Does Preoperative Chemoradiation Therapy in Locally Advanced Rectal Cancer Increase Rate of Sphincter Preserving Surgery? A Prospective Clinical Trial

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ABSTRACT

Objective: To evaluate the influence of preoperative chemoradiation in locally advanced rectal cancer on ability to perform sphincter preserving surgery.

Methods: Between 1998 and 2005, a prospective clinical trial of preoperative chemoradiation therapy (CTX/XRT) that delivered 45 Gy in 25 fractions over 5 weeks with bolus infusion of 5-fluorouracil (200 mg/m^2/day) or capecitabine (2000 mg/m^2/day) was given to 42 rectal cancer patients admitted to the Department of Surgery, Siriraj Hospital, Bangkok, Thailand. The pretreatment stage distribution, as determined by endorectal ultrasonography and computed tomography of the pelvis, included uT3N0 in 90.48% and uT3N1 in 9.52% of cases. Approximately 6 weeks after completion of CTX/XRT, surgery was performed in every patient. The choice of the surgical procedure was based on the surgeon's discretion.

Results: The patient population consisted of 25 males (59.52%) and 17 females (40.48%) who had a median age of 57 years (range 32-79 years). Distal border of the tumors were located at a median of 5 cm (range 2-10 cm) above the anal verge. Thirty cases (71.43%) had distal border of the tumors within 6 cm from the anal verge. The pathological tumor stages were T1N0 in 2 cases (4.76%), T2N0 in 9 cases (21.43%), T2N1 in 4 cases (9.52%), T3N0 in 12 cases (28.57%), T3N1 in 8 cases (19.05%), T3N2 in 2 cases (4.76%) and T4N0 in 1 case (2.38%). The results included 9.52% pathological complete response, 42.86% downstaging and 50% sphincter preservation rate. Of the tumors located < 6 cm from the anal verge, sphincter preservation was accomplished in 30% of the patients. The pretreatment location of distal border of the tumors (< 6 cm vs. > 6 cm from anal verge) was the only factor predictive of sphincter preservation ($p < 0.001$). No local recurrence was detected during the period of follow up (median 23 months).

Conclusion: The administration of preoperative chemoradiation for locally advanced rectal cancer is associated with tolerable toxicity and high rates of tumor downstaging. The preoperative chemoradiation and tumor downstaging do not increase rate of sphincter preservation in locally advanced rectal cancer.

Keywords: Sphinctor preservation; Preoperative chemoradiation; Locally advanced rectal cancer

Siriraj Med J 2006;58: 743-746
E-journal: http://www.sirirajmedj.com

Sphincter preservation is the primary goal of preoperative chemoradiation for locally advanced rectal cancer. Preoperative radiation in combination with chemotherapy, as a radiosensitizer, has been used to cause tumor regression and allow complete resection of the rectal cancer with a sphincter preserving procedure.[1-4] Other advantages for the use of preoperative radiation include a lower total dose of radiation and easier displacement of the small bowel from the radiation field. No excess surgical complications have been reported as a result of preoperative radiation. A survival advantage, largely due to the decreased rates of local recurrence, has also been reported by a Swedish Rectal Cancer Trial.[5]

Our study is aimed to evaluate the influence of preoperative chemoradiation on locally advanced rectal cancer on ability to perform sphincter preserving surgery. Tumor location, pathological characteristics, and rates of local control relative to the surgical procedure performed were also analysed.

MATERIALS AND METHODS

After obtaining approval from our institutional ethics committee, a prospective study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University,

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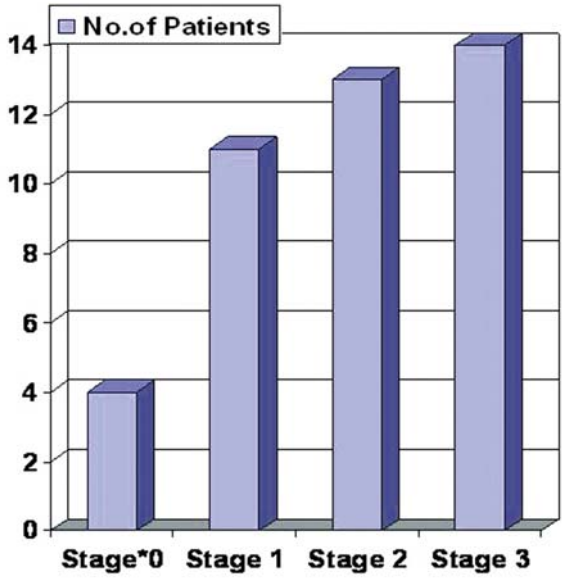


Fig 1. Stages of the retel cancer in the study

Bangkok, Thailand. Forty-two patients with locally advanced rectal cancer were treated with preoperative chemoradiation between January 1998 and April 2005.

Locally advanced rectal cancer was defined as tumor extension through the bowel wall and/or with perirectal nodal involvement without evidence of distant metastases based on clinical and/or radiographic evaluation. Tumors that directly invaded other organs or structures and/or perforated the visceral peritoneum were classified as stage T4.

Eligibility criteria included: primary rectal tumor, clinical stage T3-T4 or N1-N3 according to the TNM 1992 staging system[6]; tumor located with the distal border of the tumor ranging between 2 and 10 cm from the anal verge (measured by using rigid proctoscopy and digital rectal examination); no external sphincter involvement; no evidence of metastases; adenocarcinoma histologic features; no prior chemotherapy or radiotherapy to the pelvis; Eastern Cooperative Oncology Group 0-2 performance score; granulocyte count >3000/ml; platelet count >100,000/ml; hemoglobin concentration >10 g/ml; serum creatinine value within 1.5 mg/ml; age >18 years; and obtained informed consent.

The staging studies included: digital rectal examination, barium enema, complete colonoscopy with biopsy, endorectal ultrasonography (Fig 1), liver ultrasonography, chest x-ray, computed tomography (CT) of the abdomen and pelvis, and serum chemistry.

Preoperative chemoradiation regimen consisted of 45 Gy to the pelvis with 18 mV photons at 1.8 Gy/fraction using a 3-field belly board technique every 5 days weekly with bolus 5-fluorouracil (200 mg/m^2) or capecitabine (2,000 mg/m^2) for 5 weeks. Each week during the course of chemoradiation, acute effects were evaluated.

Surgery was performed 4-6 weeks after completion of chemoradiation. The choice of the surgical procedure (abdominoperineal resection, low anterior resection, coloanal anastomosis) was based on the discretion of two senior surgeons. Total mesorectal excision with at least 1 cm from a distal rectal margin was routinely performed for the sphincter preserving operation (Fig 2). Temporary diver-ting ileostomy after low anterior resection or coloanal anastomosis was performed according to the surgeon's discretion. No pelvic exenteration was performed among this analysis.

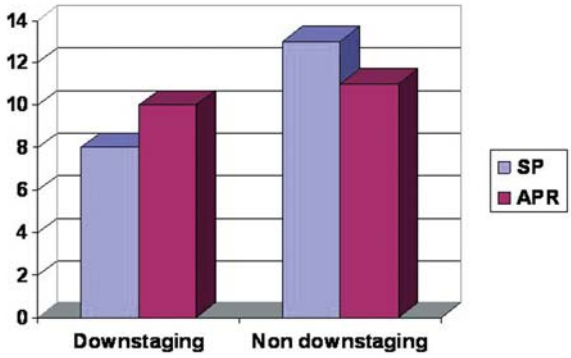


Fig 2. Surgury performed in this study

In addition, patients with histological nodal involvement received postoperative chemotherapy: bolus intravenous 5-fluorouracil 200 mg/m^2/d on days 1-5 and folinic acid 100 mg/m^2 in 6 courses with a 28-day interval. The patients were seen on routine follow-up every 3 months for the first year, every 6 months for the next 2 years, and yearly thereafter. At each follow-up visit, abdominal and digital rectal examination was performed. Liver ultrasonography, chest X-ray, pelvic CT, and carcinoembryonic antigen values were obtained at 3-12 month intervals.[11]

The data were analysed with SPSS software (version 10.0 for Windows). Chi-square test was used to compare proportions, Student's t-test to compare normally distributed data and Mann Whitney U-test to compare data without normal distribution. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

The patient population consisted of 25 males (59.52%) and 17 females (40.48%) who had a median age of 57 years (range 32-79 years). Median follow up was 23 months (range 2 to 55 months).

The pretreatment stage distribution, as determined by endorectal ultrasound (u) in 41 patients (97.62%), included uT3N0 in 37 cases (88.10%) and uT3N1 in 4 cases (9.52%). Endorectal ultrasound was not performed in 1 patient (2.38%) because of an obstructing tumor but CT scan revealed perirectal tumor extension without lymphadenopathy. Therefore, a total of 38 cases (90.48%) were classified as having a stage T3N0 tumor.

Distal border of the tumors were located at a median of 5 cm (range 2-10 cm) above the anal verge. Thirty cases (71.43%) had distal border of the tumors within 6 cm from the anal verge.

Tumor downstaging was defined by a comparison in the pretreatment TN stage (determined by clinical, radiographic and ultrasound staging) to the pathological stage. Tumor downstaging with preoperative chemoradiation was accomplished in 18 cases (42.86%). The extent of disease remained stable in 11 cases (26.19%). Thirteen cases (30.95%) had evidence of tumor progression. All specimens had no circumferential or longitudinal margin involvement.

The pathological tumor stages were T1N0 in 2 cases (4.76%), T2N0 in 9 cases (21.43%), T2N1 in 4 cases (9.52%), T3N0 in 12 cases (28.57%), T3N1 in 8 cases (19.05%), T3N2 in 2 cases (4.76%) and T4N0 in 1 case (2.38%). A complete response to preoperative chemoradiation was pathologically confirmed in 4 cases (9.52%) as shown in Fig 1.

In general, sphincter preservation (low anterior

resection or coloanal anastomosis) was possible in 21 cases (50.00%) and an abdominoperineal resection was required in 21 cases (50.00%). Fifteen cases (60.00%) of the male patients and 6 cases (35.29%) of the female patients underwent abdominoperineal resection. The female patients had more tendency to undergo sphincter preservation, although not statistically different was shown between the groups of male and female patients ($p = 0.21$).

Among the 30 tumors located < 6 cm from the anal verge, sphincter preserving surgical procedures could be performed in 9 cases (30.00%). The others underwent abdominoperineal resection. The pretreatment location of distal border of the tumors (< 6 cm vs. > 6 cm from anal verge) was the only factor predictive of sphincter preservation ($p < 0.001$).

Sphincter preserving surgery was possible in 8 of the 18 cases (44.44%) of the downstaged cases regardless of tumor location. Downstaging proved not predictive of sphincter preservation ($p = 0.53$) as shown in Fig 2. A complete response did not assure sphincter preservation because of other factors, like tumor location. No statistical relationship was observed between pretreatment nodal involvement or pathological staging and sphincter preservation ($p = 0.61$ and $p = 0.27$, respectively).

No patient had major gastrointestinal, skin, hematological or urological acute toxicity in preoperative chemoradiative course. There was no perioperative mortality. Overall surgical complications in this study were 14.29%. Of the 21 patients who underwent sphincter preservation, only 1 patient (4.76%) had anastomotic leakage. There were one (4.76%) presacral bleeding and four (19.05%) delayed healing of perineal wound in patients who underwent abdominoperineal resection.

No local recurrence was detected during the period of follow up. Eight patients died: one from carcinomatosis meningitides two months after resection with coloanal anastomosis; one from brain metastasis eight months after surgery; and the other six from multiple liver metastases 10 -18 months after surgery.

DISCUSSION

Sphincter preservation is the primary goal of preoperative irradiation for locally advanced rectal cancer. The addition of chemotherapy, as a radiation sensitizer, during the course of preoperative radiation is advocated based on the high risk for disseminated disease,[2,7] less positive radial margins[8] and enhance downstaging as well as resectability rate.[9] Preoperative chemoradiation has been shown to reduce both the size and the proliferative activity of rectal tumors when compared to pretreatment levels. Because there is significant tumor regression with preoperative therapy, distal margins of less 1 cm are acceptable and do not result in suture line recurrence.[10] A survival advantage, largely due to the decreased rates of local recurrence, has also been reported in the Swedish Rectal Cancer Trial.[5]

Tumor response and distance of the tumor from the anal verge have previously been reported to predict increased sphincter preservation.[11] Rectal carcinoma responds to preoperative chemoradiation therapy with a 10% to 15% pathologic complete response rate.[9]

The results in our experience included 9.52% pathological complete response, 42.86% downstaging and 50% sphincter preservation rate. Of the tumors located <6 cm from the anal verge, comprising 71.43% of our study population, sphincter preservation was accomplished in 30% of the patients. The indications for sphincter preserving surgery continue to expand with further experience. In one report, where the tumor was located in the distal 2 cm of the rectum, sphincter preservation was achieved in 87% of patients and good sphincter function accomplished in 86% of patients after high-dose preoperative radiation.[12]

Even though the downstaging and pathological complete response rate is comparable to other studies,[4,13] the lower rates of sphincter preservation in our experience as compared to previous reports by others can be explained by a number of factors. First, prospective determination of whether or not an abdominoperineal resection is required can be influenced by a number of variables, including the specific criteria used for sphincter preservation by the surgeon. Specific contraindications for sphincter preservation in our series included pretreatment invasion of the levator muscle. Any residual abnormality in the rectal mucosa after chemoradiation was resected in our study. Second, the most significant predictive factor of sphincter preservation is the distance of the distal border of the tumors from the anal verge, not the tumor staging. Downstaging is mainly determined by the circumferential tumor invasion and nodal status rather than down-sizing which allows more distance between tumor and the anal verge to facilitate sphincter preservation.[13] Third, there was some difference in pelvic morphology between racial phenotypes and sex.[14] Pelvic dissection and gastrointestinal reconstruction was hardly performed in narrow and deep pelvis especially when large bulky tumors were located in.

In our study, there was no local recurrence regardless of type of operation because we performed total mesorectal excision with adequate resection margin in every patient. There was only one anastomotic leakage (4.76%) in sphincter preservation group which spontaneously healed after diverting ileostomy and drainage. Postoperative surgical complications after preoperative chemoradiation was acceptable when compared to those without preoperative therapy except higher rate of delayed healing of perineal wound in patients who underwent abdominoperineal resection.

CONCLUSION

The administration of preoperative chemoradiation for locally advanced rectal cancer is associated with tolerable toxicity and high rates of tumor downstaging. The preoperative chemoradiation and tumor downstaging do not increase the rate of sphincter preservation in locally advanced rectal cancer.

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บทคัดย่อ

การให้เคมีบำบัดร่วมกับการฉายแสงก่อนการผ่าตัดแบบเก็บรักษากล้ามเนื้อหูรูดในมะเร็งลำไส้ตรงชนิดลุกลามเฉพาะที่

วิรุณ บุญนุช พ.บ., วิทูร ชินสว่างวัฒนกุล พ.บ., อัษฎา เมธเศรษฐ พ.บ., ธวัชชัย อัครวิพุธ พ.บ., วรุตม์ โล่ห์สิริวัฒน์ พ.บ., ดรินทร์ โล่ห์สิริวัฒน์ พ.บ.

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วัตถุประสงค์: เพื่อประเมินผลของการให้เคมีบำบัดร่วมกับการฉายแสงก่อนการผ่าตัดในมะเร็งลำไส้ตรงชนิดลุกลามเฉพาะที่ ในการทำผ่าตัดแบบเก็บรักษากล้ามเนื้อหูรูด

วิธีการ: การศึกษาแบบไปข้างหน้าระหว่าง ปี พ.ศ. 2541 ถึง ปี พ.ศ. 2548 ในผู้ป่วยมะเร็งลำไส้ตรงชนิดลุกลามเฉพาะที่จำนวน 42 ราย ที่ภาควิชาศัลยศาสตร์ โรงพยาบาลศิริราช โดยผู้ป่วยจะได้รับการฉายแสง (45 Gy in 25 fractions over 5 weeks) ร่วมกับเคมีบำบัด (bolus infusion of 5-fluorouracil, 200 mg/m2/day หรือ capecitabine, 2,000 mg/m2/day) ก่อนให้การผ่าตัดรักษา ระยะของมะเร็งก่อนให้การรักษาจะถูกประเมินโดย endorectal ultrasonography และ computed tomography of pelvis ซึ่งประกอบด้วย uT3N0 ร้อยละ 90.48 และ uT3N1 ร้อยละ 9.52 ผู้ป่วยจะได้รับการผ่าตัดในระยะเวลาประมาณ 6 สัปดาห์ภายหลังจากได้รับเคมีบำบัดและการฉายแสงครบ วิธีการผ่าตัดขึ้นอยู่กับศัลยแพทย์ผู้ทำการผ่าตัด

ผลการศึกษา: ผู้ป่วยชาย 25 ราย (ร้อยละ 59.52) และผู้ป่วยหญิง 17 ราย (ร้อยละ 40.48) มีอายุระหว่าง 32 ถึง 79 ปี (ค่ากลาง 57 ปี) ขอบล่างของก้อนอยู่ห่างจาก anal verge เป็นระยะ 2 ถึง 10 เซนติเมตร (ค่ากลาง 5 เซนติเมตร) พบผู้ป่วยในระยะของโรคทางพยาธิวิทยาดังนี้ T1N0 2 ราย (ร้อยละ 4.76), T2N0 9 ราย (ร้อยละ 21.43), T2N1 4 ราย (ร้อยละ 9.52), T3N0 12 ราย (ร้อยละ 28.57), T3N1 8 ราย (ร้อยละ 19.05), T3N2 2 ราย (ร้อยละ 4.76) และ T4N0 1 ราย (ร้อยละ 2.38) ผลการรักษาประกอบด้วย ผลตอบสนองดีเยี่ยม (pathological complete response) ร้อยละ 9.52 ลดระยะของโรคได้ (downstaging) ร้อยละ 42.86 และสามารถผ่าตัดเก็บรักษากล้ามเนื้อหูรูดได้ร้อยละ 50 ตำแหน่งขอบล่างของก้อนก่อนให้การรักษาเป็นองค์ประกอบเดียวที่บ่งชี้ถึงการผ่าตัดแบบเก็บรักษากล้ามเนื้อหูรูดได้อย่างมีนัยสำคัญทางสถิติ พบว่าไม่มีการกลับเป็นซ้ำในระหว่างติดตามการรักษา (ค่ากลาง 23 เดือน)

สรุป: การให้เคมีบำบัดร่วมกับการฉายแสงก่อนการผ่าตัดในผู้ป่วยมะเร็งลำไส้ตรงชนิดลุกลามเฉพาะที่ สามารถลดระยะของโรคได้และมีผลข้างเคียงน้อย แต่ไม่สามารถเพิ่มการผ่าตัดเก็บรักษากล้ามเนื้อหูรูดทวารหนักได้อย่างมีนัยสำคัญทางสถิติ