Preoperative Radiotherapy in Carcinoma Rectum

Vishnu Prasad Nelamangala Ramakrishnaiah ·
Cecil Thankachan Thomas · Elangovan Sundar ·
Kanipakapatnam Satyanarayana Reddy ·
Srinivasan Krishnamachari

Received: 9 May 2012 / Accepted: 31 July 2012 / Published online: 9 August 2012
© Indian Association of Surgical Oncology 2012

Abstract The present study was undertaken to address the various concerns that has limited the use of preoperative radiotherapy in rectal cancer in our institution. All patients diagnosed as having carcinoma rectum between August 2005 and July 2007 were included in the study. Group 1 patients consisted of those presenting with T2, T3 and T4 who received preoperative radiation of 25 Gy. Group 2 consisted of those with T4 tumours, who received Long course radiotherapy. Complication of radiation like dermatitis, enteritis and proctitis were noted. Before surgery CT scan and TRUS were repeated. In the postoperative period a record of abdominal, perineal wound complications and other complications were noted. The results were compared with a similar group of patients who did not receive preoperative radiotherapy. There were 21 patients (12males) with a mean age of 48.4 years (Range 18–70) in the radiotherapy group. Sixteen patients received short course (25 Gy) and five patients received long course of preoperative radiotherapy. Fourteen patients underwent definitive surgery in the form of abdominoperineal resection (APR) or anterior resection (AR). In the non-RT group there were 17 patients (8 males) with a mean age of 50.2 year. Fourteen patients underwent definitive surgery like APR (11) and AR (3). In the RT group CT scan and TRUS failed show

any significant downsizing or down staging of tumour. In the RT group, incidence of acute skin toxicity was 23.8 % (5/21), all were seen in those who received long course of radiotherapy (Group 2). Grade 2 or 3 lower G I symptoms occurred in 3 (18.6 %) patients of Group 1 and 1(20 %) patient of group 2. There was higher incidence of perineal wound complication in the RT group (19.0 % vs 5.9 %). Preoperative long course of radiotherapy may be associated with high rates of dermatitis and perineal wound infection. Short course may be associated with lower G I toxicity.

Keywords Rectal cancer · Radiotherapy · Chemotherapy · Toxicity

Introduction

Preoperative radiotherapy (PRT) has become part of standard practice offered to improve treatment outcomes in patients with rectal cancer [1]. Optimal preoperative radiotherapy for localized rectal cancer provide a modest improvement in overall survival, definite improvement in local recurrences, modest increase in the proportion of patients undergoing curative surgery, but is also accompanied by an increase in acute and late rectal and sexual function compared with surgery alone. A combination chemoradiotherapy provides further improvement in local recurrence [1]. But studies on preoperative radiotherapy in carcinoma of rectum are few from India. Hence the present study was undertaken to address the various concerns that has limited the use of preoperative radiotherapy in the management of rectal cancer in our institution and to study; complications due for preoperative radiation, effects of radiation on the tumor, the ease of surgical dissection, wound healing after surgery, postoperative complications.

V. P. Nelamangala Ramakrishnaiah (✉) · C. T. Thomas ·
S. Krishnamachari
Department of Surgery, Jawaharlal Institute of Postgraduate
Medical Education & Research (JIPMER),
Puducherry 605006, India
e-mail: vprasad285@gmail.com

E. Sundar
Department of Radio-Diagnosis, JIPMER,
Puducherry, India

K. S. Reddy
Department of Radiotherapy, JIPMER,
Puducherry, India

Method

This was a prospective clinical study done between August 2005 and July 2007. Patients with biopsy proven carcinoma rectum were included in this study. Ethical clearance for the study was obtained from the Institute Ethics Committee. After a detailed explanation of the treatment protocol, an informed consent was obtained from the patients. Patients with growth limited below the sacral promontory only were included in the study. Those above 70 years of age or with history of previous pelvic irradiation were excluded from the study.

Transrectal ultrasound (TRUS), Contrast enhanced Computed Tomography (CECT) and Chest X-ray were done to stage the disease. The ultrasonographic interpretation of rectal wall was based on the five-layer model. The presence of lymph node involvement was assumed if the node adjacent to the tumor was enlarged (>5 mm) or if it showed a round appearance with an irregular surface and a low echogenicity. For CT imaging criteria, perirectal fat infiltration was defined as an irregularity (streaking) or perirectal fat with a disrupted margin of the adjacent rectal wall (T3 lesion). T-4 lesions were those without an intact fat plane between the growth and the adjacent organs. Lymph node involvement was said to be present if nodes greater than 5 mm in diameter were found in the pelvis. Imaging was done both before and after radiation.

Following the staging, patients were given radiotherapy. (RT group) These patients were divided into two groups. Group 1 consisted of those presenting with T2, T3 or operable T4 lesions and received a total dose of 25 Gy of radiation in 5 fractions over a period of 1 week. A gap of 1 week was given before the patient was operated on. Group 2 consisted of those with inoperable tumors, as adjudged clinically, receiving 45 Gy in 25 fractions over a period of 4 weeks. A gap of 1 month was allowed prior to surgery in these patients. Five patients were part of an initial pilot study. Two of these patients had received 25 Gy in 10 fractions over a period of 2 weeks. They were included in Group 2. The rest three patients had received 45 Gy in 25 fractions. Radiation was given in two portals to the anterior and posterior pelvis. The upper border field is at the level of L4-L5 and the lower border is 2 cm below the anal verge. The lateral borders extend to 2 cm lateral to the true pelvic cavity. Radiation was given for 6 days a week for 4 weeks in the longer radiation schedule and at a stretch for 5 days in the shorter schedule.

In the waiting period leading to surgery, a note of all complications arising in relation to radiation were noted with particular reference to acute radiation-induced complications like radiation dermatitis, radiation enteritis and radiation proctitis. These were graded on the basis of the Acute Radiation Morbidity Scoring Criteria published by the

Radiation Therapy Oncology Group (RTOG). They were graded from 1 to 5. Grade 0 indicated no toxicity and grade 5 indicated toxicity that led to death of the patient. The severity of the toxicity was graded from 1 to 4 according to the published tables of the RTOG. The scoring for acute toxicity involving skin and bowel is as follows:

- Grade 0 No change
- Grade 1 Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating
- Grade 2 Tender or bright erythema, patchy moist desquamation/moderate edema
- Grade 3 Confluent, moist desquamation other than skin folds, pitting edema
- Grade 4 Ulceration, hemorrhage, necrosis

Lower G.I. toxicity

- Grade 0 No change
- Grade 1 increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
- Grade 2 Diarrhea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics
- Grade 3 Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention.
- Grade 4 Acute or Subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion.

Just prior to surgery, repeat imaging by TRUS and CT were done to record the size and stage of the tumor. The effects of radiation on the tumor were assessed by noting the incidence of down staging and downsizing. The choice of surgery was based on the intra-operative findings and the distal tissue margin available. All surgeries were performed by consultants adhering to the principles of TME. The intra-operative blood loss and the operative time were noted. The ease of surgical dissection was assessed by the operating surgeon in the form of a questionnaire. A 5-point scale for the following variables was scored: approach to the pelvis; anterior, posterior and lateral mesorectal dissection; anastomoses; abdomen closure and perineal closure. A score of 1 indicated 'very easy' dissection, a score of 5 'very difficult dissection; and a score of 3 'average'.

In the postoperative period, a record of postoperative wound healing, Perineal wound complications, abdominal wound complications and anastomatic complications were made. The postoperative histopathological report included the size of the tumor, depth or rectal wall invasion, presence or absence of involved lymph nodes. These findings were recorded and compared with similar outcomes on imaging.

Based on the pathological report patients were also offered chemotherapy with 5-fluorouracil and leucovorin. The patients were followed up in the outpatient department for the length of the study period and assessed for evidence of local recurrence. Any mortality in the immediate postoperative period or when detected on follow up was recorded.

A retrospective analysis of the intraoperative blood loss, operative time and postoperative complications was also done in patients who underwent surgery for carcinoma rectum and who did not receive radiotherapy preoperatively during the period from August 2006 to July 2007. This group was compared with the patients who received preoperative radiotherapy.

Data were entered into SPSS v.10 and analyzed statistically. Paired *t*-test and Wilcoxon signed-ranks test were used to analyze the change in tumor size on imaging studies after radiotherapy. Unpaired *t*-test was used for continuous variables like blood loss and operative time. Cohen's Kappa test was used to calculate the measure of agreement of TRUS and CT when compared with the pathological stage. Fischer's exact test was used to compare the incidence of complications in irradiated and non-irradiated patients.

Results

This study recruited 26 patients of which five were excluded - two had alternative histological diagnoses (malignant melanoma), two had tumors extending to the sigmoid colon and one patient refused preoperative radiotherapy. Of the remaining 21 patients, 5 were part of an initial pilot study.

The mean age of the RT group as a whole was 48.4 year (range, 18–70 year). There were 12 (57.1 %) males and nine (42.9 %) females. All patients presented with bleeding per rectum. The mean duration of symptoms was 5.1 months (range, 1–12 months). Per rectal examination revealed a growth in all cases. The mean distance of the tumor from the anal verge was 4.1 cm (range, 1–8 cm). Thirteen (61.9 %) of the patients had well differentiated adenocarcinoma, four (19.0 %) were moderately differentiated and four were poorly differentiated type.

Sixteen patients received 25 Gy in 5 fractions (Group 1, short term schedule), three patients received 45 Gy in 25 fractions (Group 2, long-term schedule) and two had received 25 Gy in 10 fractions (Group 2, long-term schedule). CT scan was done in 21 patients before radiotherapy and in 20 patients after radiotherapy. In one patient, due to technical reasons, CT could not be done in time before surgery. TRUS was done in 19 patients before and after radiotherapy. Two patients had obstructive growths in which TRUS was not feasible.

Fourteen patients underwent definitive surgery. Twelve patients underwent Abdomino-Perineal Resections (APR)

and two Anterior Resections (AR). Seven patients had colostomies; four for inoperable tumors and three for liver metastases detected intraoperatively.

For retrospective analysis and comparison patients of carcinoma rectum who had not received preoperative radiotherapy (non-RT group) were enlisted. Twenty-two patients, of whom 20 had definitive surgery and two had colostomies, were identified. Of the 20 cases of definitive surgery, complete records for 15 cases were available. One of these was later found to have a Hartman's procedure done for inoperable disease. In the 14 remaining patients of the non-RT group. There were 11 APR and three AR, of which one AR had a stapled anastomoses. The mean age was 50.2 year (range, 24–80 year), eight (57.1 %) were males and six (42.9 %) were females.

There was no difference with respect to T stage, N stage or size of the tumour before or after radiotherapy as shown by TRUS & CE CT scan in patients who received Preoperative radiotherapy. The incidence of downsizing was determined on the basis of pre and post-RT imaging studies. The mean decrease in size in downsized tumors on TRUS at the end of 1 week after RT was 0.33 cm. The mean decrease in size on CT was 1.25 cm. The mean increase in size of upsized tumors after RT was 0.33 cm on TRUS and 2.78 cm on CT. When all RT schedules were compared, the incidence of downsizing was 49.1 % on TRUS and 35 % on CT scan. These were 46.2 % on TRUS and 33.3 % on CT in Group 1. (Table 1) The size on CT when compared to size on HPE showed no significant difference by paired *t*-test (*p* value = 0.08). CT appeared to have better correlation with HPE. Accuracy of the staging ability of TRUS and CT were assessed by comparing the post-RT staging by TRUS and CT with the pathological stage. The accuracy of T-staging was 84.6 % in CT and 64.3 % in TRUS. CT under staged 15.4 % of tumors and no cases were over staged. TRUS over staged 35.7 % of tumors and no tumors were under staged.

The sensitivity, specificity, positive predictive value and negative predictive value for detecting rectal wall penetration was 100 %, 75 %, 90 % and 100 % for CT respectively and 90 %, 100 %, 100 % and 80 % for TRUS respectively. the sensitivity, specificity, positive predictive value and

Table 1 Comparison of pre RT and post RT imaging with respect to size of tumor

	No change	Downsized	Upsized
CT			
All RT schedules	4/20 (20 %)	7/20 (35 %)	9/20 (45 %)
25 in 5#	3/15 (20 %)	5/15 (33.3 %)	7/15 (46.6 %)
TRUS			
All RT schedules	2/17 (11.8 %)	8/17 (49.1 %)	7/17 (41.2 %)
25 in 5#	2/13 (15.4 %)	6/13 (46.2 %)	5/13 (38.4 %)

RT Radiotherapy

negative predictive value for detecting nodal involvement was 75 %, 55.5 %, 42.9 % and 83.3 % for CT respectively and 25 %, 60 %, 20 % and 66.6 % for TRUS respectively.

The mean blood loss in the RT group was 750 ml; in Group 1 the mean was 772.7 ml and in Group 2, 666.6 ml. The mean blood loss in the non-RT group was 757.1 ml. There was no significant increase in blood loss due to preoperative irradiation. ($p=0.958$) The mean operative time in the RT group was 222.5 min. The mean operative time in Non-RT group was 203.9 min. There was no significant increase in operative time in the irradiated patients. (p value of 0.362) The ease of dissection was assessed by operating surgeon using a 5-point scale. Seven variables—approaches to the pelvis; anterior, posterior and lateral mesorectal dissection, anastomoses, abdomen closure and perineal closure—were scored using the scale. The maximum score possible was 30. Ten patients were assessed by this scale. The median score of the patients was 13. (Range 12–23)

The incidence of acute toxicity to the skin was 5/21 (23.8 %), all of which occurred in Group 2 receiving long schedules of RT. Grade 3 lower gastrointestinal symptoms occurred only in 1 (4.7 %) patient receiving 25 Gy in 5#. (Table 2) There was a higher incidence of perineal wound complications in the RT group – two complete dehiscences, one partial dehiscence and one perineal abscess. One patient who had a complete dehiscence of the perineum had defaulted after radiotherapy for 1 month. He in addition had a complete dehiscence of the abdominal wound in the immediate postoperative period, which required a second surgery under general anaesthesia. This patient also developed septicemia, low total protein and died during the postoperative period. The Perineal wound complications in RT and non-RT patients were comparable (p value = 0.317). (Table 3)

Fourteen patients had undergone definitive surgery. One patient had died in the immediate postoperative period due to septicemia. Eleven (11/13; 84.6 %) of the remaining patients had responded to follow-up and there was no evidence of local recurrence. The mean follow-up was 10.2 months (range = 1–22 months).

Table 2 Incidence of complications in RT patients

	Group 1 ($n=16$)	Group 2 ($n=5$)
Skin		
Grade 0	16	0
Grade 1	0	1
Grade 2	0	4
Lower GI toxicity		
Grade 0	0	0
Grade 1	13	4
Grade 2	2	1
Grade 3	1	0

Table 3 Comparison of postoperative complications in RT and non-RT patients

Complications	RT (APR=12, AR=2)	Non-RT (APR=11, AR=3)
Abdominal wound		
Superficial Infection	3	4
Dehiscence	1	0
Perineal wound		
Superficial Infection	1	1
Dehiscence	3	1

Discussion

The Swedish [2] and Dutch [3] trials have demonstrated the efficacy of the short-term radiotherapy schedule in reducing local recurrences in patients with carcinoma of rectum. The major deterrent in using this modality has been the apprehension of complications arising in the immediate preoperative, intraoperative and postoperative period as a result of radiation. This study was done primarily to address these issues and identify if this management protocol was feasible in our setup.

In our study we had irradiated majority of the patients using 25 Gy in 5 fractions over a period of 5 days. Four other trials had used this regimen—Stockholm I [4], Stockholm II [5], Swedish trial [2] and the Dutch trial [3]. The Biological Effective Dose with this regimen is 40 Gy. Norway trial [6] and the MRC I [7] trial are studies that have used a BED<30 Gy. In the MRC II [8] trial, 40 Gy in 20 fractions (BED=48 Gy) was given. We had employed a two-field (antero-posterior) technique for irradiation of our patients. The Dutch trial, Swedish trial, Stockholm II trial had used the multiple field technique to administer radiation. The Stockholm I [4] trial, MRC I [7] trial, MRC II [8] trial and the Norway trial [6] had used two portals of administration of radiotherapy. In our study the target volume included the area below the L4-L5 level including the anal canal. Lateral fields extended to 2 cm lateral to the true pelvis. In the Stockholm I trial, the irradiated volume included the anus, perineum, rectum, inguinal lymph nodes, obturator foramina and para-vertebral lymph nodes up to the level of L2. In the Stockholm II trial the upper border of radiation was limited to the L4 vertebra. Extension beyond that was thought to be the reason for the higher postoperative mortality (8 %) seen in irradiated patients in the Stockholm I trial.

The accuracies of TRUS and CT were assessed by comparing their staging results with the histopathological staging. The accuracy of T-staging, in our study, was 64.3 % in TRUS. Garcia-Aguilar et al [9], in a study conducted at a single institute, reported the overall accuracy of TRUS for

detecting rectal wall penetration as 69 %. But in their study, 76.4 % of patients had lesions with lower T-stages (T0 to T2). Their accuracy was comparable to ours. But in a meta-analysis by Kwok et al [10], the accuracy of TRUS in detecting rectal wall penetration was 87 %. Their stage-specific accuracy was 92.4 %, 76.7 %, 85.3 % and 83.4 % for T1, T2, T3 and T4 respectively. This demonstrates that for higher stages TRUS was less accurate. In our study, 63.2 % had advanced lesions on pre-RT TRUS. TRUS has also been used to identify nodal disease. The sensitivity, specificity, positive predictive value and negative predictive value for detecting nodal involvement by TRUS were 71 %, 76 %, 69 % and 78 % in Kwok's study and 25 %, 60 %, 20 % and 66.6 % in our study. However these values were 49 %, 82 %, 65 % and 71 % in a subset of patients who had received radiotherapy according to Kwok. TRUS fared poorly in detecting metastatic nodes in our study. Kwok [10] reported accuracy for nodal detection to be 66 % for CT, 72 % for TRUS and 74 % for MRI.

The accuracy of CT scan in evaluating T-stage was 84.6 % in our study. In the meta-analysis by Kwok et al, the accuracy of CT scan in T-staging was reported to be 80 %. Our study had a comparable experience with CT scan. The sensitivity, specificity, positive predictive value and negative predictive value for detecting nodal involvement was 75 %, 55.5 %, 42.9 % and 83.3 % respectively for CT, in our study and 52 %, 78 %, 68 % and 64 % in Kwok's study. The corresponding values in irradiated patient were 35 %, 74 %, 59 % and 52 % in Kwok's study. CT scan showed better ability in predicting lymph nodal involvement and was comparable with other studies.

Down staging has been conventionally demonstrated in long-term schedules of radiation. In the Lyon R90-01 randomized trial [11], employing 39 Gy in 13 fractions, a long interval between preoperative radiotherapy and surgery was associated with a significantly better clinical tumor response (53.1 % in the short interval group v 71.7 % in the long interval group, $p=0.007$) and pathologic down staging (10.3 % in the short interval group v 26 % in the long interval group, $p=0.005$). Dutch trial [3] employed short-term radiotherapy and found no significant difference in tumor classification between irradiated and non-irradiated groups. In our study, there were no significant differences between the pre-RT and post-RT stages as determined by TRUS and CT. Even though the Dutch trial could not demonstrate down staging due to short-term radiotherapy, they found that the mean diameter of irradiated tumours was 4.0 cm compared with 4.5 cm for the non-irradiated tumors ($p<0.001$).

In the short-term schedule compliance has not been a problem. In the Swedish trial 14 of 897 patients had radiotherapy discontinued due to neurotoxicity. In our study, there were no incidences of toxicity, which precluded patients from continuing radiotherapy. The incidence of

acute toxicity to the skin, in our study, was 5/21 (23.8 %), all of which occurred in Group 2 receiving long schedules of RT. This was unacceptable to most patients. However their lesions healed well in time for scheduled surgery. This consideration led us to offer only the short course radiotherapy to subsequent patients, who had no skin reactions (0 %) attributable to radiotherapy. In the Swedish trial [2] employing 25 Gy in 5# in 236 patients, the incidence of skin reactions was 2 %. In the Norway trial [6] (31.5 Gy in 18#), in 159 patients the incidence of skin reactions was 4.5 %. In the Dutch trial [3] there was an incidence of 1.15 % (8/695) grade 1 skin toxicity and <1 % (2/695) grade 2 toxicity.

In our study seventeen patients had grade 1 symptoms of mild diarrhea and three patients had grade 2 symptoms. Grade 3 lower gastrointestinal symptoms occurred only in one (4.7 %) patient receiving 25 Gy in 5#. In the Norway trial (31.5 Gy in 18#), in 159 patients there was a 30 % incidence of diarrhea. In the Dutch trial, there was an incidence of 10.8 % grade 1 toxicity, 2 % grade 2 toxicity and <1 % (1/695) grade 3 toxicity. Concurrent chemotherapy increases gastrointestinal toxicity as seen in INT 0114 trial [12] (22 %) and in the German trial [13] (23 %).

In the Dutch trial, there was no significant difference in median operative time or medial hospital stay between both treatment arms. Total blood loss was slightly increased (100 ml) in the RT group ($p<0.001$). Unique to our study, is an assessment of the operative ease of dissection as ascertained by a 5-point scale. The median score in the RT group was 13 (max. = 30). All of the operating surgeons felt that short-term radiotherapy, in itself, did not hamper the surgical dissection.

Abdominal wound complications arose in 4/14 (28.6 %) patients in the RT and in 4/14 (28.6 %) patients in the non-RT group. The incidence of wound infection in the Swedish trial was 9 % in the irradiated group and 10 % in the non-irradiated group. These rates are lower when compared to ours. The incidence of perineal wound complications was 4 of 12 (33.3 %) in the RT group and 1 of 11 (9.1 %) in the non-RT group. Thus, there was a trend towards more perineal wound complications in the immediate postoperative period. In the Dutch trial, the perineal wound complications following APR was 26 % in the irradiated group and 18 % in the non-irradiated group ($p=0.008$). In the Swedish trial the perineal wound infection rates were 20 % in the irradiated group and 10 % in the non-irradiated group. Our rates are comparable with their findings. But barring the one mortality in this group, other patients had an uneventful recovery from these complications. There were no cases of anastomatic dehiscence in our study. In the Swedish trial there was an incidence of anastomatic dehiscence of 11 % in the irradiated patients and 8 % in the non-irradiated patients. The effect of preoperative radiotherapy on sphincter function

has been studied in one of the prospective studies and is found to be minimal [14]. Irradiated patients in Swedish [2] trial had more ejaculation disorder than non-irradiated patients. But this has been found to equal in both irradiated and non-irradiated patients in MRC-CR07 trial and this has been attributed mainly due to TME [15, 16]. There was one (7.14 %) case of postoperative mortality in our study. In the Dutch trial the in-hospital mortality rate was 4 % in the irradiated patients and 3.3 % in the non-irradiated patients. The higher incidence in our study is due to the small number of patients.

The limitation of our study is in finding out the rectal sphincter function and sexual function after radiotherapy & surgery.

Conclusions

In patients with carcinoma rectum, preoperative short course radiotherapy may not produce significant down staging or downsizing of rectal cancer. Preoperative long course radiotherapy may be associated with higher rates of dermatitis, perineal wound infection. Short course radiotherapy may be associated with lower G I toxicity. CT scan may be more accurate than TRUS in staging of carcinoma rectum. Preoperative short course radiotherapy does not alter the operation technique or blood loss intraoperatively.

References

- Wong RK, Tandan V, De Silva S, Figueredo A (2007) Preoperative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane database Sys Rev* (2):CD00210
- Påhlman L, Glimelius B et al (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. *Swedish Rectal Cancer Trial. N Engl J Med* 336(14):980–987
- Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Dutch Colorectal Cancer Group et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345(9):638–646
- Cedermark B, Johansson H, Rutqvist LE, Wilking N (1995) The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. *Stockholm Colorectal Cancer Study Group. Cancer* 75(9):2269–2275
- Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B, Stockholm Colorectal Cancer Study Group (2001) The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. *Cancer* 92(4):896–902
- Horn A, Halvorsen JF, Dahl O (1990) Preoperative radiotherapy in operable rectal cancer. *Dis Colon Rectum* 33(10):823–828
- The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. *Br J Surg.* (1984) 71(1):21–5
- Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Medical Research Council Rectal Cancer Working Party. *Lancet.* (1996) 348(9042):1605–10
- Garcia-Aguilar J, Pollack J, Lee SH, Hernandez de Anda E, Mellgren A, Wong WD, Finne CO, Rothenberger DA, Madoff RD (2002) Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. *Dis Colon Rectum* 45(1):10–15
- Kwok H, Bissett IP, Hill GL (2000) Preoperative staging of rectal cancer. *Int J Colorectal Dis* 15(1):9–20
- Glehen O, Chapet O, Adham M, Nemoz JC, Gerard JP, Lyons Oncology Group (2003) Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer. *Br J Surg* 90(8):996–998
- Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T et al (2006) Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol* 24(22):3542–3547
- Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, German Rectal Cancer Study Group et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351(17):1731–1740
- Birnbaum EH, Dreznik Z, Myerson RJ, Lacey DL, Fry RD, Kodner IJ, Fleshman JW (1992) Early effect of external beam radiation therapy on the anal sphincter: a study using anal manometry and transrectal ultrasound. *Dis Colon Rectum* 35(8):757–761
- Suppiah A, Hartley JE, Monson JR (2009) Advances in radiotherapy in operable rectal cancer. *Dig Surg* 26(3):187–199, Epub 2009 Jun 3
- Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 373(9666):811–820