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

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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 these 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.

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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...
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 cuff 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>
<thead>
<tr>
<th>Table 1. Patients’ characteristics: 1994–2000, Jiangsu Cancer Hospital and Research Institute</th>
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<tr>
<td><strong>No. of patients</strong></td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
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<tr>
<td>≤ 40</td>
</tr>
<tr>
<td>40–60</td>
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<tr>
<td>≥ 60</td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Distance between tumor and anal verge</strong></td>
</tr>
<tr>
<td>5 cm</td>
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<td>4 cm</td>
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<tr>
<td>≤ 3</td>
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<tr>
<td><strong>Histopathology</strong></td>
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<tr>
<td>Well differentiated</td>
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<td>Moderately differentiated</td>
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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.

**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.

**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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 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 downstaging and the chance of sphincter-preservation 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 postoperatively because of anastomotic leakage. A possible explanation is the short interval between the completion of radiotherapy and TATA.
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.

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References

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**Capsule**

### Origin and adaptation of HIV

The origins of the human immunodeficiency virus type-1 (HIV-1) can be traced to the simian immunodeficiency virus (SIV) in primates. Nevertheless, the strain of SIV most closely related to HIV has been detected only occasionally in captive chimpanzees, and a recognizable reservoir in wild apes has been lacking. Studying endangered primates in their natural habitat, Keele et al. (Science 2006;313:523) detected antibodies directed against SIV, as well as SIV nucleic acid in fecal samples, from wild-living species of chimpanzee, and found infection prevalences as high as 35%. Comparisons of the HIV and SIV genomes and phylogeographic clustering of the newly identified SIV strains allowed the origins of present-day human HIV-1 virus groups to be traced to distinct chimpanzee communities. In a related review, Heeney et al. (p. 462) discuss HIV in humans and consider how host factors are contributing to the evolution of resistance to the virus.

Eitan Israel

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**Capsule**

### Linking the clock and the cell cycle

The circadian clock is linked to the cell cycle in ways that are not clear. Pregueiro et al. investigated the relation between these two fundamental cellular processes in the fungus Neurospora. When a gene called period-4 (prd-4) contains a mutation, Neurospora’s clock runs with a shorter period. The protein PRD-4 is orthologous to checkpoint kinase 2, a mammalian cell cycle regulator, and PRD-4 is both regulated by and regulates the circadian clock. DNA damaging agents can reset the clock in a time-of-day dependent manner, and this circadian-phase resetting is wholly dependent on PRD-4.

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