Transabdominal Transanal Resection of Distal Rectal Cancer after High Dose Preoperative Radiotherapy: a Chinese Experience in Preserving Sphincter Function

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Key words: rectal cancer, sphincter preservation, radiotherapy

Abstract

Background: The combination of high dose preoperative radiotherapy and transanal abdominal transanal radical proctosigmoidectomy and colo-anal anastomosis as a sphincter-preserving method has never been performed in mainland China.

Objectives: To assess the feasibility and efficacy of high dose preoperative radiotherapy and TATA as a sphincter-preserving method in Jiangsu, an economically well-developed region of China with a population of 70 million people.

Methods: From September 1994 to September 2000, 25 consecutive patients with pathologically confirmed distal rectal adenocarcinoma were treated preoperatively with a total dose of 45–46 Gy at 1.8–2.0 Gy per fraction during 5 weeks. Sphincter-preserving surgery by TATA was performed 4–6 weeks after radiotherapy.

Results: Acute toxicity of preoperative radiotherapy was tolerable. Eight percent of the patients presented pathologic complete tumor response after preoperative radiotherapy. All patients underwent TATA as scheduled. During a median follow-up of 70 months, the 5 year survival rate was 88%. The 5 year survival rate for those tumors down-staged to pathological T0 or to pT1 was 100%.

Conclusions: High dose preoperative radiotherapy and TATA as a sphincter-preserving method was feasible and efficient in Chinese patients with distal rectal cancer. In this study, the subset of patients with a good response to radiotherapy had a better clinical outcome.

IMAJ 2006;8:675–678

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With the dramatic changes in socioeconomic circumstances and lifestyles in mainland China in the past two decades, the mortality rate from colorectal cancer began to increase from 1995, especially in urban areas [1]. However, aside from these external influences, there are racial differences between Caucasians and Chinese with regard to colorectal cancers [2]. Chinese patients are more likely to suffer from distal colorectal cancer (74% of Chinese patients vs. 63% of Caucasian patients) and develop the disease at a significantly earlier age than Caucasians (mean age at diagnosis 48 years in Oriental vs. 69 years in Caucasian patients). In Chinese distal rectal cancer patients, 81–98% of lesions were located within 7 cm from the anal verge [3].

In terms of treatment, preoperative therapy has become standard in Europe and North America. The potential advantages of the preoperative approach include decreased pelvic recurrence, improved overall survival, and sphincter preservation. One approach attempted was the administration of high dose external radiotherapy preoperatively, which not only achieved down-staging of the tumor but also increased the safety of a sphincter-preserving procedure [4-10]. The feasibility of this treatment has been confirmed elsewhere [11]. That study showed that 5 year Kaplan-Meier actuarial survival was 85% with local recurrence around 14%, and the optimal surgical approach was transanal abdominal transanal radical proctosigmoidectomy and colo-anal anastomosis [11]. However, this method has never been attempted in mainland China.

We report our experience with high dose preoperative radiotherapy and sphincter preservation surgery with TATA in a group of distal rectal cancer patients in Jiangsu. [General information on Jiangsu province can be found on the website: http://english.peopledaily.com.cn/data/province/jiangsu.htm.] We encountered acute toxicity and down-staging effects following radiotherapy, and complications and sphincter function after TATA and during long-term follow-up in all patients.

Patients and Methods

Patients entering the study had histologically diagnosed rectal adenocarcinoma. All patients were initially considered operable, with distal tumor extent within 5 cm of the anal verge. We recruited men or women younger than 70 years of age with Eastern Cooperative Oncology Group performance status of 2 or more and adequate hematologic, renal and liver function. Written informed consent was required from all patients. Patients were excluded from the study if they had had previous anticancer treatment, synchronous colonic tumor, any previous history of malignant tumor, inflammatory bowel disease or ischemic heart disease, or if they were pregnant. The study protocol was approved by the Ethics Committee of Jiangsu Cancer Hospital and Research Institute.

The distance between the anal verge and inferior edge of the cancer was assessed by proctoscopy and digital examination. We established the Tumor Node Metastasis staging with maximum possible accuracy.

Treatment

Treatment consists of radiotherapy and surgery. Patients received

TATA = transanal abdominal transanal radical proctosigmoidectomy

preoperative high dose radiation therapy using a three-field technique. Dosimetry was optimized using a two-dimensional treatment planning system on the basis of CT scans. The whole target volume received a total dose of 45 Gy at 1.8–2.0 Gy per fraction in 5 weeks. The National Cancer Institute Common Toxicity Table (Version 2.0) was used to report and grade acute toxicity in this study.

TATA was performed 4–6 weeks after the completion of radiotherapy. Chemotherapy was not administered preoperatively. The protocol of this study followed the Jefferson Sphincter Preservation Program with minor modification [5,6]. TATA has become well recognized for sphincter preservation of distal rectal cancer since it was first performed in 1984 and has been described in detail elsewhere [6,11]. Key features of TATA include resection of the entire rectum as well as sigmoid, a distal cull of 2 cm or less and no radiated descending colon used for the low rectal or colo-anal anastomosis. Along with the recognition and development of total mesorectal excision [12], the TME technique was used in TATA, which included sharp dissection within the true pelvis around the integral mesentery under direct vision, envelopment of the entire mid-rectum, and preservation of the hypogastric plexus.

Pathologic examination

Resected specimens were opened anteriorly and pinned to a corkboard for fixation. After fixation, the area of the tumor was sliced transversally. Slices in which the tumor was close to the circumferential resection margin and slices with areas marked by the surgeon as suggestive of incomplete tumor removal were embedded. Margins, residual tumor, and lymph nodes were carefully examined by two pathologists. Tumor at the circumferential resection margin or a minimal distance of 1 mm or less between the tumor and CRM was defined as CRM-positive. The operative specimen was staged according to the TNM staging system (Pathologic TNM classification, International Union Against Cancer, 1987). Complete response was defined as the absence of any residual tumor cells detected in the operative specimen.

Quality control

Surgeons participating in this study in the Jiangsu Cancer Hospital and Research Institute attended courses and were monitored by a specially trained instructor surgeon who had accumulated experience in the treatment protocol [11]. All surgical procedures were supervised by this surgeon. The results of histopathologic examination of all specimens were reviewed by a supervising pathologist.

Patient monitoring and follow-up

Once a week during radiotherapy we monitored systemic toxicities by blood assessments and organ function tests, as well as adverse effects within radiated fields (including diarrhea, abdominal abscess, hemafecia and skin change). Before surgery, tumor conditions were reevaluated by abdominal and pelvic CT scans, as well as by digital examination. Response to radiotherapy was assessed by comparison with the initial tumor size before radiation.

After surgery, all patients were closely followed at 3–6 monthly intervals for patterns of recurrence and metastasis based on patient symptoms, physical examination, carcinoembryonic antigen level, chest X-ray, and abdominal and pelvic CT scans. Local and distant recurrence was confirmed radiologically and checked by a radiation oncologist and a participating surgeon.

Statistical analysis

The aim of this study on distal rectal cancer was to evaluate the feasibility of a sphincter-preserving regimen. The primary endpoints were acute toxicity of radiotherapy, and complications of TATA. Our secondary objectives were tumor response rate after radiotherapy, 5 year survival, and recurrence rate. Survival was estimated from the start of treatment using the Kaplan-Meier product limit method. Data on patients who were alive were censored at the time of the last follow-up. All calculations were conducted by using STATA (Stata Corp. Stata Statistical Software. Release 6. Stata Corporation. College Station, TX, 1999).

Results

From September 1994 to September 2000, 25 consecutive patients (13 males, 12 females; mean age 50.6 years) with primary cancers involving the distal rectum (up to 5 cm or less from the anal verge) were enrolled in the study and underwent high dose preoperative radiation and TATA in the Department of Surgery of Jiangsu Cancer Hospital & Research Institute, China. Characteristics of the study population are given in Table 1. Five patients (20.0%) were less than 40 years old. All patients completed radiotherapy without modification, and all underwent TATA after a 4–6 week rest period, fulfilling the protocol.

Table 1. Patients' characteristics: 1994–2000, Jiangsu Cancer Hospital and Research Institute

No. of patients	25
Age (yrs)	
≤ 40	5
40–60	12
≥ 60	8
Mean	50.6
Gender	
Male	13
Female	12
Distance between tumor and anal verge	
5 cm	14
4 cm	9
≤ 3	2
Histopathology	
Well differentiated	1
Moderately differentiated	18
Undefined	6

TME = total mesorectal excision
CRM = circumferential resection margin
TNM = Tumor Node Metastasis (staging)

Table 2 lists the effects and toxicity of radiotherapy. The maximum mean tumor dimension obtained from endoscopic measurement before radiation and from freshly resected tumor specimen was 3.1 cm (95% confidence interval 2.9–3.4) and 2.1 cm (95% CI 1.8–2.5 cm), respectively, with statistical significance ($P < 0.01$). Partial response was defined as a 50% reduction in the product of the two perpendicular diameters of the primary tumor. Such response was observed in 6 patients (24%); in addition, two patients achieved complete response (8.0%). NCI grade 2/3 radiotherapy-related toxicity was detected in 8 patients (32%). All recovered without special treatment.

Table 2. Effect and toxicity of radiotherapy: 1994–2000, Jiangsu Cancer Hospital and Research Institute

No. of patients	25
Maximum size of tumor before radiotherapy	
2–2.5 cm	3
3–3.5 cm	18
4–4.5 cm	4
Maximum size of tumor after radiotherapy	
0 cm	2
1–1.5 cm	6
2–2.5 cm	10
3–3.5 cm	6
4–4.5 cm	1
Toxicity of radiotherapy (NCI-CTC grade)	
1	11
1–2	6
2	7
3	1

NCI-CTC: National Cancer Institute Common Toxicity Criteria.

Surgical complications

TATA was performed in all 25 patients, with a median interval time after radiotherapy of 5 weeks (range 4–6 weeks). In all cases, a total gross tumor resection with no macroscopic residual disease was possible. No operative mortality occurred in this group. Three patients developed anastomotic leak, and a diverting stoma was considered necessary when the leak was confirmed. Incontinence was experienced by four patients and permanent colostomy was constructed. Twenty-one patients had acceptable sphincter function as defined by Park's criteria.

Pathologic examination of operative specimens

In two patients no residual cancer cells could be identified and tumor was staged pathologic T0 N0 or pathologic CR (8%). In three patients (12%) with incomplete resection, microscopic tumor remained after resection of gross disease [Table 3]. Positive lymph node metastases were present in 3 patients (12%). CRM was examined in all patients and was found to be free of cancer cells in all 25 patients. There was no involvement of the distal margin.

Table 3. Patients' condition after surgery: 1994–2000, Jiangsu Cancer Hospital and Research Institute

Pathologic stage	No. of patients	Local recurrence	Metastasis	Died
pT0 N0 M0	2	0	0	0
pT1 N0 M0	3	0	0	0
pT2 N0 M0	8	0	0	0
pT3 N0 M0	5	0	0	0
pT4 N0 M0	4	1	1	2
pT* N+M0	3	0	1	1

* With incomplete resection, margin histologically involved, microscopic tumor remains after resection of gross disease.

Survival and local recurrence

After a median follow-up of 70 months (range 22–100 months), the overall survival rate was 88%. One patient developed liver metastasis after 11 months, another had lung metastasis after 2 years, and a third with T4 N0 M0 developed local recurrence after 10 months. These three patients died.

Discussion

Although sphincter-preserving treatment for distal rectal cancer has aroused great interest, no standard schedule has been universally adopted. This study was undertaken to assess the feasibility of the current high dose preoperative radiation and TATA as a sphincter-preservation method among Oriental people in Jiangsu, China. Acute toxicity of high dose preoperative radiation was well tolerated; all patients underwent TATA as scheduled. However, anastomotic leakage was found to be a major clinical problem in rectal anastomosis. We know that a high index of suspicion in clinical practice is highly associated with detection of anastomotic leaks. The reported leakage rate after TATA was 6% [5]. It should be noted that 3 of our 25 patients (12.0%) required a temporary colostomy postoperatively because of anastomotic leakage. A possible explanation is the short interval between the completion of radiotherapy and TATA. Previous reports concluded that a long interval could increase tumor down-staging and the chance of sphincter-preserving surgery and decrease surgical complications. Eight weeks was considered an ideal interval [10]. Another possible explanation is that we did not routinely perform temporary colostomy and we used the TME technique in TATA. TME removes the pain-sensitive peritoneum, which prevents early detection of anastomotic leak [13]. Therefore, we recommend a diversion if there is any doubt regarding the quality of the anastomosis; we routinely perform a temporary colostomy.

The 88% 5 year actual survival rate is comparable to that in other ethnic groups, where the figure was 85% for TATA [11]. In our study, only one patient developed local recurrence (4%), which could be attributed to the recognition and wide use of TME; four patients needed permanent fecal diversion due to incontinence, and the remaining patients had acceptable sphincter function; patients whose tumors were down-staged to pathologic T0 and pT1 by preoperative radiotherapy seem to have an excel-

CI = confidence interval
NCI = National Cancer Institute

lent outcome, namely, 100% 5 year survival rate and no local recurrence at a median follow-up of 70 months.

In conclusion, our study demonstrates the feasibility and efficiency of preoperative high dose radiotherapy with TATA as a sphincter-preserving method in the treatment of selected rectal cancer patients in mainland China.

Acknowledgments. This work was supported by a research grant (H9526) from the Health Bureau of Jiangsu Province.

References

1. Yang L, Parkin DM, Li L, et al. Time trends in cancer mortality in China: 1987-1999. *Int J Cancer* 2003;106:771–83.
2. Qing SH, Rao KY, Jiang HY, et al. Racial differences in the anatomical distribution of colorectal cancer: a study of differences between American and Chinese patients. *World J Gastroenterol* 2003;9:721–5.
3. Liu Y. Colorectal cancer. In: Tang ZY, ed. Modern Oncology. 1st edn. Shanghai: Shanghai Yi Xue Chu Ban She, 1993:523–4.
4. Marks G, Mohiuddin M, Borenstein BD. Preoperative radiation therapy and sphincter preservation by the combined abdominotranssacral technique for selected rectal cancers. *Dis Colon Rectum* 1985;28:565–71.
5. Marks G, Mohiuddin M, Goldstein SD. Sphincter preservation for cancer of the distal rectum using high dose preoperative radiation. *Int J Radiat Oncol Biol Phys* 1988;15:1065–8.
6. Marks G, Mohiuddin M, Masoni L. The reality of radical sphincter preservation surgery for cancer of the distal 3 cm of rectum following high-dose radiation. *Int J Radiat Oncol Biol Phys* 1993;27:779–83.
7. Mohiuddin M, Marks G. High dose preoperative irradiation for cancer of the rectum, 1976-1988. *Int J Radiat Oncol Biol Phys* 1991;20:37–43.
8. Gerard JP, Chapet O, Nemoz C, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. *J Clin Oncol* 2004;22:2404–9.
9. Rouanet P, Fabre JM, Dubois JB, et al. Conservative surgery for low rectal carcinoma after high-dose radiation. Functional and oncologic results. *Ann Surg* 1955;221:67–73.
10. Francois Y, Nemoz CJ, Baulieux J, 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.
11. Bannon JP, Marks GJ, Mohiuddin M, et al. Radical and local excisional methods of sphincter-sparing surgery after high-dose radiation for cancer of the distal 3 cm of the rectum. *Ann Surg Oncol* 1995;2:221–7.
12. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;i:1479–82.
13. Karanjia ND, Corder AP, Bearn P, et al. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. *Br J Surg* 1994;81:1224–6.

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