Genitourinary Involvement in Colorectal Cancer: Pre-operative Diagnostic Utility of CEA, Computed Tomography and Cystoscopy in Predicting Surgical Involvement

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Objective: This study aims to describe the demographics, clinical characteristics of patients, and the sensitivity and specifity of the clinical, laboratory, radiologic, diagnostic parameters in detecting histopathologically-proven urinary tract involvement in primary colorectal cancer patients referred to the urology service in the Philippine General Hospital.

Methods: This was a retrospective, cross-sectional study. The study included patients referred to the Division of Urology from the Division of Colon, Rectal and Anal Surgery January 1, 2018 to December 31, 2018. All patients diagnosed with colorectal malignancy and referred to the Urology service were included in the study, including their cystoscopy, axial tomography, CEA and symptom assessment scores.

Results: Fifty-eight patients were included in the study and, 43% were rectal cancers and 33% were sigmoid cancers. Sensitivities and specificities were as follows. Symptoms 40%, 84%, Cystoscopy, 45%, 100%; Axial tomography 75%, 79%. Surgical involvement correlated with histopathologic involvement with a specificity of 52%. CEA did not discriminate between cohorts of positive or negative involvement.

Conclusion: Cystoscopy, axial tomography and symptom assessment had high positive predictive values. All diagnostics had low negative predictive values when taken in isolation. Surgical assessment correlated with histopathologic findings in half of the population. CEA did not discriminate between those with surgical involvement and those without. A multi-modality assessment strengthens detection of surgical involvement preoperatively.

Keywords: colorectal cancer, surgical involvement, diagnostic accuracy, preoperative cystoscopy

Introduction

Assessing pre-operative risk for a multi visceral involvement in surgical oncologic cases is important to plan for the appropriate multidisciplinary management. The diagnostic accuracy of investigative tools in the preoperative period to determine urologic organ involvement in colorectal conditions is still controversial. Few studies to date addressing this dilemma.[1-5]

A study by Talamonti in 1993 with a limited sample size of 70 found that a total of 41.7% of patients were symptomatic genitourinary-wise and correlated with malignant bladder invasion in

97%. In a study by Luo in 2013, an involvement of the bladder by CT scan significantly correlated with histopathologic findings of invasion. Other diagnostic modalities were not tested for accuracy by this study. In assessing the outcomes of these multi-visceral resections, McNamara emphasized that a negative resection margin is the single most important prognostic factor in terms of disease-free survival and distant control. This has been taken as the standard-of-care in locally advanced colorectal malignancy as multiple studies corroborate the improved survival in R0 resections. This underscores the importance of pre-operative diagnostics and thorough planning.

This study aims to describe the patient demographics, clinical characteristics and treatment outcomes for colorectal malignancies referred to the urology service for co management of symptoms, genitourinary tract involvement and operative management. Secondarily, this study also aims to determine the sensitivity and specificity of the clinical, laboratory, radiologic, diagnostic parameters mentioned above in detecting histopathologically-proven urinary tract involvement in the primary colorectal cancer in the preoperative period.

Methods

This was a retrospective, cross sectional study. The study included patients referred to the Division of Urology from the Division of Colon, Rectal and Anal Surgery January 1, 2018 to December 31, 2018. All patients diagnosed with colorectal malignancy and referred to the Urology service were included in the study. These included patients referred for assessment of genitourinary symptoms within the time period aforementioned, not necessarily relating to the cancer patients referred for clinical suspicion of genitourinary involvement, patients referred intraoperatively for genitourinary involvement independent of whether or not a multivisceral resection was carried out. Patients were taken at point of referral and were not stratified according to the stage of their care (data as regards neoadjuvant or adjuvant treatment were not included in the study). A chart review of all these cases was done, as well as a review of

the corresponding patient reports in the weekly colorectal and urologic conferences.

The following data were collected for all patients: age, sex and location of primary tumor. For patients referred for genitourinary (GU) involvement in the primary cancer site: they were grouped into those With GU Surgical Involvement and those Without GU Surgical Involvement, based on the intraoperative decision to do an en-bloc multivisceral resection. GU Histopathologic Involvement is a post-operative finding of microscopic invasion of the genitourinary organ by the primary tumor, as read by a pathologist.

For each patient, a review of pre-operative diagnostics was done: The CEA value on admission was recorded. The CT scan (abdominal CT scan with oral, rectal and IV contrast) findings were reviewed. Involvement by CT scan or a positive CT scan was defined as follows: any abnormality noted in the CT scan by the radiologist or the surgeon related to the primary tumor. The involvement was stratified into the organ involved: kidney (loss of plane, fistula), ureter (hydronephrosis, encasement), bladder (loss of plane, intraluminal mass, fistula), prostate (loss of plane), urethra (loss of plane) and seminal vesicle (loss of plane).

Symptoms were assessed by the attending urologist of the patient. Measures were dichotomous (recorded as positive for the presence of any symptom), and were not graded according to degree. As such, no scale or scoring system was used. Hematuria was defined as microscopic hematuria or >3 RBC/hpf.

The cystoscopy – if done – was reviewed. Involvement by cystoscopy or a positive cystoscopy was defined as follows: bladder abnormality noted by rigid or flexible cystoscopy: fistula, mucosal irregularity or edema, intraluminal mass. External compression with no bladder mucosal changes is considered as non-involvement.

The intraoperative findings were reviewed to determine surgical involvement. Positive involvement was described as follows: adherence or inseparability from a GU organ necessitating an en-bloc resection. Surgical involvement is similar to the sT stage in TNM classification, as defined above. In contrast, histopathologic involvement (similar to the pT stage in the TNM classification) is microscopic invasion of the GU organ with cancer cells. The surgical

involvement is determined by the surgeon, while the histopathologic involvement is determined by the pathologist who reviews the tumor specimen after the resection is done.

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables and median and inter quartile range for non-normally distributed continuous variables. Mann Whitney U test was used to determine the difference of CEA (ng/ml) during OR between patients with and without GU surgical and histopath involvement. Sensitivity, Specificity, NPV, PPV and Likelihood Ratios were used to determine the diagnostic accuracy of Cystoscopy and CT scan to predict GU Surgical Involvement, as well as GU Surgical Involvement to predict GU Histopath Involvement. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

The study protocol was approved by the University of the Philippines Research Ethics Board (UPM-REB) and was implemented in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki.

Results

In 2018, 123 patients were referred by the Colorectal Service to the Urology Service. Of these patients, 58 patients were referred for co-management of colorectal cancer and were included in the study.

Table 1 indicates the primary tumor site from where the cancer originated. Most referrals are for rectal and sigmoid malignancies.

Twenty patients had stage IV disease for which only a diverting stoma without definitive resection of the tumor was performed. One patient underwent long-course chemoradiotherapy and no definitive resection was done during the study's time period; two patients did not consent to definitive resection; one patient had no data available. Thirty-four patients had their definitive resections; GU surgical and histopathologic involvement data were available for all but one patient. Table 2 shows the breakdown of occurrences of suspected genitourinary tract

Table 1. Frequency distribution of primary maligancy of colorectal service patients referred to the urology service patients.

Primary Tumor Site	Number of Patients	Percentage of Total Cancer Involvement Referrals (n=58)
Primary peritoneal	7	12%
Ascending colon	5	9%
Transverse colon	0	0%
Descending colon	2	3%
Sigmoid	19	33%
Rectum	25	43%
Anus	0	0%

Table 2. Organ involvement occurrences for cancer.

Organ	Number of Occurrences	Total Occurrences (%)
Bladder	27	48%
Ureter, left	3	5%
Ureter, right	3	5%
Ureter, bilateral	5	9%
Prostate	12	21%
Seminal vesicle	1	2%
Kidney, right	1	2%
Kidney, left	2	4%
Adrenal (any laterality)	2	4%

involvement. For each patient, each organ was counted separately.

Table 3 shows the disease characteristics of the referrals. Thirty two percent of patients were symptomatic (hematuria, lower urinary tract symptoms, fecaluria). Eight patients (24%) had histopathologic GU invasion.

Tables 4-6 show the diagnostic accuracies for the various diagnostic modalities to assess possible surgical involvement. Cystoscopy was only 45% sensitive in detecting surgical involvement, but was 100% specific. A Triple Contrast CT scan, on the other hand was 75% sensitive and 77% specific for detecting surgical involvement. Symptoms had a specificity of 86% and were more specific than CT scan findings. All tools had high positive predictive values but only modest negative predictive values.

Table 7 shows the concordance of assessment of surgical involvement (as a shared decision among general surgeons and urologists present during the operation) with histopathologic findings. Surgical involvement had a 100% sensitivity and a 52% specificity in detecting histologic extension of the cancer into the adjacent genitorurinary tract organ.

Carcinoembryonic Antigen was also analyzed in 32 patients for whom data were available. Table

Table 3. Disease characteristics of referrals for cancer involvement and cancer surgery.

	Median (IQR)
Median CEA (ng/ml) (n=32)	11.1 (3.21 to 60.80)

	Frequency (%)
Symptoms (n=34)	
Yes	11 (32.35)
No	23 (67.65)
Cystoscopy (n=18)	
Positive for Involvement	6 (33.33)
Negative for Involvement	12 (66.67)
CT Scan (n=34)	
Positive for Involvement	19 (55.88)
Negative for Involvement	15 (44.12)
GU Surgical Involvement (n=33)	
With	20 (60.61)
Without	13 (39.39)
GU Histopath Involvement (n=33)	
With	8 (24.24)
Without	25 (75.76)

Table 4. Diagnostic accuracy of cystoscopy to predict GU surgical involvement.

		GU Surgical Involvement		
		With (%)	Without (%)	Total
Cystoscopy	Yes	5	0	5
	No	6	6	12
	Total	11	6	17

Sensitivity 45.45% (16.75-76.62); Specificity 100% (54.07-100); PPV 100%; NPV 50% (36.83–63.17)

Table 5. Diagnostic accuracy of CT scan (triple contrast) to predict GU surgical involvement.

| | | GU Surgical Involvement | | |
		With (%)	Without (%)	Total
CT scan	Yes	15	3	18
	No	5	10	15
	Total	20	13	33

Sensitivity 75% (50.90-91.34); Specificity 76.92% (46.19-94.96); PPV 83.33% (64.23-93.30); NPV 66.67% (46.95–81.88)

Table 6. Diagnostic accuracy of symptoms to predict GU surgical involvement.

| | | GU Surgical Involvement | | |
		With (%)	Without (%)	Total
Symptoms	Yes	8	2	10
	No	12	11	23
	Total	20	13	33

Sensitivity 40% (19.12-63.95); Specificity 84.62% (54.55-98.08); PPV 80% (50.08-94.10); NPV 47.83% (37.44-58.40)

Table 7. Diagnostic accuracy of GU surgical involvement to predict GU histopathological involvement.

| | | GU Surgical Involvement | | |
		With (%)	Without (%)	Total
Symptoms	Yes	8	12	20
	No	0	13	13
	Total	8	25	33

Sensitivity 100% (63.06-100); Specificity 52% (31.31-72.20)

8 shows the relationship of CEA and GU cancer involvement. The tumor marker did not discriminate cases into with and without involvement. There was no significant difference in the median CEA of the cohorts compared.

Discussion

Carcinomas that arise from the sigmoid and rectum have the highest percentage of urogenital tract involvement in various studies This study reflects the same outcome: injuries to the sigmoid and rectum account for the greatest number of referrals, at 33% and 43% of total referrals for cancer involvement. 5.8% and 2.7%, respectively in a study by Kobayashi in 2003. In a similar study by Campos in 20106, a more focused study on locally-advanced (T3 and T4) colorectal malignancies, as expected, revealed a higher rate of urogenital involvement at 13.2% of patients.

In a local study by Cabungcal in 2007, of 154 co-managed Urology and Colorectal Service colorectal carcinoma patients, 48.7% were proven to have involvement of urologic structures intra-operatively.[7] Of these, 12% involved the ureters, 49% involved the bladder dome, 37% involved the bladder base. In 51 male patient referrals,

Table 8. CEA across cases.

	With GU Surgical Involvement	Without GU Surgical Involvement	
	Median (IQR)		p-value
CEA (ng/ml)	11.6 (3.12-25.64)	9.35 (3.19-66.45)	0.746
	With GU Histopath Involvement	Without GU Histopath Involvement	
CEA (ng/ml)	11.6 (3.12-14)	10.15 (3.14-64)	0.706

intraoperatively, 11% involved the prostate, 4% involved the kidneys, 0.1% involved the seminal vesicles. As an update in the same insitution, 48% of suspected organ involvement are in the bladder, followed by the prostate at 21%.

In terms of symptoms, a study by Talamonti in 1993 that a total of 41.7% of patients were symptomatic genitourinary-wise and correlated with malignant bladder invasion in 97%.[1] This was similar to the findings of the study with 32% symptomatic patients, specificity was high at 86% even surpassing that of a triple contrast scan. This is because most of the patients are from indigent areas and are in the T3-T4 stages of the disease, with advanced symptoms present (fecaluria from cancer fistulas, bladder outlet obstruction from very low rectal tumors).

In a study by Chaleoykitti in 2005, 35 patients were stratified into an adhesion and non-adhesion group based on pre-operative symptoms, urinalysis, CT scan, cystoscopy, ultrasonography and intravenous pyelography. The findings in these diagnostic tests were compared to intraoperative findings. Symptoms were 19.2% sensitive and 100% specific. Computed tomography had a 61% sensitivity and 100% specificity. Cystoscopy had a 75% sensitivity and a 100% specificity.[3] These were comparable to the findings in this study.

In a study by Sundborg of cervical cancer cases and using a specific set of criteria to define bladder involvement by CT scan the positive predictive value of a CT scan for bladder invasion is 60%, and the negative predictive value is 100%.[8]

In this study, symptoms had a sensitivity of 40% and a specificity of 85%. Axial tomography had a sensitivity of 75% and a specificity of 77%. Cystoscopy had a sensitivity of 45% and a specificity

of 100%. This brings the likelihood ratio of a symptomatic patient to 2.6, and that of a positive CT scan to 3.25. Using the Fagan Nomogram, a likelihood ratio of 2-5 causes small (but sometimes significant) changes in post-test probability.[9] This reinforces the multi-modality approach in assessing surgical involvement. These three tests (history, cystoscopy, axial tomography) taken together, strengthen detection of GU involvement for patients with high index of suspicion.

One of the strengths of the study is the wealth of late-stage cancer cases. One of the limitations of the study is the small sample size. Limitations are: the documentation quality: the standardization of symptom-specific questions and reporting CT scan involvement may be improved; how neoadjuvant treatment could have affected results may also be explored in futures studies.

Conclusion

The colorectal service referred a total of 123 patients in 2018. Of these, the largest percentage (38%) are those referred for possible cancer involvement of the genitourinary tract based on preoperative diagnostics for definitive multivisceral resection. Cystoscopy, Axial tomography and symptom assessment had high positive predictive values. All diagnostics had low negative predictive values when taken in isolation. Surgical assessment correlated with histopathologic findings in half of the population. CEA did not discriminate between those with surgical involvement and those without. A multi-modality assessment strengthens detection of surgical involvement pre-operatively.

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