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Preoperative Indicators of Poor Outcome in Locally Advanced Rectal Cancer at a County Hospital

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Abstract

Background: Locally advanced rectal cancer (LARC) is associated with high rates of both local and metastatic recurrence. Preoperative predictors can help determine which patients are at risk for recurrence.

Methods: A retrospective analysis of LARC patients at a county institution. Patients were grouped into that disease free at 2 years *vs*. those with unrepeatability or recurrence. Variables analyzed were available preoperatively and included demographics, tumor characteristics, and laboratory values.

Results: Out of96 patients, 55 had a successful outcome (SO) and 31 had an unsuccessful outcome (UO). On univariate analysis, significant predictors of UO were larger tumor size (p=0.002), extension into levator ani muscles (p=0.001), lower albumin (p=0.006), lower hemoglobin (p=0.02), and lower MCV (p=0.04). The only significant variable on multivariate analysis was extension into levators (OR 5.6, CI 1.5-21.1).

Conclusion: LARC patients found to have these high risk characteristics are more likely to have an unresectable cancer or recurrence. These patients should be considered for additional imaging after neoadjuvant chemoradiation, as it may lead to a change in the operative plan.

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Introduction

The usual method for predicting outcomes in patients with rectal cancer prior to surgery has classically been by local staging with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) and distant staging with computed tomography (CT). Studies have shown additional factors available preoperatively can predict worse outcome in rectal cancer, most notably an elevated carcinoembryonic antigen (CEA) and anemia [1-7]. Other predictive factors have included: older age, male sex, clinically positive lymph nodes, tumor histologic grade, CRP, and ca-19-9 [8-13]. Patients with locally advanced rectal cancer (LARC) routinely receive neoadjuvant chemoradiotherapy (CRT) as it decreases local recurrence and improves disease free survival as compared with postoperative CRT [14,15]. However, recurrence is still high with rates of local and metastatic recurrence of 2-7% and 18-33%, respectively [16,17]. While recurrence has been shown to be associated with positive circumferential resection margins (CRM), identifying those at risk for a positive CRM has not been clearly elucidated [18]. Our objective was to assess factors available preoperatively and their ability to predict outcomes in patients with LARC, with the hope that this may change management and improve patient expectations.

Methods

After institutional review board approval, a retrospective review of medical records and CT imaging at a county teaching hospital was completed. All patients were operated on for curative intent with LARC (American Joint committee on Cancer [AJCC] stage II or III) between 2006 and 2014 and had at least two years of follow-up. All patients received preoperative neoadjuvant CRT of fractionated radiation of 45-50 Gy and either Capecitabin or 5-Fluorouracil.

Patients were initially divided into two groups based on their outcome. Curative resection and absence of disease at two years is considered a Successful Outcome (SO), while unrepeatability, local recurrence, and distant metastasis are considered an Unsuccessful Outcome (UO). A secondary analysis was made between the SO patients and patients with recurrence only (RO).

Table 1: Univariate analysis of all variables assessed.

Demographics and symptomatology	Unsuccessful N=31 N(%) or Median, IQR	Successful N=55 N(%) or Median, IQR	Odds ratio (95%CI) or median Difference (95%CI)	p-value
Age at diagnosis	52, 42-60	54, 49-58	-2, (-5.6-1.6)	0.4
Male gender	19 (61.3%)	36 (65.5%)	0.8 (0.3-2.1)	0.7
BMI	25.1, 22.3-28.3	26.5, 22.5-28.7	-1.4 (-11.6-8.8)	0.5
Smoking	15 (48.4%)	26 (47.3%)	1.0 (0.4-2.5)	0.9
Alcohol	14 (45.2%)	21 (38.2%)	1.3 (0.5-3.3)	0.5
FH of colorectal CA	9 (29%)	7 (12.7%)	2.8 (0.9-8.5)	0.06
Duration of symptoms (days)	150, 90-270	180, 90-365	-30 (-200- 140)	0.2
Bleeding	26 (86.7%)	43 (81.1%)	1.5 (0.4-5.3)	0.8
Pain	12 (38.7%)	11 (20.3%)	2.5 (0.9-6.6)	0.07
Weight loss	12 (38.7%)	18 (33.3%)	1.3 (0.5-3.2)	0.6
Obstruction	6 (19.4%)	11 (20.4%)	0.9 (0.3-2.8)	0.9
Perforation/abscess	1 (3.2%)	1 (1.9%)	1.8 (0.1-29.3)	1.0
Tumor Characteristics				
Lesion height <7 from anal verge	19 (61.3%)	33 (60%)	1.1 (0.4-2.6)	0.9
Lesion height >7 from anal verge	12 (38.7%)	22 (40%)	0.9 (0.4-2.3)	0.9
Tumor size >/= 3	15 (60%)	17 (31.5%)	3.3, 1.2-8.7	0.02
Tumor size (cm)	3, 2.5-5	2, 1.2-3.2	1 (0.2-1.8)	0.002
Levator ani extension, pre-neoadjuvant CRT	16 (64%)	10 (23.8%)	5.7 (1.9-16.8)	0.001
cT3	23 (76.7%)	47 (88.7%)	0.4 (0.1-1.4)	0.1
cT4	7 (23.3%)	4 (7.6%)	3.7 (1.0-14.0)	0.1
N stage 1 or greater (EUS)	16 (57.1%)	23 (50%)	1.3 (0.5-3.4)	0.6
Overall clinical stage II	15 (48.4%)	26 (47.3%)	1.0 (0.4-2.5)	0.9
Overall clinical stage III	16 (51.6%)	29 (52.7%)	1.0 (0.4-2.3)	0.9
Poor differentiation	6 (20%)	3 (5.5%)	4.3 (1.0-18.8)	0.06
Laboratory values				
Pre-neoadjuvant CEA>5	19 (63.3%)	22 (50%)	1.7 (0.7-4.5)	0.3
Preoperative CEA> 5	5 (22.7%)	9 (19.2%)	1.2 (0.4-4.3)	0.8
Albumin at diagnosis	3.3, 2.9-3.6	3.7, 3.4-3.9	-0.4 (-0.5- -0.3)	0.006
Hgb at diagnosis	11.4, 8.8-12.7	12.7, 11.2-14.2	-0.7 (-1.3- -0.1)	0.02
MCV at diagnosis	83.7, 69.7-88.8	88.5, 80.2-91.8	-4.8 (-9.5- -0.1)	0.04

Variables assessed were available preoperatively and included demographics, such as age, sex, body mass index (BMI), ethnicity, smoking/alcohol use, and family history of colorectal cancer. We also looked at presenting symptoms, tumor characteristics such as tumor distance from the anal verge, tumor size (measured on pathology), extension into the levator muscles seen on initial CT, depth of penetration seen on EUS (clinical T stage), nodal status, AJCC clinical stage, and histologic degree of differentiation. Finally we assessed laboratory values; CEA both before and after neoadjuvant CRT, albumin at diagnosis, hemoglobin at diagnosis, and mean corpuscular volume (MCV) at diagnosis.

CT scans were analyzed by radiologists at the time of data collection and included only CT scans obtained prior to neoadjuvant CRT. Levator ani extension was defined as soft tissue density or fat stranding extending from the suspected rectal mass into these muscles. The lack of a clear fat plane was considered invasion. On multi-planar evaluation, if the fat planes were homogeneous and similar in Hounsfield Units to adjacent perirectal fat, it was considered negative.

Table 2: Multivariate analysis.

	OR	CI	P value
Albumin	1.6	0.26-9.7	0.6
Hemoglobin	0.88	0.62-1.2	0.5
MCV	0.98	0.9-1.1	0.7
Levator Ani extension on CT	5.6	1.5-21.1	0.01
Tumor Size	1.3	0.96-1.8	0.09

Instances of involvement within 2mm of the levator ani muscle were considered involved.

The data were entered and maintained in a Microsoft Excel (Excel; Microsoft Corp, Redmond, WA) worksheet and were then exported and translated into native SAS (SAS Institute, Cary, NC) format. Data were then analyzed using SAS 9.4. A univariate analysis was performed to compare the SO and the UO cohorts, as well as the SO to the RO cohort. Categorical characteristics (e.g. gender, smoking, etc.) are described as proportions or percentages, and

Table 3: Characteristics of unsuccessful outcome patients with extension into levator ani muscles.

Type of surgery performed	Distal Margin	Circumferential resection margin	Location of recurrence (if applicable)
APR, with sidewall resection	2.5	Positive	Small bowel
Diverting colostomy	NA	NA	NA
pelvic exenteration	6	1	Liver, lung, spine
	3.5		
	2.5		
LAR	3.5	Positive	Omentum, peritoneum
LAR	2.5	Not recorded	Lung
APR	7	0.5	Liver, lung
APR	3.5	0.9	Local
Diverting colostomy	NA	NA	NA
APR, en bloc posterior vaginectomy	2.5	Not recorded	Liver
APR	5.5	Positive	Inguinal nodes
APR	6	Positive	Liver
LAR	Positive	0.2	Local
APR	1.2	0.8	Inguinal nodes
Diverting colostomy	NA	NA	NA
LAR with permanent colostomy	NA	Positive	NA
Diverting colostomy	NA	NA	NA

proportional differences are described as odds ratios with 95%CI. Chi-squared or Fisher's exact p-values are described, as appropriate. Continuous variables (e.g., age, distance from anal verge, etc.) are described as medians and interquartile ranges, and the differences between the cohorts are described as median differences with the associated 95% CI. The reported p-values are derived from the non-parametric Wilcox on rank sum test, used to describe the difference between non-normally distributed continuous variables. There was no correction made for multiple testing. A multivariable analysis incorporating significant univariate factors was also performed to identify independent predictors of UO.

Results

There were a total of 96 patients with LARC operated on for curative intent. Ten patients were excluded due to having less than 2 years of follow-up. Fifty-five patients had a successful outcome and 31 patients had an unsuccessful outcome. Of the 31 patients with an unsuccessful outcome, 10 patients were found to be unresectable at the time of surgery, 11 patients developed local recurrence, and 10 patients developed distant metastasis. The mean time to diagnosis of the recurrence was 1.25 years.

There were several significant indicators for an unsuccessful outcome on univariate analysis seen in table 1. These included tumor size both as a continuous variable (p=0.002) and when dichotomized to >/=3 cm (p=0.02), extension into levator ani muscles (p=0.001), albumin at diagnosis (p=0.006), hemoglobin at diagnosis (p=0.02), and MCV at diagnosis (p=0.04). Multivariate analysis (Table 2) including the five variables found to be significant on univariate analysis, identified that extension into the levator ani muscles was the only independent predictor of UO (OR 5.6, CI, 1.5-21.1). Table 3 shows the UO patients with extension into levator ani muscles: 6 of 11 patients had a positive resection margin, 5 corresponding to positive CRM. Of the 10 patients with SO and extension into levator muscles, 9 of 10 underwent abdominoperineal resection (APR) and one had a positive CRM.

When comparing SO with RO patients, univariate analysis of the same variables yielded significance for extension into the levator ani muscles 23.8% SO *vs*. 64.7% RO (p=0.003), and tumor size 2.0 (1.2-3.2) SO *vs*. 3.0(2.2-4.5) RO, (p=0.02).

Discussion

The goal of this study was to identify characteristics that may be identified preoperatively that are associated with unrepeatability or local recurrence. This could result in a decrease in unnecessary operations for those that are unresectable, or an opportunity to provide tailored treatment (i.e. additional chemotherapy, extended resection margin) for patients with high risk features.

This study found various predictors that can identify patients at high risk for unrepeatability or recurrence. The strongest predictor of poor outcome was levator ani extension identified on pre-neoadjuvant CRT CT scan. On review of these CT scans, 26 out of the 67 CT scans reviewed had this finding and 62% of these patients had a poor outcome. This shows that a majority of patients with tumor extension into the levator ani muscles went on to have either an unresectable tumor or recurrence. Therefore, this finding alone may warrant additional preoperative evaluation.

The high likelihood of poor outcome with levator ani muscle extension is likely related to its ability to lead to a positive CRM. Nagtegaal and Quirke have shown that a positive CRM is the most significant finding leading to recurrence [18]. In our study, five out of six patients with positive CRM and levator ani muscle extension had a poor outcome. If this finding remains present on repeat imaging after neoadjuvant CRT, then additional considerations for management should be made. This could include surgical planning for a wider CRM, possibly necessitating en bloc resection of adjacent organs, or additional systemic chemotherapy prior to operation.

Additionally, our study found that larger tumor size and

specifically tumors greater than 3 cm are associated with both an unsuccessful outcome and recurrence. This indicates that tumor size may be an important prognostic indicator in addition to the AJCC clinical stage. While it may seem intuitive that a larger tumor is associated with poor outcome, current staging of rectal cancer includes depth of penetration only, and does not account for tumor size [19]. The tumor size in our study was measured on gross pathology after formalin fixation, however this value could be estimated on a preoperative imaging study and used as a predictor of outcome.

The laboratory findings included a significantly lower albumin, hemoglobin, and MCV at the time of diagnosis are predictive of an unsuccessful outcome. Low albumin serves as a marker for malnutrition, and low hemoglobin and MCV are markers for microcytic anemia. Regarding malnutrition, this is likely due to the more advanced disease state of the patients with unsuccessful outcome. Regarding anemia, studies have reported increased likelihood of local recurrence, decreased survival as well as reduced effectiveness of neoadjuvant CRT in anemic patients [4-7]. It is possible that this effect is due to the previously reported decreased efficacy of radiotherapy in hypoxic tissue, leading to ineffective CRT [5]. It is also possible these tumors are further along in the oncogenic process, are more prone for blood loss, and the resulting anemia is just an indicator for more advanced disease. Regardless, these laboratory indicators show only that a lower value raises the likelihood of UO without a definitive cut-point; studies have used multiple cutoffs for hemoglobin measurements in showing prognostic significance and there is no consensus value at this point [5,7]. Therefore, additional studies are needed to determine a specific value relevant for predicting a poor outcome.

Limitations of this study include the retrospective nature of the chart review, and a small sample size. Given a larger sample size, other factors may have been found to be predictive of UO. There were also ten patients that were operated on for curative intent but were unresectable. The authors of this study recognize this number is high, and believe this is due to our patient populations' advanced disease and our lack of re-imaging these patients to detect adequacy of response to neoadjuvant CRT. These patients represent the most significant clinical application of this research. If these patients were identified preoperatively as high risk for poor outcome and had additional preoperative imaging, many may have avoided an operation.

Conclusion

This study identified significant predictors of poor outcome. These high-risk patients represent a patient population that would benefit from re-staging CT, MRI, or EUS after neoadjuvant CRT. This additional information could help with advanced surgical planning to obtain better radial clearance, or it may warrant delaying surgery for administration of additional chemotherapy to further downstage the tumor.

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