Section: Surgical Oncology

Original Research Article

CORRELATION OF PET/CT WITH POST-OPERATIVE HISTOPATHOLOGY IN RECTAL CANCER

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ABSTRACT

Background: Aim: To investigate the role of PET/CT in preoperative staging of rectal cancer in comparison with intraoperative findings and histopathology. **Materials and Methods:** A prospective observational correlational study conducted between August 2015 to December 2016 including 45 patients. **Result:** SUV of tumour varied with histology. Bowel wall invasion in PET/CT (soft tissue stranding/infilteration seen in imaging) did not correlate with pathological T-stage of tumour. Size of largest lymph node in PET/CT showed significant correlation with number of involved nodes (p=0.004) but not with ratio of involved to examined nodes. SUV of lymph node was higher in those with metastatic nodes compared to nonmetastatic nodes, but it did not show statistically significant correlation with number of involved node or ratio of involved to examined nodes. In patients who received neoadjuvant chemoradiation, SUV of primary tumour correlated with the response to treatment (p=0.009). **Conclusion:** PET/CT in rectal cancer is useful for assessing lymph node metastasis and response to neoadjuvant treatment, while its usefulness in assessing bowel wall invasion requires further evaluation. Further larger studies would be helpful in establishing the role of PET/CT in locoregional staging of rectal cancer.

INTRODUCTION

Colorectal cancer is third most common malignancy in the world (third most common among men and second most common among women).There were an estimated 1,360,000 (746000 in men and 614000 in women) cases of colorectal cancers worldwide in the year 2012, with an estimated 694,000 (374000 in men and 320000 in women) deaths.[1]

Positron emission tomography (PET) is a nuclear medicine, functional imaging technique that produces a three-dimensional image of functional processes in the body. Positron-emitting radionuclide (tracer) is introduced into the body on abiologically active molecule. The system detects pairs of gamma rays emitted indirectly by the tracer. Three dimensional images of tracer concentration within the body are then constructed by computer analysis. If the biologically active molecule chosen for PET is fluoro deoxy glucose (FDG), an analogue of glucose, the concentrations of tracer imaged will indicate tissue metabolic activity as it corresponds to the regional glucose uptake. This can be used to detect the spread and metastasis of cancer. If three dimensional imaging of the patient is done with a CT scan in the same session it is known as PET/CT.

PET/CT can be used as a method to detect the local, regional and distant spread of rectal cancer. In case of patients who have undergone neoadjuvant treatment, PET/CT is done after about 6 weeks, which is followed by surgery. We plan to study the usefulness of PET/CT in detecting the extent of disease in rectal cancer by comparing with intraoperative findings and histopathology for correlations.

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MATERIALS AND METHODS

A prospective observational correlational study conducted in Healthcare Global Hospital, Bengaluru and Bangalore Institute of Oncology, Bengaluru between August 2015 to December 2016.

Sample Size with Calculation

According to Olivera Ivanov et al, PET/CT has a sensitivity of 86.7% for detecting lymph node metastasis in rectal cancer72. With the above sensitivity, precision of 10% and desired confidence level (1- alpha) of 95%, we used the below formula to calculate the sample size.

Estimating single proportion (Absolute precision)

Formula:

$$n = \frac{z_{1-\frac{\alpha}{2}}^2 \, p(1-p)}{d^2}$$

Where, p : Expected proportion d : Absolute precision

1- □/2 : Desired Confidence level

The required sample size was 44.

Inclusion Criteria

1. Patients with histologically proven rectal cancer
2. Patients who donot have confirmed distant metastasis
3. Patients who underwent PET/CT before surgery
4. Patients who are fit for surgery

Exclusion Criteria

1. Confirmed distant metastases
2. Patients who have not undergone PET/CT before surgery
3. Patients who were found unresectable during surgery
4. Patient not willing for surgery
5. Patient does not undergo surgery for any other reason

Methodology

Forty-five patients of rectal cancer were included in our study, out of whom one was a case of locally recurrent rectal cancer. History of all the patients were taken and general and per rectal examination had been done for all the patients. Colonoscopy was done in all the patients and malignancy proved with biopsy.

In colonoscopy, we classified the tumors into those arising from lower rectum, mid-rectum and upper rectum. Tumors with distal margin involving the lower 7.5 cm from anal verge, including 2.5 cm of anal canal were grouped as lower rectal lesions. Tumors with distal margins involving the rectum 7.5 to 12.5 cm from anal verge (or 5-10 cm from anal sphincters) were grouped as mid-rectal tumors. Tumors with distal margins situated in the rectum more than 12.5 cm from anal verge or 10 cm from anal sphincters were classified as upper rectal tumors. After the staging investigation, 16 patient were planned for neoadjuvant chemoradiation therapy. 29 patients were planned for surgery. Initial staging investigation for 38 patients was PET/CT (for all the 29 patients who were planned for surgery and for 9 patients out of 16 who were planned for neoadjuvant chemoradiation). In 7 patients out of 19 who were planned for neoadjuvant chemoradiation, PET/CT was not done as they already had a CECT of abdomen done.

Procedure of PET/CT

Whole body CT scan covered a region from vertex to upper thighs. 1 ml/kg of iodinated contrast agent was given intravenously, and rectal contrast using a diluted solution of an ionic contrast agent (sodium diatrizoate, meglumine diatrizoate) was given. A limited breath holding technique was used to avoid motion induced artifacts in the area of the diaphragm. The PET component had an axial field of view of 15.5 cm (per bed position) with an in-plane spatial resolution of 4.6 mm. PET images were acquired 60 minutes following the administration of 5.5 MBq/kg of FDG covering the same field of view as with CT. The acquisition time was 3 minutes per bed position. Images were scatter corrected. Image reconstruction was done with and without PET attenuation correction. PET attenuation correction was based on CT data. Before the injection of the radioactive tracer, a blood sample was taken to ensure blood glucose levels were within the normal range. The diabetic patients were ensured to have a good control of blood sugar levels before the scan.

In PET/CT, the rectum was identified from sigmoid colon by the absence of mesentery. The position of the tumor in the rectum, enlarged lymph nodes (based on maximum diameter), SUV of the primary tumor and the lymph nodes were noted.

Surgery

Surgery was done for the patients. During surgery, the rectal/rectosigmoid tumors above the peritoneal reflection were grouped as upper rectal tumors; those tumors present at the peritoneal reflection were classified as mid-rectal tumors; and the ones well below the peritoneal reflection close to the pelvic floor and situated in the anorectum were classified as lower rectal tumors.

Abdominoperineal resection, low anterior resection, anterior resection or ultra-low anterior resection was done depending on the position of the tumor and the safety of sphincters. One patient had tumour infilterating the urinary bladder, where partial cystectomy was done with anterior resection, and another patient had tumour infilterating prostate where prostatectomy was done with abdominoperineal resection. All the cases underwent total mesorectal excision.

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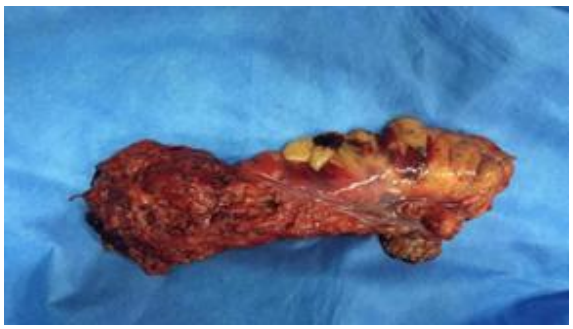

Figure 1: specimen of low anterior resection

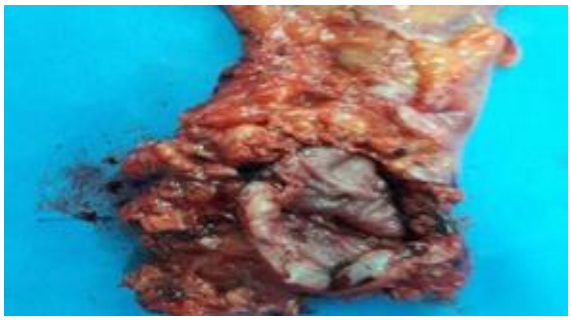

Figure 2: Specimen of low anterior resection showing the tumor Histopathological examination:

The specimen were sent for histopathology, where gross and microscopic examination were done. Type of tumor, grade of tumor, T stage (bowel wall invasion), status of lymph nodes, response to treatment (in patients who received preoperative treatment) and other characteristics were noted.

Figure 3: Low anterior resection specimen being grossed (arrow indicating the lesion)

Primary Outcomes assessed:

- Site of the primary tumor in PET/CT and colonoscopy and in surgery
- SUV of primary tumor and histology
- Size of lymph nodes in the PET/CT and gross size of lymph node
- Size of lymph node in PET/CT and number of lymph nodes involved
- Size of lymph node in PET/CT and percentage of lymph nodes involved
- SUV of lymph node in PET/CT and number of lymph nodes involved
- SUV of lymph node in PET/CT and percentage of lymph nodes involved

Secondary Outcomes assessed

- SUV of the primary tumor in patients who received neoadjuvant chemoradiation and pathological response
- Change in SUV of the primary tumour in patients who received neoadjuvant chemoradiation and pathological response
- Change in thickness of the primary tumour in patients who received neoadjuvant chemoradiation and pathological response

Statistical Analysis

The information regarding all the cases was recorded in a master chart. The Statistical analysis was performed on a computer by SPSS 23.0. In Descriptive statistics , the continuous variable will be expressed as Mean and Standard deviation . Categorical variables will be expressed as frequency and percentage. Under parametric test,

Karl Pearson correlation was used between two variables when the data followed normal distribution. Under non parametric test, where data did not follow normal distribution, Spearman rank correlation was used between two variables, Chi-square test was used to find out association between two categorical variables and Kruskal Wallis test was used to find the differences in SUV among histological groups. Sensitivity and specifivity will be found out under diagnostic test.

$P<0.05$ was considered as statistically significant.

RESULTS

Mean age of the patients was 58 years, the youngest being 28-year-old and the oldest being 87-year-old.

Table 1: Age wise distribution of cases

Age	No. of patients
0-19	0
20-39	4
40-59	17
60-79	21
80 or more	3
Total	**45**

There were 29 male and 16 female patients in our study.

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On colonoscopy, there were 18 cases of upper rectal tumor, 9 cases of mid rectal tumors and 18 cases of lower rectal tumors.

In PET/CT, 20 tumors were classified as upper third, 10 as middle third and 15 as lower third tumors.

Intraoperatively, 18 tumors were found to be upper rectal, 10 tumors were found to be mid-rectal and 17 tumors were found to be lower rectal tumors.

Abdominoperineal resection was done in 9 patients, low anterior resection was done in 14 patients, anterior resection was done in 16 patients, ultralow anterior resection was done in 4 patients, anterior resection with partial cystectomy was done in one patient and abdominoperineal resection with prostatectomy was done in one patient. Out of these patients 11 of them required temporary ileostomy, whereas 10 patients had permanent colostomy.

On final post-operative histopathological examination, 6 cases did not show any tumor in the primary site. Majority of patients (30 patients) had moderately differentiated adenocarcinoma, 2 patients had well differentiated adenocarcinoma and 4 patients had poorly differentiated adenocarcinoma. There were also 2 cases of mucinous adenocarcinoma and 1 case of signet ring cell type adenocarcinoma.

Out of the 45 patients 6 patients had pT0 (complete response of the primary tumour to neaoadjuvant therapy, one patient among them had a single metastatic lymph node), 13 patients had pT2 tumor (invasion into the muscularis propria), 22 patients had pT3 tumor (invasion beyond muscularis propria but not into the peritoneum), 2 patients had pT4a tumor(invasion into the visceral peritoneum) and 2 patients had pT4b tumor (invasion into the adjacent organs).

Of the two pT4b cases, one case showed tumor infilteration into urinary bladder and the other case showed infilteration into prostate.

Out of 45 patients, 23 patients did not have any involvement of lymph nodes on histopathology. The highest number of lymph nodes involved in a patient was 14. In the patients who had taken preoperative chemoradiation therapy, the highest number of lymph nodes involved was 6, and 8 cases out of 16 patients did not have any lymph node involvement in histopathology.

In patients who did not take preoperative chemoradiation, the highest number of lymph nodes involved was 14, 15 out of 29 patients did not have any evidence of pathological involvement of lymph nodes.

Table 2: Nodal staging of the tumors who received/did not receive neoadjuvant chemoradiation

	N0	N1a	N1b	N1c	N2a	N2b
Neoadjuvant chemoradiation given	8	5	2	0	1	0
No neoadjuvant chemoradiation	15	6	5	0	2	1

On histopathological staging, 5 patients had Stage 0 (no tumour seen in histopathology, complete pathological response), 6 patients had Stage I, 12 patients had Stage II, 21 patients had Stage III. One patient had ypT0N1a disease.

Table 3: Pathological Staging of the cases in our study

STAGE 0	**T0N0**	**5**
STAGE I	T2N0	6
STAGE IIA	T3N0	11
STAGE IIB		0
STAGE IIC	T4bN0	1
STAGE IIIA	T2N1a	2
	T2N1b	4
STAGE IIIB	T2N2a	1
	T3N1a	7
	T3N1b	2
	T3N2a	1
	T4aN1a	1
STAGE IIIC	T3N2b	1
	T4aN2a	1
	T4bN1b	1
	T0N1	1
TOTAL		45

Location of tumor

Site of tumor which was detected in the PET/CT was compared with that found in the colonoscopy and during surgery and was found to match well.

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Table 4: Comparison of site of tumor in PET/CT and during surgery

		Site of tumor in surgery		
		Upper third	**Mid third**	**Lower third**
Site of tumour in PET/CT	Upper third	18	2	0
	Mid third	0	7	3
	Lower third	0	1	14
Total		18	10	17

We compared the site of the tumor as seen in PET/CT with the type of surgery done for the patient and stoma done during the surgery. The patients who were depicted to have upper third tumors underwent anterior resection (16 patients-80%) or low anterior resection (3 patients15%) and one patient underwent anterior resection along with partial cystectomy, none of them requiring abdominoperineal resection or ultralow anterior resection.

Among the patients who had middle third tumors according to PET/CT, 8 (80%) of them underwent low anterior resection, one of them underwent abdominoperineal resection, and one patient underwent ultralow anterior resection.

Out of the 15 patients who were showing lower third tumor in PET/CT, 8 (53.33%) of them underwent abdominoperineal resection, 3 (20%) of them underwent low anterior resection, 3 (20%) of them underwent ultralow anterior resection, and one patient underwent abdominoperineal resection with prostatectomy.

Out of 20 patients who had upper third tumors in PET/CT, only 2 (10%) patients underwent temporary diverting ileostomy, none of them required permanent colostomy.

Of the 10 patients who had middle third tumors in PET/CT, 4 (40%) of them required temporary ileostomy and 1 (10%) of them required permanent colostomy.

Among 15 patients depicted to have lower third tumor in the PET/CT, 9 (60%) patients underwent permanent colostomy, and 5 (33.3%) patients underwent temporary ileostomy. Only one patient among them did not require any stoma.

Standard Uptake Value

Standard uptake value of the primary tumor ranged from minimal nonsignificant uptake (which was taken as 0) to 45.8. Mean SUV was
15.56 (S.D=11.46).

In patients who did not receive neoadjuvant chemoradiation therapy (n=29), SUV ranged from 5.2 to 45.8 with mean SUV of 21.09 (S.D=10.39).

In patients who underwent neoadjuvant chemoradiation (n=16), SUV ranged from 0 to 15.7 with mean SUV of 5.53 (S.D=4.16).

The SUV of the primary tumor is clearly higher in the cases who did not receive
neoadjuvant chemoradiation compared to those who received chemoradiation.

There were 4 patients among the ones who took chemoradiation, whose SUV was
negligible or nil.

We compared the SUV with the histology of the primary tumor, and there is a statistically significant correlation (P=0.001).

In patients where no tumor cells was seen in the microscopy in the primary tumour(n=6, five of them had complete pathological response and one of them had a single node with metastasis), the mean SUV was 2.33 (S.D=2.63), the maximum SUV was 5.5, and three cases showed insignificant SUV. In patients with well differentiated adenocarcinoma (n=2), mean SUV was 4.85.

In patients with moderately differentiated adenocarcinoma (n=30, highest in our series), mean SUV was 19.44 (S.D= 11), least SUV was 4.9 and highest SUV was 45.8.

In patients with poorly differentiated adenocarcinoma (n=4), mean SUV was 16.48 (S.D=11.422). In the patient with mucinous adenocarcinoma histology, mean SUV was 5.75, and in the patient with signet ring type adenocarcinoma SUV was 15.7.

Bowel Wall Invasion

PET/CT showed soft tissue stranding around the rectum in 27 patients and in 2 patients it showed infilteration to surrounding structures. This was compared with the bowel wall invasion in the histopathology (T staging).

Table 5: Soft tissue stranding and infilteration seen in PET/CT Vs T stage (bowel wall invasion)

	T Stage				
	T0	**T1**	**T2**	**T3**	**T4**
No stranding	4	0	4	6	2
Stranding present	2	0	9	15	1
Infilteration and stranding	0	0	1	1	1

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There was no statistical significance correlation of T-stage (bowel wall invasion) with soft tissue stranding and/or infiltration shown by the PET/CT (P=0.444).
In two patients there was infiltration into surrounding structures found during surgery, in one patients into the bladder and in another patient into the prostate. The infiltration into the bladder was shown by CT component of the scan, but the infiltration into the prostate was not shown by the scan.

Size of the lymph nodes

The mean size of the largest lymph node in PET/CT was 1.07 cm, while the mean size of largest lymph node as measured during the pathological examination was 1.06 cm.
The largest node in our series measured 5.8 cm in PET/CT and 5.5 cm in pathological examination.
We did the comparison of size of lymph node detected on PET/CT with the actual size of lymph node in the pathology examination, number of lymph nodes involved, and the percentage of lymph nodes involved.
Size of the lymph nodes detected in the PET/CT correlated well with the actual size of the lymph nodes (P<0.001).
On correlating the size of lymph nodes in PET/CT with the number of positive lymph nodes there statistically significant correlation (P=0.004). On analyzing separately in patients who took neoadjuvant treatment and who did not take neoadjuvant treatment, there was statistically significant correlation between size of lymph node as in PET/CT and the number of lymph nodes (P=0.029 in the cases who did not receive neoadjuvant therapy and P=0.036 in the cases who received neoadjuvant treatment)
The mean size of lymph nodes in patients with non-metastatic lymph nodes was 0.76 cm (S.D= 0.59), and the mean size of lymph nodes in patients with metastatic lymph nodes was 1.4 cm (S.D=1.27).
Using PET/CT for detection of positive lymph nodes based on size (>0.8 cm), sensitivity was 72.73%, specificity was 60.87%, positive predictive value was 64% and negative predictive value was 70%.
There was statistically significant correlation between size of lymph node and number of positive lymph nodes.

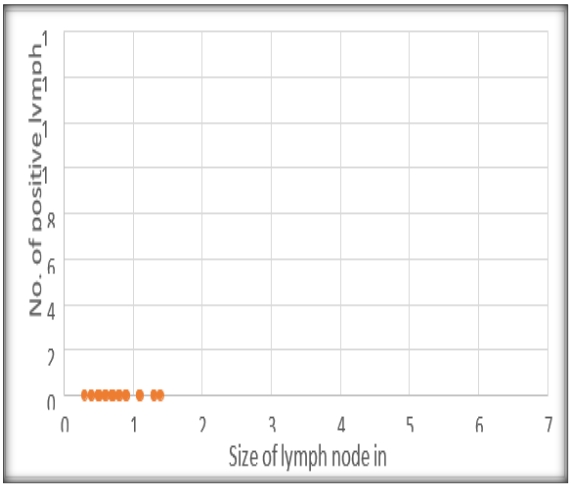

Figure 1: Scatter plot of size of non-metastatic lymph nodes

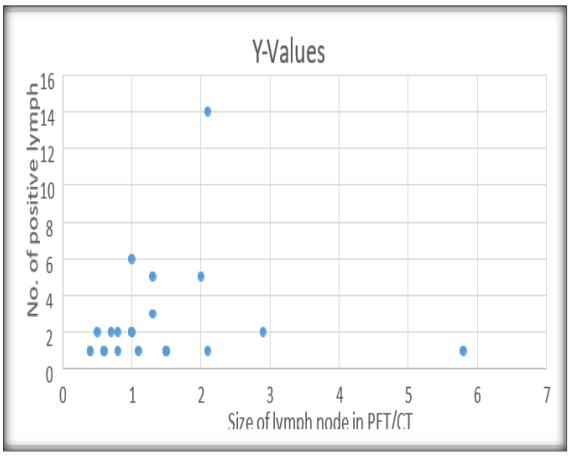

Figure 2: Scatter plot of size of lymph nodes which showed metastasis

The correlation between the percentage of lymph nodes showing metastasis and the
size of lymph node detected on PET/CT was not statistically significant (P=0.095).

SUV of Lymph Nodes

The mean SUV of lymph nodes was 2.81 (S.D=4.91), highest being 27.9 and insignificant (taken as 0) in 22 cases. SUV of the lymph node did not correlate significantly with the number of positive lymph nodes (P=0.11) or percentage of positive lymph nodes (P=0.215).
However, the mean SUV of lymph nodes in patients with non-metastatic lymph nodes was 1.1 (S.D=1.87, with 15 cases, 65.22%, having SUV of 0), and the mean SUV of lymph nodes in patients with metastatic lymph nodes was 4.6 (S.D=6.28, with 7 cases, 31.82% having SUV of 0). Although there is no statistical significance, there is a large difference between the SUV of lymph nodes in patients with metastatic and nonmetastatic lymph nodes.

PATIENTS WHO RECEIVED NEOADJUVANT CHEMORADIATION

Out of the 16 patients who received chemoradiation, 6 patients had complete response of the primary tumor (grade 0; 5 of them had complete pathological

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response, one patient had no tumor seen in the primary site but one positive lymph node), 5 patients had moderate response (grade1) to neoadjuvant treatment and 5 patients had minimal response (grade 2). Correlation between SUV of the primary tumor and tumor response was analysed. There was significant correlation between SUV of the primary tumor and tumor response (P=0.009).

In 9 of the patients who took neoadjuvant chemoradiation, PET/CT scan had been done before and after the neoadjuvant therapy.

We analysed the decrease in the thickness of the rectal wall at the tumor site and the decrease in SUV. The maximum decrease in thickness of the rectal wall was 10mm and mean reduction in thickness was 3.8 mm (S.D=3.85). In 3 cases, there was no change in thickness of rectal wall. The highest reduction in SUV of the tumor was 12.1, the least reduction was 4.4, and the mean reduction in SUV was 6.98 (S.D=2.34).

In these patients, on further analysis, there was no statistically significant correlation between tumor response and change in the SUV (P=0.18).

Table 6: SUV of primary tumor with tumor response to neoadjuvant therapy

		Tumour Response in the Primary			
		complete response (grade 0)	**moderate response (grade 1)**	**minimal response (grade 2)**	**no response (grade 3)**
SUV of primary	**0-2.5**	3	1	0	0
	2.5-5.0	2	1	0	0
	5.0-10	1	3	4	0
	10.0-20	0	0	1	0

But the patients who had complete pathological response showed larger decrease in SUV (mean decrease in SUV =9.53) when compared to those who had moderate (mean decrease in SUV=6.13) or minimal response (mean decrease in SUV= 5.27).

Tumor response did not show any correlation with change in thickness of the tumor (P=0.157)

In four patients PET/CT showed enlarged lymph nodes in the inferior mesenteric group. This was helpful for careful proximal ligation of the inferior mesenteric artery during surgery, so that the enlarged lymph node could be extracted.

DISCUSSION

Biopsy proven 45 patients with rectal cancer were included in our study. Except 4 patients all the patients were above 40 years of age.

In a study by Rebecca Siegel et al, done in the United States, the probability of developing colorectal cancer increases with increasing age. The probability was 1 in 80 (males) and 1 in 112 (females) between 60 to 69 years; and 1 in 26 (males) and 1 in 28 (females) over 70 years of age59. The age of the patients in our study is in agreement with this.

Among the 10 patients who had middle third tumors according to PET/CT, 8 of them underwent low anterior resection, 1 patient underwent ultra-low anterior resection and 1 of them underwent abdominoperineal resection. Four patients required temporary stoma and 1 of them required permanent stoma.

We analysed the data comparing the site of the tumor as seen by PET/CT with the requirement of stoma (temporary or permanent), there. Among the upper third tumors, the incidence of stoma is less, and with distal situation of the tumor, the incidence of stoma increases.

In our study we compared the presence of soft tissue stranding around the rectum and infilteration with the T-stage (bowel wall invasion). There was no statistically significant correlation between the presence of soft tissue stranding and extent of bowel wall involvement. We imply that the presence of soft tissue stranding not only signifies perirectal tissue invasion, but is also seen in desmoplastic reaction of the tissues.

Out of two cases where where infilteration was seen, one patient had infilteration into the urinary bladder and the other patient had pT3 disease in the primary. Another patient who had infilteration into the prostate was not shown in the the scan.

Kim et al says in his study on rectal cancer staging with MRI, that presence of lymph nodes > 8 mm was seen only in the nodepositive group.72

We correlated the size of the lymph nodes in the scan with the number of positive lymph nodes in cases who had received neoadjuvant chemoradiation and in cases who did not receive neoadjuvant chemoradiation, and in both we found statistically significant correlation.

Ratio of metastatic to examined lymph nodes in rectal cancer was evaluated for its value in the prognosis of disease by Peschaud et al. Their study found that lymph node ratio was a significant prognostic factor for both overall and disease free survival in patients with rectal cancer, even in patients with fewer than 12 lymph nodes examined. 73

There was significant statistical correlation

On analyzing the 6 cases who had no tumour seen in the primary site (5 of them had complete pathological response, one of them had a single node with metastasis), the maximum SUV was 5.5, and 3 cases had insignificant SUV, where as in other cases the SUV was much higher. With a cutoff of 5 for the SUV, sensitivity was 83.33% and specificity was 80% in our study, to predict the histological absence of tumour cells in the primary site.

Neoadjuvant chemoradiation is advised in low rectal cancers. Studies have reported it to be helpful in

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sphincter preservation in low lying tumors80,81. MRI is said to have a high accuracy for T staging of rectal cancer in various studies82,83. We suggest complementary imaging with MRI in low lying tumors where sphincter preservation is the aim.

CONCLUSION

The location of tumor, and enlarged local and regional lymph nodes in rectal cancer is predicted well by PET/CT, which correlates with the surgical and gross examination findings. As the lymph node metastasis correlates with the lymph node size seen in the PET/CT, size criteria can be used for predicting lymph node metastasis. SUV is higher in metastatic nodes than in non-metastatic nodes, although the association is not statistically significant. A larger study might show significant association which is not apparent in our study. PET/CT was not good for assessing bowel wall invasion (T-stage) according to our study. SUV in PET/CT correlates with the histology of the tumor in a subset of rectal cancer. Patients with neoadjuvant treatment showed comparative difference of SUV (pre and post concurrent chemoradiation therapy), and the SUV of the primary tumor in the PET/CT (post neaoadjuvant therapy) correlated with the response to neoadjuvant therapy.

We conclude that, PET/CT in staging for rectal cancer is useful for locating the tumor, detecting lymph node metastasis and analyzing the response to neoadjuvant treatment, while it is not good for assessing bowel wall invasion. Further larger studies would be helpful in establishing the role of PET/CT in rectal cancer staging.

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