What is the optimal treatment in clinical stage T3N0M0 rectal cancer?

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Summary

Purpose: Some previous studies suggested that certain rectal cancer patients with stage T3N0 and favorable features may be adequately treated with surgery and adjuvant chemotherapy. However, the optimal management of clinical (c) T3N0 rectal adenocarcinoma based on preoperative imaging is unclear. In this study, we aimed to determine the frequency of lymph node metastases in patients clinically staged as T3N0 rectal adenocarcinoma following preoperative chemoradiotherapy (CTR).

Methods: The medical records of 105 patients with clinico-imaging stage T3N0M0 rectal cancer who received preoperative CRT between 2004-2011 were retrospectively analyzed. Chemotherapy used concurrently with preoperative radiotherapy (RT) was protracted 5-fluorouracil (5FU) infusion.

Results: Twenty-seven percent of the patients clinically staged as T3N0 before preoperative CRT had pathological (p) lymph node involvement on surgical material. The rate of pathological lymph node involvement was 0% in pT1, 20% in pT2 , 35% in pT3 and 34% in pT4 patients. A significant association was demonstrated between pT stages and pN status (p=0.03).

Conclusion: Our study demonstrated that the accuracy of preoperative imaging for staging rectal cancer is limited because at least 27% of the patients may have undetected lymph node involvement after preoperative CRT in surgical material.

Key words: clinical T3, N0 rectal adenocarcinoma, preoperative imaging, understaged

Introduction

Locally advanced rectal cancer (LARC) has a high local recurrence risk due to the absence of surrounding serosa. Technical difficulties in obtaining wide surgical margins of resection also increase the risk of recurrence. Surgical resection is the cornerstone of curative treatment for LARC. For patients with larger or more invasive tumors, preoperative CRT has been utilized to promote tumor regression in an attempt to convert a planned abdominoperineal resection (APR) to a sphincter-sparing surgical procedure. Combined modality therapy consisting of surgery, radiotherapy and chemotherapy is recommended for the majority of patients with stage II and III rectal carcinoma. The German Rectal Cancer Study Group compared preoperative vs postoperative CRT in the treatment of clinical stage II/III rectal cancer. Results of this study indicated that preoperative CRT was associated with significant reduction in local recurrence and treatment-associated toxicity; however, there was no overall survival difference [1]. One possible drawback of preoperative CRT is overtreatment of early lesions which would not require adjuvant therapy [1,2]. The German study demonstrated that 18% of the patients staged clinically by endorectal ultrasound (ERUS) as having cT3, cT4 or node positive rectal cancers were overstaged [1]. Although RT has been associated with

decreased local recurrence rate of rectal cancer, it has also been associated with increased toxicity such as hematologic toxicity, and radiation-induced injury relative to surgery [3,4]. Some previous studies suggested that some patients with disease carrying a lower risk of local recurrence, such as proximal rectal cancer, clear surgical margin, stage T3N0M0 and favorable features may be adequately treated with surgery and chemotherapy [3,5,6]. However, Guillem et al. demonstrated that 22% of rectal carcinoma patients who received preoperative CRT and were staged as cT3N0M0 disease by either ERUS or magnetic resonance imaging (MRI) had undetected lymph node metastases [2]. Additionally, Lombardi et al. demonstrated that pathological analyses showed lymph node involvement in 28% of patients with clinical stage T3N0M0, suggesting that many patients are understaged, and would benefit from preoperative CRT [7]. However, optimal management of clinical T3N0M0 rectal adenocarcinoma based on preoperative imaging (ERUS and MRI) is unclear. In this study, we aimed to determine the incidence of lymph node metastases among patients with clinical stage T3N0M0 after preoperative CRT from resected pathological specimens of rectal adenocarcinoma.

Methods

Patients

The medical records of 105 patients with clinical stage T3N0M0 rectal cancer who had received preoperative CRT between 2004-2011 were retrospectively analyzed. Patients with histological diagnosis of rectal adenocarcinoma were enrolled in the study, provided that the tumor was located 15 cm distal to the anal verge. Preoperative staging was performed either with thoracic and abdominal computed tomography (CT) or abdominal and pelvic MRI and ERUS. The distance of the inferior aspect of the tumor from the anal verge was determined by rigid proctoscopy and colonoscopy. The clinical stage was determined from the findings on MRI, CT and ERUS. MRI and ERUS were performed to assess the depth of local tumor invasion. Patients were not included in the study if they had metastatic disease, positive surgical margins or incomplete CRT. Patients who had not undergone surgery for various reasons were excluded. Written informed consent of the patients or their next of kin was obtained prior to the study.

Imaging techniques
Thoracic and abdominal computed tomography

Diagnostic CT of the chest and abdomen/pelvis was

performed. Images with 40×0.72 mm collimation were obtained. Axial, coronal and sagittal reformations with different slice thicknesses were acquired using maximum intensity projection (MIP)+ multiplanar reformation (MPR) before and after administration of iomeprol contrast medium 1 ml/kg (60–100 ml) from the xiphoid process to the pubic symphysis within venous, early arterial and portal phases for the abdomen and pelvis. For the thorax, axial images with 40×0.72 mm collimation and coronal and sagittal reformations using MIP+MPR before and after administration of 1 ml/kg (60–100 ml) iomeprol contrast medium were obtained from the thoracic inlet to the inferior of the suprarenal glands. Lymph node metastases were considered to be present if at least one node with a diameter of 1 cm was found, or two or more nodes were demonstrated, irrespective of their size.

ERUS

Ultrasound T stage was determined according to the 5-layer model proposed by Hildebrandt and Feifel [8]. Circular hypoechoic structures of at least 3mm in diameter were classified as malignant lymph nodes. Nodes with a diameter<3mm or nodes with central hyperechogenicity were considered benign.

MRI

Imaging was performed by a 1.5 Tesla MR device using endorectal and pelvic phased-array coil and spinal coil was activated at the same time. MRI diagnosis of T3 lesions was based on the presence of tumor signal intensity extending through the muscle layers into the perirectal fat. Lymph nodes with either heterogeneous signal intensity or irregular borders were considered to be suggestive of metastatic disease, regardless of node size [9].

Treatment

Chemotherapy used concurrently with preoperative RT consisted of protracted 5-fluorouracil (5FU) infusion (225 mg/m²/day). Four cycles of postoperative adjuvant bolus 5FU (425 mg/m²/day) and leucovorin (20 mg/m²/day) (Mayo regimen) on days 1-5 every 28 days were administered to the patients in all cases. Eighty-two percent of the patients received 50.4 Gy RT and 18% received 45 Gy in 5 weeks. Surgical resection was considered 6-8 weeks after completion of preoperative CRT. APR or sphincter-sparing surgery was performed according to the surgeon's preference. Surgical resection included total mesorectal excision. Tumors in the upper and middle rectum were managed with low anterior resection (LAR), coloanal anastomosis and preservation of the anal sphincter. Tumors in the distal rectum were usually managed with APR, which obligates permanent colostomy with high rate of surgical complications.

Pathological examination

All examinations were performed by a pathologist specialized in colorectal cancers.

The 6th edition of the American Joint Committee on Cancer TNM system was used for staging [10]. If viable tumor cells were absent in the resected specimen, pathologic complete response was confirmed.

Statistics

Statistical analyses were performed using SPSS for Windows version 15.0 (standard version) software package. Quantitative (numerical) data were expressed as mean ± standard deviation (SD). For two-group comparisons, paired Student's t-test or when necessary Mann-Whitney U test were used. For non-numerical data, Yates' corrected chi-square test and Fisher's exact test were used when they were suitable for 2x2 contingency tables, Analysis of correlations between numerical parameters was made using Spearman's (rho) correlation test. For the comparison of groups, Student's t-test or one-way or multi-factor analysis of variance (ANOVA) was used.

Results

Patients

A total of 105 patients (44 females, 61 males) were studied. Median age at diagnosis was 58 years (range 26–76). Median distance of the tumor from the anal verge was 6 cm (range 0–15). Staging of cases was performed by MR plus CT in 57 patients (54%), MR plus ERUS in 23 patients (22%) and ERUS plus CT in 25 patients (24%). As for the surgical procedures, 35 patients (33%) underwent APR and 70 patients (67%) LAR. The interval between CRT and surgery ranged from 4 to 12 weeks, with a median of 7 weeks. Patient characteristics are summarized in Table 1.

Pathological analysis

The median number of lymph nodes harvested was 11 (range 3–35). After preoperative CRT, of all 105 patients, 20 (19%) of them achieved pCR of the primary tumor site (pT0) and the regional lymph nodes. Overall, pathologic analysis showed presence of lymph node involvement in 28 of 105 patients (27%). The rate of lymph node involvement was 20% (2/10) in pT2 patients, 35% (25/70) in pT3 patients and 34% (1/3) in pT4 patients. A significant association was demonstrated between pathologic stages and lymph node status (pN) (p=0.03). There were no statistical significant associations between lymph node involvement and patient age, gender, number of lymph node

Table 1. Clinical characteristics of the 105 study patients

Characteristics	N (%)
Age (years), median (range)	58 (26-75)
Sex	
Males	61 (58)
Females	44 (42)
Distance from anal verge (cm), median (range)	6 (0-15)
Imaging used for staging	
MRI+CT	57 (54)
MRI+ERUS	23 (22)
CT+ERUS	25 (24)
Type of surgery	
LAR	70 (67)
APR	35 (33)
Time to surgery (weeks), median (range)	7 (4-12)
Pathologic T stage	
pT0	20 (19)
pT1	2 (2)
pT2	10 (10)
pT3	70 (66)
pT4	3 (3)
Lymph node harvested, median (range)	11 (3-35)

LAR: low anterior resection, APR: abdominoperineal resection, MRI: magnetic resonance imaging, CT: computerized tomography, ERUS: endorectal ultrasound

harvested, distance from the anal verge and imaging modality of preoperative CRT. Tumor characteristics in relation to the lymph node-positive and lymph node-negative groups are shown in Table 2.

Discussion

Following the 1990 National Institutes of Health Consensus Conference, adjuvant chemoradiation for all pT3 and/or pN+ rectal adenocarcinomas has become the standard of care [11]. However, several previous studies demonstrated that patients undergoing sharp mesorectal resection for pT3N0M0 stage rectal cancer with favorable pathologic features experience a low recurrence rate after surgery alone and it was suggested that these patients may not benefit significantly from postoperative CRT [12-15].

In the study by Gunderson et al., patients with pT3N0M0 stage rectal cancer had been identified as a prognostic subgroup at intermediate risk, further suggesting that postoperative CRT may be excessive for some patients with T3N0M0 disease [5]. Park et al. in their retrospective study demonstrated that adjuvant RT did not seem to provide

Table 2. Association of positive/negative lymph nodes and tumor characteristics /clinical variables

Characteristics	Lymph node- positive N=28 (27%) N (%)	Lymph node- negative N=77 (73%) N (%)	p-value
Age (years), median (range)	57 (32-76)	58.5 (26-75)	0.2
Sex			0.1
Males	14 (52)	47 (60)	
Females	13 (48)	31 (40)	
Imaging used for clinical staging			
MRI+CT	15 (53.5)	42 (54.5)	0.6
MRI+ERUS	6 (22)	17 (22)	
CT+ERUS	7 (25)	18 (23)	
Type of surgery			0.28
LAR	19 (68)	51 (66)	
APR	9 (32)	26 (34)	
Distance from anal verge, cm (range)	6 (0-15)	7 (3-15)	0.15
Lymph node harvested	12 (6-28)	11 (3-35)	0.4
Depth of tumor invasion			0.03
pT0	0	20 (100)	
pT1	0	2 (100)	
pT2	2 (20)	8 (80)	
pT3	25 (35)	45 (65)	
pT4	1 (34)	2 (66)	

For abbreviations see footnote of Table 1

additional benefit in reducing the recurrence rate of T3N0 (stage IIA) rectal cancer and suggested that the role of RT needs to be carefully evaluated in selected patients with stage II A rectal cancer [16].

The German Rectal Cancer Study Group compared preoperative CRT with postoperative CRT for the treatment of clinical stage T3T4 and/or N-positive rectal cancer. The results of this study indicated that preoperative CRT was associated with a significant reduction in local recurrence and treatment-associated toxicity compared to patients who received postoperative CRT [1]. On the other hand, a European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated that patients who received preoperative RT and either concurrent or postoperative chemotherapy had significantly lower rates of local recurrence compared to patients who received preoperative RT alone [17]. Based on these trials, preoperative CRT is recommended as a standard treatment modality for locally advanced rectal cancer [1,17]. However, for preoperative CRT the findings are not clear because the study populations in preoperative CRT trials consisted of patients with different clinical stages including cT3-cT4 and/or cN positive tumors. Thus, it was not possible to demonstrate whether there was any

benefit from preoperative CRT in each subgroup.

In this study, we aimed to demonstrate the incidence of pathological lymph node metastasis after surgical resection among patients clinically staged as T3N0M0 rectal cancer who had undergone preoperative CRT. We showed that 27% of the patients with rectal cancer staged as cT3N0 before preoperative CRT were shown to have lymph node involvement at the surgical material. We also demonstrated a significant association between pT stages and lymph node involvement. On the other hand, there were no statistically significant associations between lymph node involvement and patient age, gender, number of lymph node harvested, distance from the anal verge and imaging modality of preoperative CRT. These results are consistent with those reported in recent studies by Guillem et al. and Lombardi et al. [2,7]. Guillem et al. demonstrated in their large retrospective multicenter study that 22% of 188 patients staged before preoperative CRT as having cT3N0 rectal cancer by either REUS or MRI had pathological lymph node metastases. Lombardi et al. demonstrated that 28% of 32 patients staged before preoperative CRT as having cT3N0 rectal cancer had pathological positive lymph node involvement and their multivariate analyses indicated that the node-positive group had a statisti-

cally significantly higher number of pT3 tumors.

Bipat et al. reported that results from a meta-analysis of 90 studies demonstrated that ERUS and MRI had similar high sensitivities for assessing the depth of tumor penetration into the muscularis propria (94%). However, ERUS was found be more specific than MRI for the evaluation of local tumor invasion [18].

The sensitivities and specificities of the three imaging modalities for accurately evaluating lymph node metastases were comparable: CT (55% and 74%), ERUS (67% and 78%), and MRI (66% and 76%) [18]. A disadvantage of ERUS was that it was highly dependent on the operator and an advantage of MRI was its ability to provide accurate imaging of soft tissue structures and mesorectal fascia [18].

The current study and two previous studies [2,7] demonstrated that at least 22-28% of patients with rectal cancer clinically staged as cT3N0 before preoperative CRT were identified to have pathologically lymph node metastases. Therefore, it seems that preoperative CRT imaging is likely to result in underestimation and thus undertreatment of a significant number of cT3N0 rectal cancer patients.

However, the German study [1] demonstrated that among patients who were randomly assigned to undergo their first operation in the postoperative CRT arm, 18% with clinically staged cT3 and cT4 rectal adenocarcinoma or lymph node involvement by ERUS were overstaged (pathologic stage I). Therefore, the detection of lymph node involvement and tumor depth are major considerations for the radiologist during the preoperative evaluation of patients with rectal cancer. Newer modalities have improved the ability for assessing tumor depth and nodal involvement, including three-dimensional ERUS, a new-generation multidetector row spiral CT and MRI with use of superparamagnetic iron oxide as contrast agent [19-21].

The current preoperative CRT imaging presents certain limitations and clinicopathologic features of a primary rectal cancer may help determine those tumors which are more likely to be associated with lymph node involvement. Several previous studies have shown an association between clinicopathological features of patients and prognosis in cT3N0 disease, including well to moderately differentiated histology, extention of 2 mm or less into the perirectal fat, without lymphatic or vascular invasion, upper rectal location, and adequate node dissection [6,12,14,22,23]. Preoperative biopsy has some limitations and provides less accurate information about all pathological aspects. However, analyses of tumor specimens with selected molecular markers such as epidermal growth factor receptor, TP53 and Ki-67, thymidylate synthase level showed success in helping select patients who may best respond to preoperative CRT [24].

The main limitation of this study was the bias arising from its retrospective design. Despite all these limitations the present study is one of few done in this area. Our study demonstrated that available imaging tools had limited accuracy for detecting lymph node involvement and they are not tailored for the management of patients with clinically staged T3N0 rectal adenocarcinoma.

In conclusion, our study demonstrated that the accuracy of preoperative imaging for staging rectal cancers is limited because at least 27% of the patients will have undetected lymph node involvement after preoperative CRT, as proven in surgical specimens. On the other hand, preoperative CRT may possibly represent overtreatment in subgroups of cT3N0 tumors with favorable features, leading to overstaging and overtreatment of some patients. Our study also clearly detected the need for improving preoperative staging modalities in patients with clinically staged T3N0 tumors.

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