The Surgical Outcome of Preoperative Chemoradiation Therapy for Ultra Low Rectal Cancer

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Objective: *To evaluate the surgical outcome of preoperative long-course chemoradiation therapy (PCRT) in patients with ultra low rectal cancer.*
Material and Method: *Medical records of patients with rectal adenocarcinoma located within the length of 5 cm from the anal verge, who underwent elective oncological resection between 2003 and 2006 at Siriraj Hospital, were reviewed. PCRT was performed in some patients based on tumor characteristics and surgeon's decision. Rate of sphincter preservation and other surgical outcomes were assessed.*
Results: *Ninety-three patients with an average age of 60 years were studied. Twenty-seven (29%) received PCRT. There was no difference in demographic data and location of the tumor between PCRT and non-PCRT group. Patients with PCRT had a smaller size of tumor (2.6 vs. 5.0 cm, $p < 0.001$) and better tumor staging ($p < 0.001$). Complete pathological response was found in four patients with PCRT (15%). However, there was no significant difference in SPP rate between PCRT and non-PCRT group (37% vs. 36%, $p = 0.95$). Other surgical outcomes between the two groups were also not different.*
Conclusion: *PCRT did not increase rate of sphincter preservation in patients with low rectal cancer.*

Keywords: *Chemoradiation therapy, Drug therapy, Preoperative care, Radiotherapy, Rectal cancer, Rectal neoplasms, Sphincter preservation*

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The fundamental of surgical management for resectable rectal cancer is to complete clearance of the tumor and draining lymph nodes in mesorectum. Sphincter-preserving procedures (SPP), such as low anterior resection, should be performed if feasible because patients could enjoy a better quality of life, including vitality, sexual function, and physical activity[1]. However, resection of low rectal cancer is associated with a high rate of abdominoperineal resection (APR)[2].

Several approaches have been introduced to increase the likelihood of sphincter preservation in the low rectal cancer including stapled anastomosis, intersphincteric resection and coloanal anastomosis, and preoperative long-course chemoradiation therapy (PCRT). There were controversies whether preoperative chemoradiation therapy (PCRT) could really increase the rate of SPP[3]. Interestingly, many investigators[8,9] reported a high rate of sphincter preservation in low rectal cancer without receiving PCRT, suggesting that PCRT may not be the only factor determining SPP. As the benefits of PCRT on an increased rate of SPP are debatable, patients receiving PCRT could have many potential complications such as bone marrow suppression, gastrointestinal discomfort, and poor wound healing[2].

The aim of the present study was to evaluate the surgical outcome of PCRT on rate of sphincter preservation in patients with low rectal cancer.

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Material and Method

Patients

Retrospective analysis of patients with adenocarcinoma of the lower rectum who underwent elective oncological resection between January 2003 and December 2006 at the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. Low rectal cancer was characterized as a tumor with its lower edge located within 5 cm above the anal verge. The exact length was measured by digital rectal examination and sigmoidoscopy. Patients with recurrent tumor were excluded. The present study protocol was approved by the Institutional Ethics Committee and informed consent was obtained from all patients.

In order to locally control the tumor and increase the possibility of SPP, patients were considered suitable for PCRT if there were no external sphincter involvement, no evidence of distant metastasis, no prior radiotherapy to the pelvis, Eastern Cooperative Oncology Group (ECOG score) between 0-2, granulocyte count $\geq$ 3000 cells/ml, platelet count $\geq$ 100,000/ml, hemoglobin concentration $\geq$ 10 g/ml, serum creatinine less than 1.5 mg/ml, and age over 18 years.

Preoperative chemoradiation therapy

PCRT regimen comprised of_45 Gy in 25 fractions over 5 weeks (1.8 Gy/fraction) using a 3-field belly board technique every 5 days weekly and administration of concurrent chemotherapy; either 5-fluorouracil (200mg/m^2/day) or capecitabine (2,000 mg/m^2/day). Surgery was then performed 4-8 weeks after completion of PCRT.

Surgical procedure

All patients were operated on by surgical staffs in the colorectal unit. Each patient received preoperative mechanical bowel preparation and intravenous prophylactic antibiotics. All patients lay down in the lithotomy position. Standard oncological resection with total mesorectal excision was performed in every patient. Selection of the operation either SPP or APR was left to the surgeon's decision. To perform SPP, macroscopically complete surgical resection and distal margin of at least 1 cm have to be achieved before colorectal anastomosis without pouch formation. To perform APR, extrasphincteric dissection was carried out with primary closure of perineal wound after pelvic drain was placed. Patients were discharged from the hospital when they had no fever, good appetite, and good ambulation. All patients were scheduled for follow-up at 30 days postoperatively.

Statistical analysis

The primary end point was SPP rate. Patients' demographic data including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) status, level of carcinoembryogenic antigen (CEA), tumor characteristics (tumor height from the anal verge, tumor size, TNM staging, resection margin), and treatment-related outcomes (type of operation, operative time, blood loss, postoperative complications, length of hospital stay) were also analyzed.

All data were prepared and complied using SPSS computer program (version 11.0 for Windows). Chi-square test and Mann-Whitney U test were used to compare data between groups with or without PCRT. Mean, standard deviation, range, and percentage were given. A p-value of less than 0.05 was considered statistically significant.

Results

Ninety-three patients were enrolled with the average age of 60 years (range 23-82 years). Twenty-seven patients (29%) received PCRT. There was no difference in age, gender, BMI, ASA status or location of the tumor between PCRT and non-PCRT group (Table 1). Patients with PCRT significantly had a smaller size of the tumor (2.6 vs. 5.0 cm, $p < 0.001$) and better tumor staging ($p < 0.001$). Complete pathological response was found in four patients with PCRT (15%). However, there was no significant difference in SSP rate between PCRT and non-PCRT group (37% vs. 36%, $p = 0.95$). Leakage rate of SPP and other surgical outcomes between the two groups were also the same (Table 2).

Discussion

PCRT has been widely used in the management of rectal cancer because of its convincing advantages. The EORTC 22921 trial[10] including 1011 patients found that PCRT was superior to radiotherapy alone in terms of an increasing rate of pathological response, reduction of local recurrence and slightly better rate of sphincter preservation. However, overall survival is not modified and unfortunately, PCRT may increase acute toxicity. The FFCD 9203 trial[11] including 762 patients also revealed the similar findings except no significant change in SPP rate. As PCRT can reduce intramural tumor spreading, distal resection margin of 1 cm are

Table 1. Comparison of demographic details and tumor characteristics between PCRT and non-PCRT group. Values were given as number (percentage) or mean ± SD

Variables	PCRT (n = 27)	Non-PCRT (n = 66)	p-value
Age (years)	60.3 ± 9.3	60.3 ± 13.9	0.99
Male	19 (70)	36 (55)	0.16
BMI (kg/m^2)	23.3 ± 3.2	22.8 ± 3.9	0.64
ASA status	1.8 ± 0.6	1.8 ± 0.5	0.62
CEA (ng/ml)	62.7 ± 182.9	26.7 ± 73.6	0.48
Tumor located from the anal verge (cm)	4.2 ± 1.1	4.0 ± 1.0	0.78
Maximal tumor size (cm)	2.6 ± 1.2	5.0 ± 2.0	<0.001
TNM staging			<0.001
0	4 (15)	0 (0)	
1	10 (37)	11 (17)	
2	6 (22)	12 (18)	
3	7 (26)	43 (65)	
Positive resection margin	0 (0)	3 (5)	0.58

Table 2. Comparison of SPP rate and other surgical outcomes between PCRT and non-PCRT group. Values were given as number (percentage) or mean ± SD

Variables	PCRT (n = 27)	Non-PCRT (n = 66)	p-value
SSP	10 (37)	24 (36)	0.95
Leakage in SPP	1 (10)	4 (17)	0.69
Overall complications	5 (19)	16 (24)	0.72
Operative time (minutes)	208.0 ± 77.8	219.7 ± 85.4	0.59
Blood loss (ml)	285.0 ± 159.0	452.7 ± 462.3	0.12
Hospital stay (days)	12.6 ± 10.3	11.7 ± 6.0	0.76

acceptable without an increased rate of suture line recurrence[12]. PCRT led to complete pathological response in 10-20%[2]. Hence, theoretically, PCRT could increase a rate of sphincter preservation.

In the present study, the authors found that PCRT could not increase rate of sphincter preservation in patients with low rectal cancer. The authors' finding was compatible with the two prospective randomized trials[6,7], which were specially designed to explore sphincter preservation issue in PCRT. The Lyon R90-01 trials[7] found that PCRT increased SPP rate by only 1%. The Polish trials[6], in 2002, also revealed no benefit of PCRT on SPP rate in spite of 15% rate of complete pathological response in PCRT group. There are several possible explanations for these findings. Firstly, surgeons did not reappraise their indication of APR based on only the clinical tumor response. Secondly, the down-sizing and down-staging of the tumor was too small to influence the surgical decision[13]. Bigger tumor size and higher stage of non PCRT group may be needed to create colonic obstruction, that may encourage to perform surgery in this group quicker, rather than wait for PCRT. Lastly, there could be asymmetrical shrinkage of the tumor-since the bowel wall in the anorectal region is less mobile than the remaining bowel wall, the distance between the lower edge of tumor and the dentate line was relatively unchanged after PCRT[14].

Shorter operative time and less blood loss in the PCRT group may result from the tumor shrinkage, leading to easy deep pelvic dissection and tumor removal. Several investigators have suggested that PCRT is a risk factor for anastomotic leakage. Giuliani et al[15] revealed an increasing leakage rate of 5% in patients with PCRT. A larger study in Sweden by Matthiessen et al[16] showed that PCRT was one of the independent risk factors for symptomatic anastomotic leakage in the multivariate analysis. However, many studies including the authors' experience failed to demonstrate the association between PCRT and a higher

rate of leakage in patients undergoing SPP[17,18]. The authors believed that tension-free bowel anastomosis with good blood supply is the key to success to avoid the anastomotic leakage. This would be a practice by means of high ligation of the inferior mesenteric artery and vein as well as full mobilization of the left-sided colon and splenic flexure.

It is also worth to mentioning about the limitation of the present study. Firstly, it is a non-randomized study, in which selected bias could occur. For example, the surgeon might have a tendency to use PCRT in male patients with large rectal cancer as a bulky tumor in the narrow pelvis results in difficult pelvic dissection and is associated with a high rate of APR[19]. Secondly, sample size of the study is relatively small. Therefore, multicenter, prospective randomized trials should be conducted to investigate the effect of PCRT on SPP rate of the patients with low rectal tumor.

Conclusion

Based on the present study, PCRT did not increase rate of sphincter preservation (SPP) in patients with low rectal cancer. However, larger randomized studies are required before a definite conclusion on this issue can be drawn.

References

1. Cornish JA, Tilney HS, Heriot AG, Lavery IC, Fazio VW, Tekkis PP. A meta-analysis of quality of life for abdominoperineal excision of rectum versus anterior resection for rectal cancer. Ann Surg Oncol 2007; 14: 2056-68.
2. Boonnuch W, Chinswangwatanakul V, Methasate A, Akaraviputh T, Lohsiriwat V, Lohsiriwat D. Does preoperative chemoradiation therapy in locally advanced rectal cancer increase rate of sphincter preserving surgery? a prospective clinical trial. Siriraj Med J 2006; 58: 743-6.
3. Habr-Gama A, Perez RO, Kiss DR, Rawet V, Scanavini A, Santinho PM, et al. Preoperative chemoradiation therapy for low rectal cancer. Impact on downstaging and sphincter-saving operations. Hepatogastroenterology 2004; 51: 1703-7.
4. Kim DW, Lim SB, Kim DY, Kim TH, Jung KH, Kim DH, et al. Pre-operative chemo-radiotherapy improves the sphincter preservation rate in patients with rectal cancer located within 3 cm of the anal verge. Eur J Surg Oncol 2006; 32: 162-7.
5. Rullier E, Goffre B, Bonnel C, Zerbib F, Caudry M, Saric J. Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum. Ann Surg 2001; 234: 633-40.
6. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, 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.
7. Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999; 17: 2396.
8. Guerriero O, Tufano G, Pennetti L, D'Amore E, Sarnella G, Sodano B. Sphincter-saving surgery in low rectal cancer. Chir Ital 2006; 58: 83-92.
9. Rullier E, Zerbib F, Laurent C, Bonnel C, Caudry M, Saric J, et al. Intersphincteric resection with excision of internal anal sphincter for conservative treatment of very low rectal cancer. Dis Colon Rectum 1999; 42: 1168-75.
10. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355: 1114-23.
11. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006; 24: 4620-5.
12. Ota DM, Jacobs L, Kuvshinoff B. Rectal cancer: the sphincter-sparing approach. Surg Clin North Am 2002; 82: 983-93.
13. Ortholan C, Francois E, Thomas O, Benchimol D, Baulieux J, Bosset JF, et al. Role of radiotherapy with surgery for T3 and resectable T4 rectal cancer: evidence from randomized trials. Dis Colon Rectum 2006; 49: 302-10.
14. Bujko K, Kepka L, Michalski W, Nowacki MP. Does rectal cancer shrinkage induced by preoperative radio (chemo) therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol 2006; 80: 4-12.
15. Giuliani D, Willemsen P, Van Elst F, Vanderveken M. A defunctioning stoma in the treatment of lower

third rectal carcinoma. Acta Chir Belg 2006; 106: 40-3.
16. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004; 6: 462-9.
17. Friedmann P, Garb JL, McCabe DP, Chabot JR, Park WC, Stark A, et al. Intestinal anastomosis after preoperative radiation therapy for carcinoma of the rectum. Surg Gynecol Obstet 1987; 164: 257-60.
18. Lee SI, Sohn SK, Park YA. Sphincter-preserving operations without defunctioning stoma. ANZ J Surg 2007; 77: 381-4.
19. Marusch F, Koch A, Schmidt U, Meyer L, Steinert R, Pross M, et al. Importance of rectal extirpation for the therapy concept of low rectal cancers. Chirurg 2003; 74: 341-51.

ผลของการให้เคมีบำบัดร่วมกับการฉายแสงก่อนการผ่าตัดแบบเก็บรักษากล้ามเนื้อหูรูดในมะเร็งลำไส้ตรงส่วนปลาย

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วัตถุประสงค์*: เพื่อประเมินผลของการฉายแสงร่วมกับการให้เคมีบำบัดก่อนการผ่าตัดมะเร็งลำไส้ตรงส่วนปลายต่อการทำผ่าตัด*

วัสดุและวิธีการ*: การศึกษาย้อนหลังระหว่าง ปี พ.ศ. 2546-2549 ในผู้ป่วยมะเร็งลำไส้ตรงส่วนปลายภายใน 5 เซนติเมตรจากปากทวารหนัก ที่ภาควิชาศัลยศาสตร์ โรงพยาบาลศิริราช โดยผู้ป่วยกลุ่มแรกได้รับการฉายแสง (45 Gy in 25 fractions over 5 weeks) ร่วมกับเคมีบำบัด (5-fluorouracil 200 mg/m^2/day หรือ capecitabine 2000 mg/m^2/day) ก่อนได้รับการผ่าตัด 4-8 สัปดาห์ภายหลังจากได้รับเคมีบำบัดและการฉายแสงครบ ผู้ป่วยอีกกลุ่มจะได้รับการผ่าตัดโดยไม่ได้รับการฉายแสงร่วมกับเคมีบำบัดก่อนให้การผ่าตัด วิธีการผ่าตัดของผู้ป่วยทั้งสองกลุ่มขึ้นกับดุลยพินิจของศัลยแพทย์ผู้ทำการผ่าตัด*

ผลการศึกษา*: ผู้ป่วยจำนวนรวม 93 รายมีอายุเฉลี่ย 60 ปี ผู้ป่วย 27 ราย (ร้อยละ 29) ได้รับการฉายแสงร่วมกับเคมีบำบัดก่อนการผ่าตัด ไม่มีความแตกต่างของคุณลักษณะผู้ป่วยและตำแหน่งของมะเร็งในผู้ป่วยที่ได้รับหรือไม่ได้รับการฉายแสงร่วมกับเคมีบำบัดก่อนการผ่าตัด ผู้ป่วยที่ได้รับการรักษาเสริมก่อนการผ่าตัด มีขนาดก้อนมะเร็งเล็กกว่าและระยะของโรคดีกว่า ($p < 0.001$) และมี complete pathological response ร้อยละ 15 แต่ความสำเร็จในการผ่าตัดเก็บรักษากล้ามเนื้อหูรูดทวารหนักไม่มีความแตกต่างกันในผู้ป่วยที่ได้รับหรือไม่ได้รับการฉายแสงร่วมกับเคมีบำบัดก่อนการผ่าตัด (ร้อยละ 37 และ ร้อยละ 36 ตามลำดับ, $p = 0.95$) ผลพวงจากการผ่าตัดในเรื่องอื่น ๆ ก็ไม่มีความแตกต่างเช่นกัน*

สรุป*: การฉายแสงร่วมกับการให้เคมีบำบัดก่อนการผ่าตัดมะเร็งลำไส้ตรงส่วนปลาย ไม่สามารถเพิ่มการผ่าตัดเก็บรักษากล้ามเนื้อหูรูดทวารหนักได้อย่างมีนัยสำคัญทางสถิติ*