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The negative impact of understaging rectal cancer patients

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ABSTRACT

Background: Neo-adjuvant chemoradiation followed by surgery and adjuvant therapy is standard treatment of clinical node positive rectal cancer. Understaging leads to delay in treatment with possible detrimental results. This study analyses effects of understaging stage III rectal cancer on long-term outcomes.

Methods: A consecutive series of patients, operated on in MGH between 2004 and 2015 was included. Outcomes of non-neoadjuvantly treated clinical stage I patients who turned out to have pathological stage III disease and neoadjuvantly treated clinical stage III patients were retrospectively reviewed. The latter group was subdivided into patients who had persistent nodal disease (ypN+) and patients without positive lymph nodes after neoadjuvant treatment (ypN0).

Results: Of the 204 included patients, 30 had unexpected nodal disease on pathology. Clinical stage I-patients had higher rates of local recurrence, and rectal cancer and overall mortality than ypN0-patients.

Conclusion: Understaging stage III rectal cancer led to poorer oncologic outcomes, when compared to patients without positive lymph nodes on pathology after neoadjuvant. Future research should focus on identifying patients with treatment susceptible lymph node involvement.

1. Introduction

Patients with locally advanced rectal cancers, tumors that are transmural or those with a suspicion of positive lymph nodes on preoperative imaging receive neoadjuvant therapy. Neoadjuvant treatment has been definitively shown to decrease local recurrence and may impact survival.[1,2] Despite improving imaging quality and assessment,[3,4] the accuracy of preoperative staging remains a topic of discussion, especially regarding the clinical suspicion of positive lymph nodes. Overstaging rectal cancer leads to unnecessary treatment with potential long-term side effects.[5,6] Understaging leads to a delay in adjuvant treatment with potential inherent disadvantages.

The aim of this study is to analyze the effect of unexpected lymph node involvement on surgical pathology in patients with clinical stage I rectal cancer.

2. Methods

2.1. Patients

A consecutive cohort of patients with either clinically assessed AJCC stage I rectal adenocarcinoma who subsequently turned out to have pathologically stage III disease (cT1-2N0 pTxN+) or patients with clinically assessed AJCC stage III (cTxN+) primary rectal adenocarcinoma were selected from our IRB-approved colorectal database and retrospectively reviewed. All patients had an R0 TME-resection between 2004 and the end of 2015 at the Massachusetts General Hospital. According to the NCCN guidelines, patients with clinical stage I disease did not receive neoadjuvant treatment, whereas all patients with clinical stage III disease received neo-adjuvant chemoradiation. As patients with clinical stage III disease might not have persistent nodal disease on surgical pathology after neoadjuvant treatment, the clinical stage III group was subdivided into those patients who had a complete nodal response (cN+ypN0) and those patients who had persistent nodal disease (cN+ypN+). After removal of the primary tumor, all patients received 4–6 months of postoperative chemotherapy.

Patients were excluded if they underwent a local excision, if

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they received solely neoadjuvant chemotherapy or neoadjuvant radiotherapy, or if they had baseline metastases diagnosed within 30 days after the primary removal.

2.2. Statistical analyses

Non-normally distributed data were reported as the median with its interquartile range, indicating the 25% and 75% boundaries, whereas normally distributed data were reported as the mean with its standard deviation. A chi-square test was used to compare the dichotomous outcomes, whereas a Mann Whitney *U* test was used to detect statistically significant differences between two medians or means. A *P*-value of 0.05 or less was considered statistically significant. SPSS *(IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.)* was used for all statistical analyses.

3. Results

A total of 204 patients were included, of whom 30 had presumed AJCC stage I disease. These 30 patients did not receive neoadjuvant therapy and had (unexpected) positive lymph nodes on surgical pathology. The remaining 174 patients had clinical AJCC stage III and received neoadjuvant chemoradiation therapy. The pathology report of 62 patients of these patients revealed persistent lymph node involvement (cN+ypN+), whereas 112 patients had negative lymph nodes on pathology (cN+ypN0).

3.1. Baseline characteristics

There were no statistically significant differences in baseline characteristics between the clinical stage I and the clinical stage III groups, including demographics such as age, BMI, ethnicity, intoxications, and comorbidities. Although not significantly different, 53.3% of the clinical stage I patients were female, in contrast to 37.9% of the clinical stage III patients (P = 0.112). Operative duration and admission duration were also comparable for the two groups.

The use of preoperative imaging modalities was significantly different between clinical stage I and clinical stage III patients. The latter group underwent more CT scans (97.1% vs. 90%; P = 0.063), MRI scans (88.5% vs. 66.7%; P = 0.002), PET-scans (21.3% vs. 6.7%; P = 0.060), as well as endorectal ultrasounds (19.5% vs. 13.3%; P = 0.420).

Comparing clinical stage I patients to the subgroups of patients with and without persistent nodal disease after neoadjuvant therapy (cN+ypN+/cN+ypN0) did not demonstrate any differences in previously mentioned characteristics, aside from previously mentioned differences in the use of preoperative imaging. Table 1.

3.2. Surgical pathology characteristics

Seventeen (56.7%) of the assumed clinical stage I patients turned out to have transmural disease. Depth of tumor invasion in the pathologic specimen differed significantly between clinical stage I (pN+) and clinical stage III patients with no positive lymph nodes on pathology (ypN0) (Table 2). Comparing the tumor depth of clinical stage I patients to that of clinical stage III patients with persistent nodal involvement demonstrated no significant differences (P = 0.675).

Clinical stage I patients had significantly higher rates of the following features when compared to patients with a complete nodal response but with residual tumor (cN+ypT+N-): EMVI

Table 1
Baseline characteristics.

	Clinical stage I	All clin III patients	cN+ ypN+	cN+ ypN0
n = 204	30	174	62	112
Sex, Female	16 (53.3%)	66 (37.9%)	26 (41.9%)	40 (35.7%)
Age	61 (43.9–70.7)	54.9 (49.3–65.7)	55.1 (49.1–67.4)	54.9 (48.8–65.4)
BMI	26.8 (24.2–31.5)	26.2 (23.9–30.0)	26.9 (24.8–30.0)	25.9 (23.5–30.1)
Ethnicity, White	27 (93.1%)	151 (87.3%)	51 (82.3%)	100 (90.1%)
ASA-score	2.03 +- 0.56	2.14 +- 0.47	2.15 +- 0.54	2.14 +- 0.42
Intoxications				
Smoking				
Ever	15 (50%)	86 (49.4%)	25 (40.3%)	61 (54.5%)
Current	1 (3.3%)	17 (9.8%)	3 (4.8%)	14 (12.5%)
Alcohol				
Social (<4/day)	17 (56.7%)	103 (59.2%)	36 (58.1%)	67 (59.8%)
Abuse (>3/day)	2 (6.7%)	19 (10.9%)	3 (4.8%)	16 (14.3%)
Surgical procedure				
APR[a]	7 (23.3%)	42 (24.1%)	17 (27.4%)	25 (22.3%)
LAR[a]	22 (73.3%)	126 (72.4%)	43 (69.4%)	83 (74.1%)
PE[a]	0 (0%)	5 (2.9%)	2 (3.2%)	3 (2.7%)
TP[a]	1 (3.3%)	1 (0.6%)	0 (0%)	1 (0.9%)
Surgery duration	173 (142–238)	188 (124–239)	188 (130–231)	190 (123–250)
Adm duration	4 (3.8–5)	4 (3–6)	4 (3–6.3)	4 (3–5.8)
Preop imaging				
CT	27 (90%)	169 (97.1%)	60 (96.8%)	109 (97.3%)
MRI	20 (66.7%)	154 (88.5%)**	52 (83.9%)	102 (91.1%)***
PET	2 (6.7%)	37 (21.3%)	19 (30.6%)**	18 (16.1%)
US	4 (13.3%)	34 (19.5%)	14 (22.6%)	20 (17.9%)

*P < 0.05 **P < 0.01 ***P < 0.001, significance levels of difference between clinical stage I patients and all clinical stage III patients/cN+ypN+ patients/cN+ypN0 patients. There was no significant difference between the groups when there is no asterisk stated.

[a] APR: Abdominoperineal resection, LAR: low anterior resection, PE: pelvic excenteration, TP: total proctocolectomy.

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