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Predicting Indeterminate Lesion Turned to Distance Metastasis in Patients with Rectal Cancer Undergoing Curative Resection after Preoperative Chemoradiotherapy

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ABSTRACT

Objectives: It is controversial about factors associated with indeterminate lesion turned to be malignant lesion after preoperative concurrent chemoradiotherapy(CCRT) in rectal cancer that may cause over-treating and over-diagnosing. So, The aim of this study was to evaluate the prevalence of indeterminate pulmonary nodules or liver nodule at primary staging CT and risk of indeterminate lesion being malignant to help better understanding of indeterminate lesion in rectal cancer undergoing preoperative CCRT and proper treatment.

Methods: A total of 679 patients with rectal cancer were assessed from January 2015 to December 2019. 152 patients with rectal cancer undergoing curative resection after preoperative CRT were included. Associated factors were reviewed for their effect on metastasis. The median follow-up time was 28 months.

Results: Of 152 patients, The prevalence of indeterminate lesion was 3.29% and turned to be malignant around 40% of patients. The clinical N2, preoperative FOLFOX regimen, No clinical response were significantly higher in malignant group (p 0.03, <0.001 and 0.003, respectively).

Conclusions: Such a low incidence of indeterminate lesion should not cause further preoperative diagnostic workup besides routine regimens. In addition, it is not necessary to perform excessive surveillance routinely for all rectal cancer patients underwent preoperative CCRT who have indeterminate lesion. Intensive follow up chest CT or invasive diagnosis modalities should be considered in patients who had clinical stage N2, receiving preoperative FOLFOX4 regimen and no clinical response after preoperative CCRT.

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Keywords: Rectal Cancer, Indeterminate Lesion, Preoperative Chemoradiotherapy

Introduction

According to the GLOBOCAN 2018, Rectal cancer is the eighth most incidence. Metastatic colorectal cancer (CRC) is about 20% at diagnosis [1,2]. Liver was the most common site of metastasis (70% in colon cancer/70% in rectal cancer). The second most common was the thorax (32% in colon cancer/47% in rectal cancer) [3]. Interestingly, there are indeterminate pulmonary nodules (IPN) in one-third of CRC patients and some of them are proved to be metastasis [4-7]. Nordholm-Carstensen A found 9 % of CRC patients had IPN on chest computerized tomography(CT) and 10.8 % turned to be metastases. Regional lymph node metastasis, and multiple numbers of indeterminate pulmonary nodules were factors associated with malignancy [8]. In addition, Silva M et al found that the incidence of indeterminate liver nodules (ILN) on magnetic resonance imaging (MRI) was 15.4% and 41.2% of CRC patients turned to be malignant at follow up. The ratio of positive lymph nodes to total number of lymph nodes resected was signifcantly factor of malignant nodules [9]. Generally, there are many factors associated with metastasis in rectal cancer including staging of tumor, resection margin, differentiation of tumor, chemotherapy, radiotherapy(RT) and tumor response after neoadjuvant therapy [10,11]. Stanislav Filip found relationship between molecular biomarkers and CRC metastasis including ALK, ROS1, NTRK1-3 fusions, HER2 amplification that can be the predictive treatment in each patient [12]. Interesting point, neoadjuvant or total neoadjuvant therapy is always recommended in case of rectal cancer especially clinical stage T3, T4 or node positive for improving recurrence and survival [13-15]. From previous study, there were no study about factors associated with indeterminate lesion turned to be malignant lesion after preoperative concurrent chemoradiotherapy (CCRT) in rectal cancer. It is controversial that may cause over-treating and over-diagnosing. So, The aim of this study was to evaluate the prevalence of indeterminate pulmonary nodules or liver nodule at primary staging CT and risk of indeterminate lesion being malignant to help better understanding of indeterminate lesion in rectal cancer undergoing preoperative CCRT and proper treatment in this setting.

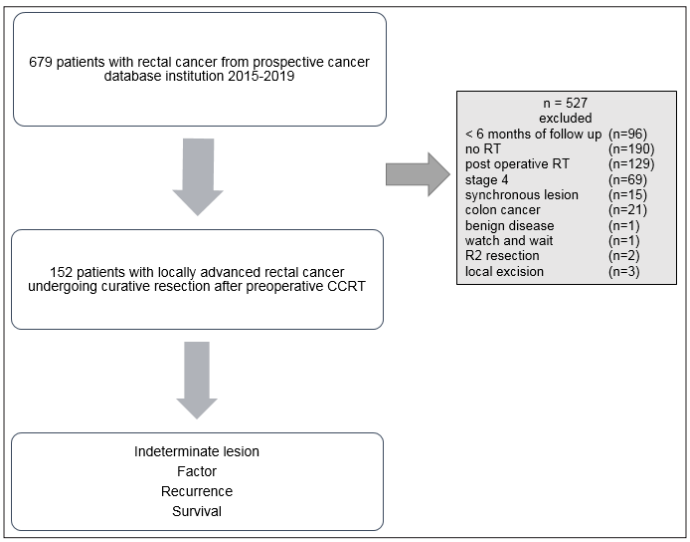
Method

All patients signed informed consent forms and current study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA.

MURA2021/668.) We reviewed the data of locally advanced rectal cancer underwent curative resection after preoperative CCRT from a prospective cancer database institution between 2015 and 2019 in Ramathibodi hospital(flow chart 2). 679 patients with rectal cancer were enrolled. Then,527 patients were excluded by less than 6 months of follow up(n=96), no RT(n=190), post operative RT(n=129), stage4(n=69), synchronous lesion(n=15), colon cancer(n=21), benign disease(n=1), watch and wait management after preoperative CCRT(n=1), R2 resection(n=2) and local excision(n=3).Finally, there were 152 patients with locally advanced rectal cancer undergoing curative resection after preoperative CCRT for data collection and analysis.

All patients had preoperative clinical assessment and staging, including medical history, digital rectal examination(DRE), colonoscopy, sigmoidoscopy, CT and MRI. All patients underwent preoperative CCRT. Data of preoperative CCRT were collected including chemosensitization regimen, waiting time from last RT to surgery, pre and post CCRT carcinoembryonic antigen(CEA) and clinical response. Operation included low anterior resection(LAR), ultra-low anterior resection(ultralowLAR), intersphincteric resection with coloanal anastomosis(ISR with CAA),abdominoperineal resection(APR), low anterior resection with end colostomy(LAR with end colostomy)surgery. Final pathology with distal rectal margin(DRM), circumferential rectal margin(CRM),number of examined lymph nodes (LNs),number of positive lymph node, perineural invasion (PNI), lymphovascular invasion (LVI), tumor and deposit, postoperative CEA, postoperative complication, adjuvant chemotherapy, and tumor gene status were collected. The following clinical outcomes were analyzed for factors related metastases or non-metastases.

Flow Chart (2) Flow Chart of Study Selection



Definition of Variables

Indeterminate Pulmonary Nodule

IPNs were defined as a noncalcified nodule smaller than 10 mm in diameter or solid nodule no greater than 20 mm at maximum diameter without malignant character including calcification, irregular margin and multiple nodules [16].

Indeterminate Liver Nodule

Small liver nodules was smaller than 10 mm and remained indeterminate despite hepatocyte specifc contrast MRI [8].

Preoperative Concurrent Chemoradiotherapy

Indications for preoperative chemoradiotherapy are T3/T4 and/or nodal metastasis at our hospital. Preoperative CCRT consisted of a radiation dose of 50.4 to 55.8Gy in 28 to 33 fraction, administered five times a week. Concurrent chemotherapy consisted of 5-fluorouracil, 1,000 mg/m2/day continuous drip for 5 days per cycle, or capecitabine, 850 mg/m2/day for 5 days per week for 5 weeks.

Technique of Total Mesorectal Excision

In case low and middle rectal cancer, surgical dissection along embryonic plane between mesorectal fascia and pelvic sidewall. While upper rectal cancer, the mesorectum was divided at 5 cm distal to tumor. All surgeons were experienced in colorectal surgery. Anastomosis was performed by circular stapling devices or handsewn. Temporary ileostomy was performed according to surgeon's preference, tumor location and intraoperative situation.

Adjuvant Therapy

Indications for adjuvant therapy included positive lymph nodes ,unfavorable prognostic factors,pT3 or T4, pathological stage3. Multidisciplinary team considered the adjuvant chemotherapy for all patients.

Follow Up

Patients were followed with history, DRE and CEA 3 month interval in first 2 year and 6 months interval thereafter. Patients underwent to CT abdomen and pelvis at 6-12 month interval and colonoscopy every 1-2 years. If recurrence was suspected, MRI ± PET/CT were performed.

Recurrence

Local recurrence(LR) was recurrence in intrapelvic area, including the anastomotic area and/or regional lymph node. Systemic recurrence or distance metastasis was the recurrence beyond the local recurrence.

Statistical Analysis

Categorical variables were compared with Chi square test. Continuous variables compared with Two-sample independent T-test. Univariate and multivariate analysis compared with the use of Cox proportional hazards. Survival and recurrence were calculated by the Kaplan-Meier method. Statistical analysis was made by STATA version14.1 P value less than 0.05 was the level of significance.

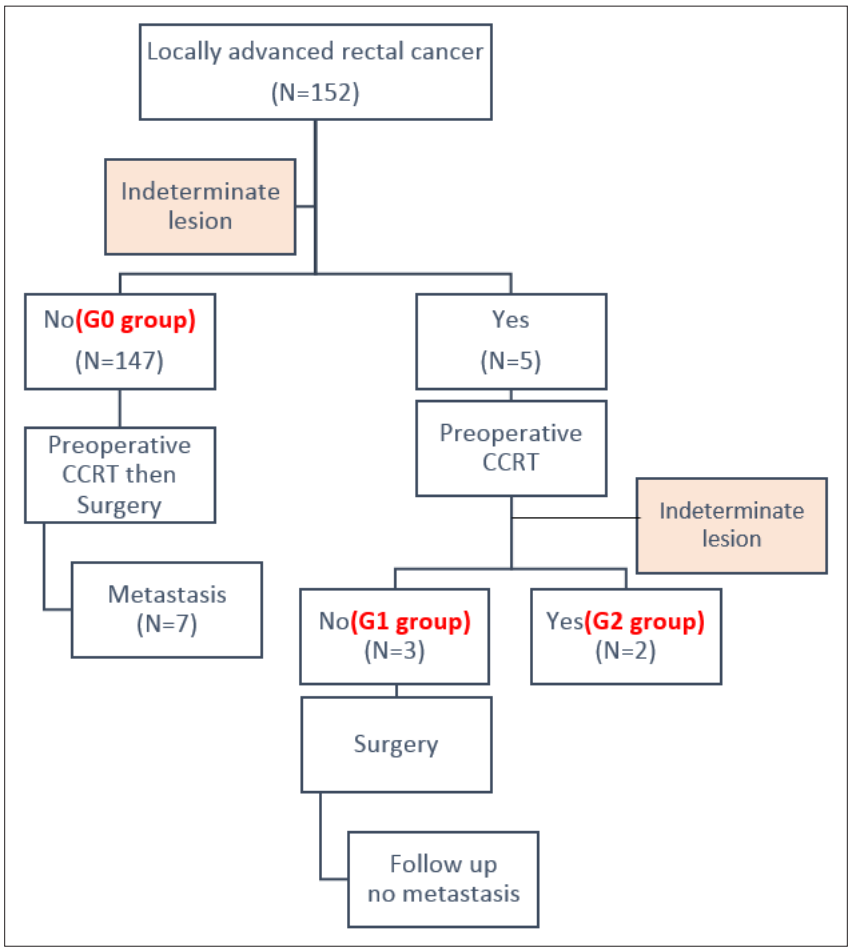
Results

Table 1: Characteristic of the patients (n = 152) between No metastasis (M0) group and distance metastasis (M1) group

Variable	M0 (n = 143)	M1 (n = 7)	p-value
Age; mean ± SD	61.6 ± 10.8	58.4 ± 11.9	0.404
Gender; n (%)			
Male	92 (64.3)	4 (44.4)	0.230
Female	51 (35.7)	5 (55.6)	
Location (cm from AV); median (IQR)	7 (5, 9)	7 (4, 10)	0.916
Preoperative biopsy; n (%)			
1 = Well differentiation	30 (21.0)	2 (22.2)	0.738
2 = Moderate differentiation	107 (74.8)	6 (66.7)	
3 = Poorly differentiation	4 (2.8)	1 (11.1)	
4 = Unknown differentiation	-	-	
5 = Fragment of dysplastic cell	1 (0.7)	0 (0)	
6 = Tubular adenoma high grade	1 (0.7)	0 (0)	
Tumor length (cm); median (IQR)	4 (3, 5.3)	5.5 (4, 8.3)	0.034
Clinical T stage; n (%)			
0 = T0	-	-	
1 = T1	-	-	
2 = T2	6 (4.2)	0 (0)	0.920
3 = T3	118 (82.5)	8 (88.9)	
4 = T4	19 (13.3)	1 (11.1)	
Clinical N stage; n (%)			
0 = N0	46 (32.2)	2 (22.2)	0.420
1 = N1	77 (53.9)	4 (44.4)	
2 = N2	19 (14)	3 (33.3)	
Preoperative CMT regimens; n (%)			
1 = 5 FU + LV	67 (46.9)	1 (11.1)	0.023
2 = Xeloda	74 (51.8)	7 (77.8)	
3 = XELOX	-	-	
4 = FOLFOX	2 (1.4)	1 (11.1)	
Waiting time from last RT to surgery(day); median (IQR)	68 (60, 87)	88 (71, 90)	0.345
preCCRT CEA; median (IQR)	5.6 (2.8, 14.1)	9.7 (5.2, 10.2)	0.284
postCCRT CEA; median (IQR)	3.2 (2.2, 4.9)	5.1 (3, 14)	0.108
Post operative CEA; median (IQR)	2.5 (1.7, 3.9)	2 (1.8, 10.9)	0.725
Clinical Response; n (%)			
0 = no	2 (1.4)	3 (33.3)	<0.001
1 = partial (by scope)	117 (81.8)	3 (33.3)	
2 = cCR (complete clinical response	14 (9.8)	0 (0)	
3 = not assessed	10 (7.0)	3 (33.3)	
Operation; n (%)			
1 = LAR	68 (47.6)	1 (20)	0.093
2 = ultralowLAR	5 (3.5)	1 (20)	
3 = APR	20 (14)	2 (40)	
4 = LAR with end colostomy	18 (12.6)	0 (0)	
5 = diversion then LAR	7 (4.9)	0 (0)	
6 = diversion then ultralowLAR	-	-	
7 = diversion then APR	3 (2.1)	1 (20)	

8 = Laparoscopic LAR	16 (11.2)	0 (0)	
9 = ISR with CCA	2 (1.4)	0 (0)	
10 = Laparoscopic APR	4 (2.8)	0 (0)	
Complication; n (%)			
1 = surgical site infection(SSI)	4 (2.8)	0 (0)	0.611
2 = perineal SSI	3 (2.1)	0 (0)	0.661
3 = presacral collection	8 (5.6)	0 (0)	0.466
4 = anastomotic stricture	-	-	-
5 = urinary retention	1 (0.7)	0 (0)	0.801
6 = Lt ureter injury	1 (0.7)	0 (0)	0.801
Specimen; n (%)			
0 = no residual tumor	20 (14)	0 (0)	0.005
1 = well differentiation	12 (8.4)	2 (40)	
2 = moderate differentiation	102 (71.3)	2 (40)	
3 = poorly differentiation	2 (1.4)	1 (20)	
4 = residual tumor, could not be classified to differentiation			
Tumor deposit; n (%)	6 (42.9)	1 (100)	0.268
Tumor gene status, n			
KRAS mutation		2	
BRAF mutation		1	
dMMR			
pMMR		3	
PI3K mutation		2	
ALI; median (IQR)	34 (24.3)	2 (40)	0.424
PNI; median (IQR)	26 (18.8)	1 (20)	0.948
CRM(cm); median (IQR)	1 (0.5, 2)	0.1 (0.1, 0.2)	0.013
Distal resection margin(cm); median (IQR)	2 (1, 3.9)	2 (1.6, 4.3)	0.832
ycT downstaging; n (%)			
0 =	15 (10.5)	4 (66.7)	0.001
1 =	126 (88.1)	2 (33.3)	
2 =	-	-	
3 =	1 (0.7)	0 (0)	
4 =	1 (0.7)	0 (0)	
ypT stage; n (%)			
0 =	23 (16.1)	0 (0)	0.120
1 =	4 (2.8)	0 (0)	
2 =	39 (27.3)	0 (0)	
3 =	73 (51.1)	4 (80)	
4 =	4 (2.8)	1 (20)	
N downstaging; n (%)	92 (64.3)	1 (16.7)	0.018
Positive LN;			
mean ± sd	0.9 ± 1.7	0.2 ± 0.4	0.350
median (IQR)	0 (0,1)	0 (0, 0)	0.409
LN all; median (IQR)	13 (8, 19)	3 (3, 17)	0.255
Timing of receiving adjuvant treatment from surgery(day); median (IQR)	43 (33, 56)	56.5 (32, 81)	0.723
Postoperative adjuvant regimen; n (%)			
1 = FOLFOX	20 (19.6)	0 (0)	0.635
2 = XELOX	30 (29.4)	1 (50)	

3 = 5FU/LV	25 (24.5)	1 (50)	
4 = Xeloda	27 (26.5)	0 (0)	
Cycles; median (IQR)	6 (6, 8)	4.5 (3, 6)	0.113
Recurrence; n (%)			
0 = no	117 (81.8)	2 (22.2)	<0.001
1 = liver	1 (0.7)	0 (0)	
2 = lung	6 (4.2)	4 (44.4)	
3 = LR	4 (2.8)	1 (11.1)	
4 = > 1 locations without LR	11 (7.7)	2 (22.2)	
5 = >1location with LR	4 (2.8)	0 (0)	



Flow Chart 2: Indeterminate Lesion in Rectal Cancer

Table 2: Characteristic of Indeterminate Lesion in G1 and G2 Group

Patients	Characteristic of indeterminate lesion	Progression after CCRT	Management	OS(months)
1	1.7 cm subpleural opacities nodule in LLL Small hepatic lesion S3,4,6	No	Usual surveillance	18
2	Small lung nodule	No	Usual surveillance	29
3	0.3 cm groundglass nodular opacity in RUL, prominent both hilar nodes	No	Usual surveillance	29
4	Multiple non-calcified solid pulmonary and subpleural nodules at RUL,RLL,LUL 0.3-0.7 cm	Lung metastasis	Systemic treatment	22
5	Multiple tiny pulmonary nodules, too small to characterize	Lung metastasis	Systemic treatment	2

Table 3: Characteristic of The Patients (n = 152) Among G0,G1 and G2 Group

Variable	G0 (n = 147)	G1 (n = 3)	G2 (n = 2)	p-value
Age; mean ± SD	61.3 ± 10.9	66 ± 13.7	61 ± 1.4	0.826
Gender; n (%)				
Male	92 (62.6)	3 (100)	1 (50)	0.383
Female	55 (37.4)	0 (0)	1 (50)	
Location (cm from AV); median (IQR)	7 (5, 9)	8 (5, 10)	7.5 (7, 8)	0.817
Preoperative biopsy; n (%)				
1 = Well differentiation	32 (21.8)	0 (0)	0 (0)	0.987
2 = Moderate differentiation	108 (73.5)	3 (100)	2 (100)	
3 = Poorly differentiation	5 (3.4)	0 (0)	0 (0)	
4 = Unknown differentiation	-	-	-	
5 = Fragment of dysplastic cell	1 (0.7)	0 (0)	0 (0)	
6 = Tubular adenoma high grade	1 (0.7)	0 (0)	0 (0)	
Tumor length (cm); median (IQR)	4 (3, 5.3)	5.5 (2.6, 6.5)	10.3 (8.3, 12.2)	0.069
Clinical T stage; n (%)				
0 = T0	-	-	-	
1 = T1	-	-	-	
2 = T2	6 (4.1)	0 (0)	0 (0)	0.983
3 = T3	121 (82.3)	3 (100)	2 (100)	
4 = T4	19 (13.6)	0 (0)	0 (0)	
Clinical N stage; n (%)				
0 = T0	48 (32.7)	0 (0)	0 (0)	0.030
1 = N1	79 (53.7)	2 (66.7)	0 (0)	
2 = N2	19 (13.6)	1 (33.3)	2 (100)	
Preoperative CMT regimens; n (%)				
1 = 5 FU + LV	67 (45.6)	1 (33.3)	0 (0)	<0.001
2 = Xeloda	78 (53.1)	2 (66.7)	1 (50)	
3 = XELOX	-	-	-	
4 = FOLFOX	2 (1.4)	0 (0)	1 (50)	
preCCEA; median (IQR)	5.6 (3.1, 13.6)	6.5 (1.9, 16.2)	9.7 (9.7, 9.7)	0.881
postCCEA; median (IQR)	3.2 (2.2, 5.2)	4.5 (2.5, 6.5)	4.1 (4.1, 4.1)	0.839
Clinical Response; n (%)				
0 = no	4 (2.7)	0 (0)	1 (50)	0.003
1 = partial (by scope)	117 (79.6)	3 (100)	0 (0)	
2 = cCR (complete clinical response	14 (9.5)	0 (0)	0 (0)	
3 = not assessed	12 (8.2)	0 (0)	1 (50)	
Recurrence; n (%)				
0 = no	115 (78.2)	3 (100)	1 (50)	0.712
1 = liver	1 (0.7)	0 (0)	0 (0)	
2 = lung	9 (6.1)	0 (0)	1 (50)	
3 = LR	5 (3.4)	0 (0)	0 (0)	
4 = > 1 locations without LR	13 (8.8)	0 (0)	0 (0)	
5 = >1location with LR	4 (2.7)	0 (0)	0 (0)	

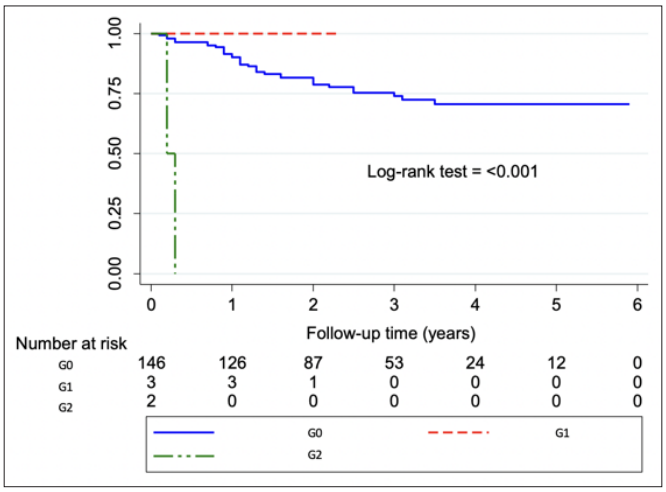


Figure 1: Kaplan-Meier Curves Evaluating Survival of Recurrence

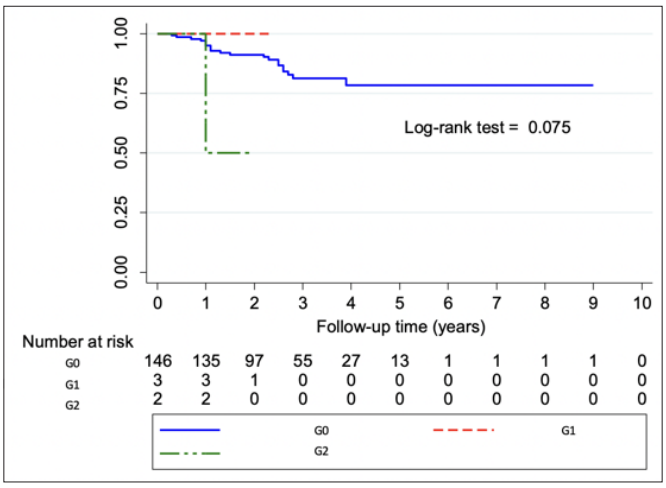


Figure 2: Kaplan-Meier Curves Evaluating Survival of Death

Clinical and Pathologic Characteristics

Characteristics of each group were described in Table 1. Most of characteristics including age, gender, location, preoperative histology, clinical stage, waiting time from RT to surgery, CEA level ,operation, pathological T down stage, postoperative pathology, DRM, CRM, timing from surgery to adjuvant treatment and regimen of postoperative chemotherapy were no significant difference between 2 groups. The tumor length was significantly higher in group M1 (p 0.034). According to CCRT regimen, xeloda and 5FU/LV regimen were significantly higher in group M0 and FOLFOX was significantly higher in group M1(p 0.023). No clinical response was significantly higher in group M1 (p<0.001). Poorly differentiated tumor was significantly higher in group M1(p=0.005). Pathological N down stage was significantly higher in group M0(p=0.018).Post operative complication,there was no significant difference between 2 groups.

Interesting point of characteristics among G1 G2 and G3 were described in flow chart (1), table 2 and Table 3. The prevalence of IPN was 3.29% and turned to be malignant around 40% of patients.

Flow chart (2) illustrated the indeterminate lesion in rectal cancer patients(N=152). 5 patients had indeterminate lesion and underwent preoperative CCRT. Follow-up imaging after CCCT, we found 2 patients turned to be malignant and no change of lesion in 3 patients. Turning to another flow of no indeterminate lesion group, a total of 147 patients receiving curative resection after preoperative CCRT developed distance metastasis in 7 patients who did not have any previous indeterminate lesion.

Characteristic of indeterminate lesion of G1 and G2 were demonstrated in 5 patients at table 2. All of them had IPN and 1 of patient had ILN.

Characteristics among G1G2 and G3 were described in table 3. The clinical N2 was significantly higher in group G2 (p 0.03). According to preoperative FOLFOX regimen was significantly higher in group G2(p<0.001). Moreover, no clinical response was significantly higher in group G2 (p 0.003). Moreover, disease free survival of patients in G1 and G0 were significantly higher than that of patients in G2(P<0.001). There were no statistically significant differences in overall survival among 3 groups (p=0.075).

Discussion

The prevalence of indeterminate lesion was 3.29%. The prevalence was less than the 9% reported by Nordholm-Carstensen et al and 15.4% reported by Silva et al because our study only focused on rectal cancer patients underwent preoperative CCRT [8,9]. Moreover, a variation in definitions, CT scan protocols might reflected the result. This study reveals 40% of indeterminate lesion turned to be malignant. This is higher than the 10% reported by Nordholm-Carstensen et al and similar to the 41.2% reported by Silva et al [8,9]. The factors associated indeterminate lesion turned to malignant were patients who had clinical stage N2, receiving preoperative FOLFOX4 regimen and no clinical response after preoperative CCRT. Similarly from previous study showed lymph node metastasis was signifcantly factor of malignant nodules [8,9]. So, these factors might be used to determine the high risk group of patient.

Interestingly, we are better understanding the nature of indeterminate lesion that it is low incidence but if the lesion is suspected to be malignant, we should intensive follow up imaging after preoperative CCRT especially in high risk group as above. Due to 40% of patients turned to be malignant if they had indeterminate lesion. Moreover, if imaging showed negative result after preoperative CCRT, repetitive chest CT scan results unnecessary radiation exposure and patient anxiety. We can follow up as usual due to no patient developed metastasis and no significant difference of survival.

The tumor length was significantly higher in group M1 (p 0.034). According to CCRT regimen, xeloda and 5FU/LV regimen were significantly higher in group M0 and FOLFOX was significantly higher in group M1(p 0.023). No clinical response was significantly higher in group M1 (p<0.001). Poorly differentiated tumor was significantly higher in group M1(p=0.005). Pathological N down stage was significantly higher in group M0(p=0.018).The result were similar from previous study Future studies should incorporate these characteristics for development an risk stratification model [10,11].

Our study is a retrospective review conducted at a single institution; thus, it has some limitations. First, the study is statistically underpowered for a valid statistical analysis with small sample size in incidence of indeterminate lesion. Second, types of CT scanners affect the detectable radiological characteristics. Third, the radiological expertise available for assessing the CT scans.

Conclusion

Such a low incidence of indeterminate lesion should not cause further preoperative diagnostic workup besides routine regimens. In addition, it is not necessary to perform excessive surveillance routinely for all rectal cancer patients underwent preoperative CCRT who have indeterminate lesion. Intensive follow up chest CT or invasive diagnosis modalities should be considered in patients who had clinical stage N2, receiving preoperative FOLFOX4 regimen and no clinical response after preoperative CCRT. Moreover, longer period follow up should be considered in high risk pateints for developing distance metastases including large tumor length, patients receiving adjuvant FOLFOX4, no clinical response of tumor after preoperative CCRT and poorly differentiated tumor [17].

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Surgical research unit, Ramathibodi hospital, Mahidol university, Thailand

Ethical Approval

Human Research Ethics Committee, Ramathibodi Hospital, Mahidol University COA. MURA2021/668.

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Author Contribution

Miss Yada Phengsalae Yada collected and analyzed the data.

Conflicts of Interest

None

Statement Conflict of Interest : No conflict of interest in this study

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