients had pathological node negative status, where as in adjuvant arm 5patients had pN2b, 4patients had pN0, 2 patients had pN1 and 2 patients had pN2a. In neoadjuvant arm most of the patients were pathological stage 0, I & IIA, where as in adjuvant arm most of the patients were pathological stage IIIB & IIIC. In neoadjuvant arm most of the patients were pathological stage IIA, I and 0, where as in adjuvant arm most of the patients were pathological stage IIIC & IIIB. 3 patients had complete response and 12 patients had partial response. *Conclusion:* Pathologic response (p CR& p PR) in patients who underwent Neoadjuvant chemo radiotherapy arm was good. Chemo radiotherapy down staged the tumour in all patients in the neoadjuvant arm. Haematological toxicities were more pronounced in Neoadjuvant arm, while Gastrointestinal and Genitourinary toxicities were more in Adjuvant arm.

Keywords: Colorectal Cancer; Neoadjuvant Chemo Radiotherapy; Haematological Toxicities.

Introduction

Colorectal cancer remains a major worldwide health problem. In the United States alone, it is estimated that there will be 148,610 patients diagnosed with colorectal cancer and 55,170 deaths this year. Worldwide, approximately 1 million new cases per year are diagnosed, with 529,000 deaths.

Incidence rate in India in men is 1.6-5/100,000 and in women is 0-2.8/100, 000 [1]. Incidence rate in Bangalore is 3.68 in men and 2.46 in women per 100,000 populations. Highest incidence has been reported in Impala west district 4.5/100,000 followed by Bangalore 4.4/100,000 [2]. Colorectal cancer (CRC) incidence rates are much lower in India than in Western countries. The high incidence of CRC in the West is attributed mainly to lifestyle factors including physical activity, smoking, and dietary factors. The lower incidence in India may be due to the large proportion of the population who are life-long vegetarians. The median age is in the seventh decade; however, colorectal adenocarcinomas can occur any time in adulthood [3]. The highest rates are found in developed nations like Europe, North America & Australasia and the lowest in Middle Africa and South Asia [1]. Surgery is the mainstay for treatment of carcinoma rectum. In patients who are staged postoperatively as pT3 &T4, N1-2 or any high risk features adjuvant chemo radiotherapy is recommended. Radio logically if the patients are found to be unresectable or if sphincter has to be preserved, neo adjuvant chemo radiotherapy followed by surgery and adjuvant chemotherapy is recommended. Preoperative chemo radiotherapy followed by postoperative chemotherapy is currently being practiced based on the improved local control, toxicity profile, and incidence of sphincter preservation as seen from the German Chirugische Arbeitsgemeinschaft Onkologie/Arbeitsgemeinschaft dioonkologie/ Arbeitsgemeinschaft Internistische Onkologie (CAO/ARO/AIO) 94 trial [4] and National Surgical Adjuvant Breast and Bowel project R-03 trail [5]. German rectal cancer trail & NSABP R-03 trail studied the pathological response, toxicity (gastrointestinal, genitourinary, haematological) differences in the neo adjuvant chemo radiation & adjuvant chemo radiation and loco regional control rate. These two trials showed improvement in local control, reduced toxicities in favour of preoperative chemo radiotherapy. This study has been taken up to assess the pathological response in patients undergoing neo-adjuvant chemo radiotherapy and compare the toxicity with adjuvant chemo radiotherapy and to compare loco regional control rate for available period of follow up at our institute.

Materials and Methods

Patients who underwent neoadjuvant or adjuvant chemoradiation for carcinoma rectum at our Institution were enrolled into study after obtaining Ethics committee Clearance. The total number of patients 30 (neoadjuvant 15 + adjuvant 15).

Inclusion Criteria

All patients with histopathological diagnosis of carcinoma rectum. Adenocarcinoma of rectum. Patients belonging to M0 (without metastasis).

Exclusion Criteria

Patients treated with palliative intent. Patients unfit for receiving chemotherapy.

Results

Number of patients in the neoadjuvant and adjuvant arm were 15 each respectively. Patient distribution in both neoadjuvant and adjuvant arms were equal.

Only one patient had lymphnodes positive in the neoadjuvant arm, where as in the adjuvant arm, majority of patients (except four patients) had pathological node positive disease. The difference in yield of lymphnodes between the groups were

Table 1: Shows sex distribution, location of tumour, histological differentiation of tumour

Sex	Neoadjuvant	Adjuvant
Male	12	11
Female	3	4
Location		
Upper & Middle	1	0
Upper	3	7
Middle	2	1
Lower	9	7
Histology		
Well Differentiated	3	2
Moderately Differentiated	9	11
Poorly Differentiated	3	2

statistically significant as assessed by two tailed t test P=0.023. Similarly number of positive lymphnodes were more in patients who underwent surgery first (mean ± SEM = 6.33 ± 2.12) compared those who underwent neoadjuvant concurrent chemo radiotherapy and then underwent surgery (mean ± SEM=0.28±0.28), the difference is statistically significant P <0.0001.

Table 3 shows that in neoadjuvant arm majority of patients had pathological T1 status, where as in adjuvant arm majority of patients had pathological T3 status. In neoadjuvant arm most of the patients had pathologically node negative status, where as in adjuvant arm 5 patients had pN2b, 4 patients had pN0, 2 patients had pN1a and 2 patients had pN2a. In the neoadjuvant arm only one patient had pathological positive lymphnodes. In the adjuvant arm, majority of patients (except four) had pathological node positive disease. In neoadjuvant arm majority of patients had pathological T2 status, where as in adjuvant arm majority of patients had pathological T3 status. In neoadjuvant arm most of the patients had pathological node negative status, where as in adjuvant arm 5patients had pN2b,

Table 2: Lymphnodes involvement in neoadjuvant and adjuvant arm

Neoadjuvant		Adjuvant	
No. of LN examined	**No. of LN positive**	**No. of LN examined**	**No. of LN positive**
10	0	12	3
12	0	2	0
3	0	20	14
5	4	15	13
3	0	28	1
3	0	10	7
3	0	15	7
5	0	13	0
12	0	29	0
X	X	20	6
10	0	15	0
5	0	14	7
10	0	32	31
12	0	3	1
18	0	5	5
		Neoadjuvant	Adjuvant
perineural invasion (PNI)		1	0
lymphovascular invasion (LVI)		1	1

Table 3: Shows pathological TN status and pathological stage in neoadjuvant and adjuvant arm and pathological response to neoadjuvant CTRT

Pathologic T status	**Neoadjuvant**	**Adjuvant**
pT0	3	0
PT1	7	2
pT2	1	0
pT3	4	11
pT4a	0	0
pT4b	0	2
Pathologic N status		
pN0	13	4
pN1a	0	2
pN1b	0	1
pN2a	1	2
pN2b	0	5
pN3	0	1
pNX	1	0
Stage group		
0	3	0
I	7	2
IIA	4	1
IIB	0	0
IIC	0	1
IIIA	0	0
IIIB	1	4
IIIC	0	7

4patients had pN0, 2 patients had pN1 and 2 patients had pN2a. In neoadjuvant arm most of the patients were pathological stage 0, I & IIA, where as in adjuvant arm most of the patients were pathological stage IIIB & IIIC. In neoadjuvant arm most of the patients were pathological stage IIA, I and 0, where as in adjuvant arm most of the patients were pathological stage IIIC & IIIB. 3 patients had complete response and 12 patients had partial response.

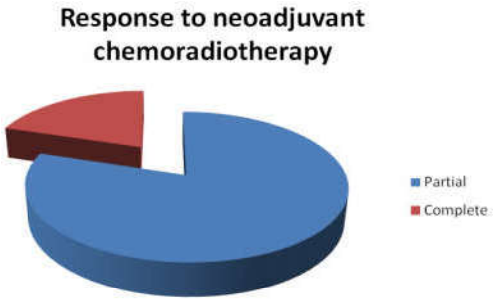

Fig. 1: Pathological response to neoadjuvant CTRT.
3 patients had complete response and 12 patients had partial response

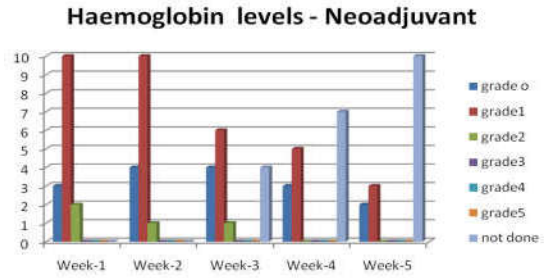

Fig. 2: In neoadjuvant arm majority of patients had garde1 toxicity in all weeks.
Only a few patients developed grade 2 toxicity in week 1, 2, & 3, none of them developed grade 3, 4 or 5 toxicities.

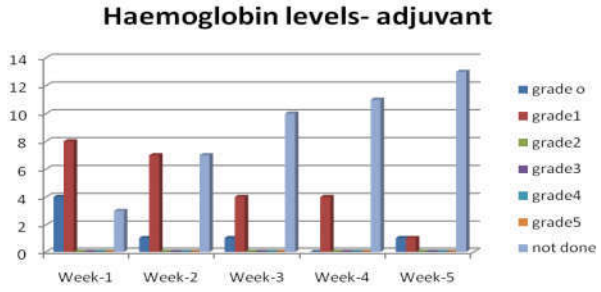

Fig. 3: In adjuvant arm majority of patients had grade1 toxicity in all weeks

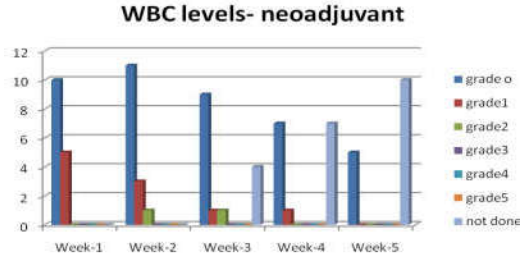

Fig. 4: In neoadjuvant arm few of the patients had grade1 toxicity in week1, 2, 3 & 4 and grade 2 toxicity in week 2 & 3.

Discussion

Many studies have been reported regarding colorectal cancer. Guckenberger et al, in 2009, introduced a new regimen for short-course RT, administering twice-daily doses of 2.9 Gy for 1 wk (total dose, 29 Gy) to 118 patients. That regimen

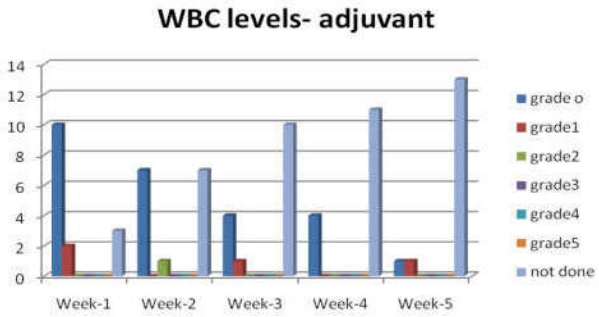

Fig. 5: In adjuvant arm patients had grade1 toxicity in week 1, 3 & 5 and grade 2 toxicity in week 2

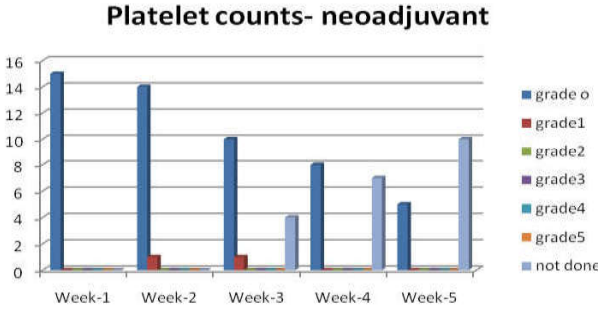

Fig. 6: In neoadjuvant arm very few patients had low platelet count in week 2 and 3

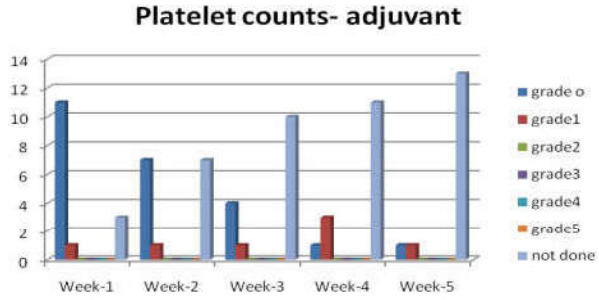

Fig. 7: In adjuvant arm few patients had low platelet counts (grade 1) in every week

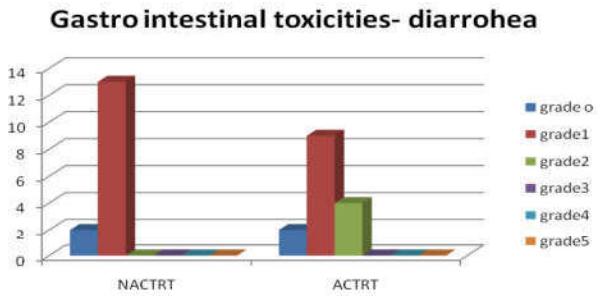

Fig. 8: In neoadjuvant arm majority of patients had grade1 toxicity, in adjuvant arm patients had both grade1 and grade2 toxicities

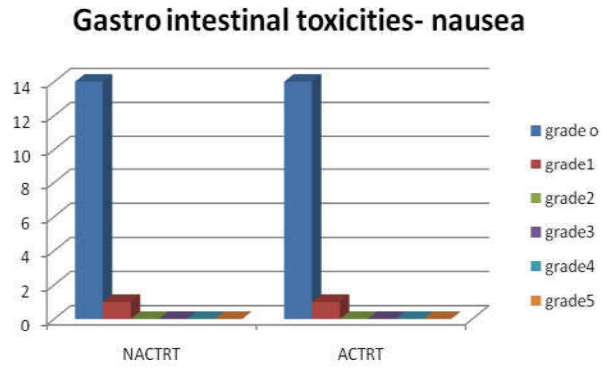

Fig. 9: One patient in both neoadjuvant and adjuvant arm had nausea

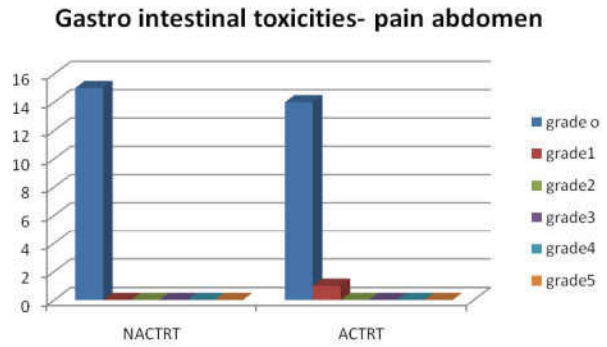

Fig. 10: In adjuvant arm one patient had pain abdomen while none of the patients in neoadjuvant arm developed the same

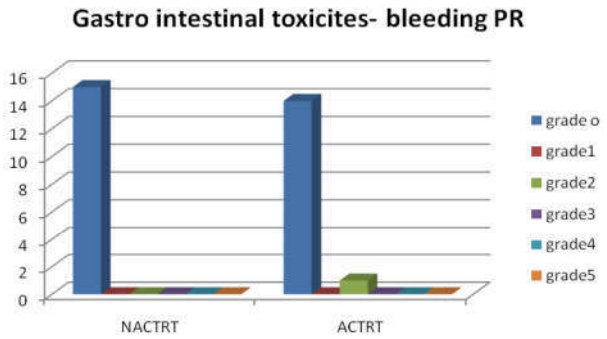

Fig. 11: In adjuvant arm one patient had bleeding per rectum, while none of the patients in neoadjuvant arm developed the same

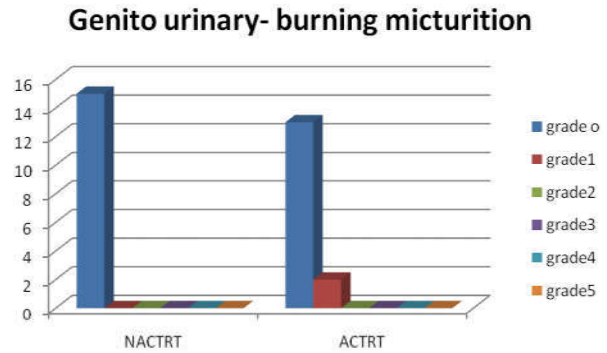

Fig. 12: Two patients developed burning micturition in adjuvant arm but none of the patients in the neoadjuvant arm had the same

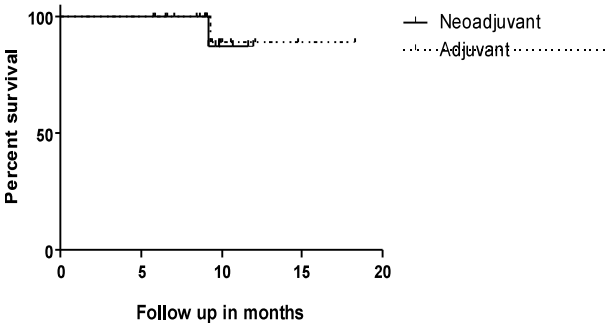

Fig. 13: There was no difference in disease free survival at a median follow-up period of 9.4 months in both neoadjuvant and adjuvant CTRT arms (P=0.86)

lowered the single dose and allowed a 6-h tissue recovery period between treatments, but the daily dose was the same as with standard short-course RT (5 Gy daily × 5 d). The 188 patients had clinical stage II (50%), III (41.5%), and IV (8.5%) rectal cancer; they all received adjuvant 5-FU-based chemotherapy. The median follow-up time was 46 mo. Late toxicity (gradeII) occurred in 11% of the patients. The local control rate was 92%. The 5-year survival rate of 67% compared favourably with previously reported rates in randomized trials that also evaluated daily dosing of short-course RT (58%-82%) [6]. Roh M S et al, in the United States, the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial also compared neoadjuvant CMT and adjuvant CMT in patients with locally advanced rectal cancer; the NSABP R-03 trial was similar to the German rectal cancer group trial published in 2004. Both arms of the NSABP R-03 trial used long-course RT, and the chemotherapy regimen was 5-FU-based with leucovorin. The study was initially powered for a sample size of 900, but had to close early due to poor accrual. In all, 123 patients were randomized to neoadjuvant CMT and 131 to adjuvant CMT. The surgical technique was not standardized, but rather left to the discretion of the surgeon. Primary endpoints were the disease-free survival and overall survival rates. The overall survival rates (74.5% with neoadjuvant CMT *vs.* 65.6% with adjuvant CMT, $P = 0.065$) and the loco regional recurrence rates [Hazard ratio (HR), 0.86, 95% CI: 0.41-1.81, $P = 0.693$] did not significantly differ - in contrast to the 5-year disease-free survival rates (64.7% *vs.* 53.4%, $P = 0.011$). Of note, the rate of complete pathologic response was 15% in the neoadjuvant CMT group but the rates of sphincter preservation (48% with neoadjuvant CMT *vs.* 39% with adjuvant CMT) did not significantly differ, per the opinion of the operating surgeon. It is difficult to draw conclusions from the NSABP R-03 trial, because it was underpowered and not standardized in operating technique [7].

Sebag-Montefiore D et al, in 2009, the MRC and National Cancer Institute of Canada (NCIC) combined CR07/CTG C016 trial addressed the issue of selective adjuvant CMT based on operative margins. The trial randomized 1 350 patients to 2 arms: (1) neoadjuvant short-course RT; or (2) initial surgery with selective adjuvant long-course RT and 5-FUbased chemotherapy based on circumferential (CRM) involvement. The surgical technique was not standardized. Median follow-up time was 4 years; the primary outcome measure was local recurrence. In the selective adjuvant arm, 12% of the patients had a positive CRM, 78% of whom then underwent adjuvant RT. In the neoadjuvant arm, a 61% relative risk reduction (HR, 0.39, CI: 0.27-0.58, $P < 0.0001$) was found for local recurrence, and a 24% improvement (HR, 0.76, CI: 0.62-0.93, $P = 0.013$) was found for disease-free survival. But the 2 arms did not significantly differ in overall survival rates. The MRC CR07/ NCIC-CTG C016 investigators concluded that neoadjuvant short-course RT was effective therapy in patients with operable rectal cancer [8].

Uday B. Patel et al, all curative resections for rectal cancer were prospectively evaluated for (macroscopic assessment of mesorectal excision) MAME between 1998 and 2007. Mesorectal specimens were graded into 3 types: complete, nearly complete, and incomplete categories. Univariate and multivariate analyses identified independent risk factors for noncomplete mesorectum categories as well as local and overall tumour recurrence. Of 359 specimens, 294 (81.9%) underwent evaluation; 82.3% were "complete." Abdominoperineal resection (APR) was the sole covariate associated with inadequate mesorectal excision (odds ratio [OR] = 2.7; $P = .003$). Independent predictors of local recurrence were circumferential resection margin (CRM) involvement (OR = 3.6; $P = .027$) and noncomplete mesorectum (OR = 4.4; $P = .008$). CRM+ (OR = 3.1; $P = .004$), poorly differentiated tumours (OR = 14.2; $P = .010$), nodal involvement (OR = 2.9; $P = .010$), and APR (OR = 2.9; $P = .006$) were independent risk factors for overall recurrence. In lower third tumours, noncomplete mesorectum occurred more frequently in APR compared with sphincter-saving procedures (31.1% vs. 18.8%; $P = .088$). This study demonstrates the value of auditing MAME. Good proficiency of mesorectal excision is associated with lower tumour recurrences after curative surgery, and is a morphological tool found to be useful in clinical practice [9].

Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts et al (Maas trail) Neoadjuvant chemo radiotherapy for rectal cancer can result in complete disappearance of tumour and involved nodes. In patients without residual tumour on imaging and endoscopy (clinical complete response [cCR]) a wait-and-see-policy (omission of surgery with follow-up) might be considered instead of surgery. The purpose of this prospective cohort study was to evaluate feasibility and safety of a wait-and-see policy with strict selection criteria and follow-up. A wait-and-see policy with strict selection criteria, up-to-date imaging techniques, and follow-up is feasible and results in promising outcome at least as good as that of patients with a pCR after surgery. Twenty-one patients with cCR were included in the wait-and-see policy group. Mean follow-up was 25 ± 19 months. One patient developed a local recurrence and had surgery as salvage treatment. The other 20 patients are alive without disease. The control group consisted of 20 patients with a pCR after surgery who had a mean follow-up of 35 ± 23 months. For these patients with a pCR, cumulative probabilities of 2-year disease-free survival and overall survival were 93% and 91%, respectively. A wait-and-see policy with strict selection criteria, up-to-date imaging techniques, and follow-up is feasible and results in promising outcome at least as good as that of patients with a pCR after surgery. The proposed selection criteria and follow-up could form the basis for future randomized studies [10].

Danish study Jenson et al, the purpose of this study was to analyse the results of preoperative short course radiotherapy in a consecutive, national cohort of patients with rectal cancer. Through a validated, prospective national database we identified 520 Danish patients who presented with high-risk mobile tumours in the lower two thirds of the rectum and were referred for preoperative radiotherapy with 5 x 5 Gy. The inclusion period was 56 months. Radiotherapy data was retrospectively collected. Of the 520 patients, 514 completed radiotherapy and 506 had surgery. Surgery was considered curative in 439 patients. The 3-year local recurrence rate was 4.0% (95% CI 2.5-6.5%) and the distant recurrence rate at 3 years was 18.7% (95% CI 15.4-22.5%). The 5-year disease free survival rate was 40.2% (95% CI 27.0-53.1%) and overall survival 50.4% (95% CI 36.1-63.1%). Most tumours (61%) were classified as T3 or T4 and 41% of the local recurrences occurred in patients with a fixed tumour at surgery. This study confirms data from randomised studies that the short course 5 x 5 Gy regimes is a feasible treatment for locally advanced rectal cancer even when applied in a population outside clinical trials [11].

TROG trial – Ngan 2012 et al, Eligible patients had ultrasound- or magnetic resonance imaging-staged

T3N0-2M0 rectal adenocarcinoma within 12 cm from anal verge. Short course consist of pelvic radiotherapy 5 × 5 Gy in 1 week, early surgery, and six courses of adjuvant chemotherapy. LC was 50.4 Gy, 1.8 Gy/ fraction, in 5.5 weeks, with continuous infusional fluorouracil 225 mg/m (2) per day, surgery in 4 to 6 weeks, and four courses of chemotherapy. Three hundred twenty-six patients were randomly assigned; 163 patients to SC and 163 to LC. Median potential follow-up time was 5.9 years (range, 3.0 to 7.8 years). Three-year LR rates (cumulative incidence) were 7.5% for SC and 4.4% for LC (difference, 3.1%; 95% CI, -2.1 to 8.3; P = .24). For distal tumours (< 5 cm), six of 48 SC patients and one of 31 LC patients experienced local recurrence (P = .21). Five-year distant recurrence rates were 27% for SC and 30% for LC (log-rank P = 0.92; hazard ratio [HR] for LC: SC, 1.04; 95% CI, 0.69 to 1.56). Overall survival rates at 5 years were 74% for SC and 70% for LC (log-rank P = 0.62; HR, 1.12; 95% CI, 0.76 to 1.67). Late toxicity rates were not substantially different (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer G3-4: SC, 5.8%; LC, 8.2%; P = .53. Three-year LR rates between SC and LC were not statistically significantly different; the CI for the difference is consistent with either no clinically important difference or differences in favour of LC. LC may be more effective in reducing LR for distal tumours. No differences in rates of distant recurrence, relapse-free survival, overall survival, or late toxicity were detected [12].

Pooled analysis – Bonnetain 2012 EJC Two thousand two hundred forty-six patients were enrolled. Overall, 899 patients had stage II disease, including 330 low-risk and 569 high-risk patients. A total of 315 patients were ages 70 to 75 years. For stage II patients, the hazard ratio (HR) for comparing FOLFOX4 with FL (leucovarin) was 0.84 (95% CI, 0.62 to 01.14) for disease-free survival (DFS), 0.70 (95% CI, 0.49 to 0.99) for time to recurrence (TTR), and 1.00 (95% CI, 0.70 to 1.41) for overall survival (OS). There was no interaction between treatment and stage or age. Low-risk stage II patients did not benefit from oxaliplatin. In high-risk stage II patients, the HR comparing FOLFOX4 with FL was 0.72 (95% CI, 0.51 to 1.01) for DFS, 0.62 (95% CI, 0.41 to 0.92) for TTR, and 0.91 (95% CI, 0.61 to 1.36) for OS. In elderly patients, the HR comparing FOLFOX4 with FL was 0.93 (95% CI, 0.64 to 1.35) for DFS, 0.72 (95% CI, 0.47 to 1.11) for TTR, and 1.10 (95% CI, 0.73 to 1.65) for OS. The results of these subset analyses show no statistically significant benefit (OS and DFS) for the addition of oxaliplatin to FL as adjuvant treatment for either stage II or elderly patients [13].

Gérard JP, The ACCORD 12 trial investigated the value of two different preoperative chemo radiotherapy (CT-RT) regimens in T3-4 Nx M0 resectable rectal cancer. Clinical results are reported after follow-up of 3 years. Between November 2005 and July 2008, a total of 598 patients were randomly assigned to preoperative CT-RT with CAP45 (45-Gy RT for 5 weeks with concurrent capecitabine) or CAPOX50 (50-Gy RT for 5 weeks with concurrent capecitabine and oxaliplatin). Total mesorectal excision was planned 6 weeks after CT-RT. The primary end point was sterilization of the operative specimen, which was achieved in 13.9% versus 19.2% of patients, respectively ($P < .09$). Clinical results were analyzed for all randomly assigned patients according to the intention-to-treat principle. At 3 years, no significant difference in clinical outcome was achieved with the intensified CAPOX regimen. When compared with other recent randomized trials, these results indicate that concurrent administration of oxaliplatin and RT is not recommended [14].

Conclusions

Pathologic response (p CR& p PR) in patients who underwent Neoadjuvant chemo radiotherapy arm was good. Chemo radiotherapy down staged the tumour in all patients in the neoadjuvant arm. No difference was found between the 2 arms in terms of loco regional control. Disease free survival was same in both treatment arms. Haematological toxicities were more pronounced in Neoadjuvant arm ,while Gastrointestinal and Genitourinary toxicities were more in Adjuvant arm.

References

1. Jemal A, Murray T, Ward E, et al . Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–130.
2. Three year report of the Population Based Cancer Registries, 2006-2008. First Report of 20 PBCRs in India. National Cancer Registry Programme, Indian Council of Medical Research, Bangalore, November 2010 Page 71 & 79 .
3. Garcia-Alvarez A, Serra-Majem L, Ribas-Barba L, et al. Obesity and overweight trends in Catalonia, Spain (1992-2003): gender and socio-economic determinants. Public Health Nutr. 2007;10:1368-1378.
4. Sauer R, Becker H, Hohenberger P, et al: Preoperative chemo radiotherapy as compared with postoperative chemo radiotherapy for locally advanced rectal cancer. N Engl J Med 2004;351:11-20.

5. Mark S. Roh, Linda H. Colangelo, Michael J. O'Connell, et al:Preoperative Multimodality Therapy as compared with postoperative multimodality therapy NSABP R-O3 trial: J American society of clinical Oncology 2009;27:5124-5130.
6. Guckenberger M, Wulf J, Thalheimer A, Wehner D, Thiede A, Muller G, Sailer M, Flentje M. Prospective phase II study of preoperative short-course radiotherapy for rectal cancer with twice daily fractions of 2.9 Gy to a total dose of 29 Gy—longterm results. Radiat Oncol 2009;4:a 67.
7. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, Kahlenberg MS, Baez-Diaz L, Ursiny CS, Petrelli NJ, Wolmark N. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27:5124-5130.
8. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de Metz C, Myint AS, Bessell E, Griffiths G, Thompson LC, Parmar M. Preoperative radiotherapy versus selective postoperative chemo radiotherapy in patients with rectal cancer (MRC CR07 and NCICCTG C016): a multicentre, randomised trial. Lancet 2009;373: 811-820.
9. Uday B. Patel, Fiona Taylor, Lennart Blomqvist, Christopher George, Hywel Evans, Paris Tekkis Magnetic Resonance Imaging–Detected Tumour Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes J Clin Oncol 29 2011 by American Society of Clinical Oncology.
10. Maas 2011-Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, van Dam RM, Jansen RL, Sosef M, Leijtens JW, Hulsewé KW, Buijsen J, Beets GL Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer J Clin Oncol. 2011 Dec 10;29(35): 4633-40.
11. Danish study Jensen, Altaf R, Harling H, Jensen M, Laurberg S, Lindegaard JC, Muhic A, Vestermark L, Jakobsen A, Bulow S; Clinical outcome in 520 consecutive Danish rectal cancer patients treated with short course preoperative radiotherapy Danish Colorectal Cancer Gro Eur J Surg Oncol. 2010 Mar; 36(3):237-43.
12. Ngan 2012 Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, Ackland SP, Schache D, McClure B, McLachlan SA, McKendrick J, Leong T, Hartopeanu C, Zalcberg J, Mackay J. Randomized trial of short-course radiotherapy versus long-course chemo radiation comparing rates of local recurrence in patients with T3 rectal cancer J Clin Oncol. 2012 Nov 1;30(31):3827-33.
13. Bonnetain F, Bosset JF, Gerard JP, et al. What is the clinical benefit of preoperative chemo radiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? Eur J Cancer. 2012;48: 1781–1790.
14. Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V Comparison of two neoadjuvant chemo radiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2.