PERITONEAL WASH CYTOLOGY POSITIVITY IN CLINICALLY AND RADIOLOGICALLY PROVEN NON-METASTATIC ADENOCARCINOMA STOMACH – A TERTIARY CARE HOSPITAL STUDY

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ABSTRACT

BACKGROUND

The presence of intra-peritoneal free cancer cells (IPFCC) in adenocarcinoma stomach has been proven to be associated with grim prognosis and is staged as M1 disease in latest TNM staging. Major resections are not indicated in these patients that will add to the morbidity and increase the cost and duration of hospital stay and also delay the commencement of palliative chemotherapy.

MATERIALS AND METHODS

Study was conducted in a tertiary care apex institute in Kerala, India. 60 consecutive cases of clinically and radiologically proven non-metastatic adeno carcinoma stomach with tissue diagnosis, who were being planned for curative resection, were selected and subjected to preoperative laparoscopic peritoneal washing. 300 ml of normal saline was introduced to peritoneal cavity. Which was aspirated after irrigating all surfaces of the peritoneal cavity. Sample was centrifuged, stained with Papanicolaou stain and cytological analysis for IPFCC was done from the Department of Pathology. Statistical analysis was done using SPSS software version 18.1 and p-value <.05 was considered as significant.

RESULTS AND DISCUSSION

31.6% (19 cases) of the clinically and radiologically proven non-metastatic adenocarcinoma stomach were restaged as metastatic disease after laparoscopic peritoneal wash cytology analysis. Of them 14(23.3% of the sample) had visible peritoneal metastasis found during laparoscopic inspection, but the remaining 5 cases did not have visible peritoneal metastasis but were positive for IPFCC which could be detected only after peritoneal wash cytology analysis and not by mere laparoscopic inspection, which accounts for 10.8% of those who were labeled as non-metastatic and curable even after preoperative diagnostic laparoscopy.

CONCLUSION

Preoperative laparoscopy and peritoneal wash cytology analysis is mandatory in clinically and radiologically proven non-metastatic carcinoma stomach, who are being planned for curative resection. Unnecessary surgery will increase morbidity and mortality.

KEYWORDS

Peritoneal cytology, Metastatic adenocarcinoma.

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INTRODUCTION: The incidence of carcinoma stomach has been decreasing worldwide during the last decade. Still it comprises a major part of cancer related death. The pattern of malignancy is also changing with more cases of proximal gastric carcinomas being reported, still the most common site remains to be the gastric antrum. The management of carcinoma stomach is greatly decided by the stage of the disease.

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The recent modifications of AJCC cancer staging of carcinoma stomach were made based on this observation. Following the confirmatory tissue diagnosis of adenocarcinoma obtained by endoscopic biopsy preoperative staging evaluation is mandatory.

In the preoperative staging of gastric adenocarcinoma, CECT imaging has been the main modality of investigation and it also decides whether the tumour is resectable or not. In early gastric adenocarcinoma, gastrectomy with adequate level of lymph node dissection is largely curative and will prolong the long term disease free survival of the patient. But in locally advanced adenocarcinoma, multi-modality treatment with the addition of chemotherapy and radiotherapy is advocated to decrease the chance of recurrence. Still the recurrence rate is very high, even with

an apparent R0 resection. If there is evidence of distant metastasis or peritoneal deposits, tumour becomes incurable and there is no role for a major gastric resection. The patient may be considered for palliative chemo radiation. Palliative surgery is indicated if there is obstruction, perforation or bleeding. The role of palliative resection in prolonging survival is not supported by major study groups.

In many of the cases, liver metastasis and large peritoneal metastasis can be detected by CT scanning alone. But ability of modern generation CT to detect small volume peritoneal deposit is questionable. This can be detected by a laparoscopic inspection.

Patients with viable cancer cells in the peritoneal cavity are bound to harbour micrometastases on the peritoneal surface and are at a high risk of suffering from peritoneal carcinomatosis. These are invariably classified into Stage IV by the Japanese Classification of Gastric Carcinoma.[1] The Japanese Treatment Guidelines for Gastric Cancer recommends chemotherapy, radiotherapy and supportive care for Stage IV gastric cancer. This concept can be accepted in countries where morbidity and mortality from gastric cancer surgery is not negligible.[2] But the prognosis of curative resection in advanced gastric cancer in general, remains dismal.[3]

The peritoneal wash cytology analysis to pick the intraperitoneal free cancer cells (IFCC) can be done at the time of initial laparoscopic evaluation. So peritoneal wash cytology should be considered before planning laparotomy to finally decide on an extensive procedure with a curative intent. Thus pre-operative laparoscopy and peritoneal wash cytology analysis will help to detect metastatic disease and unnecessary laparotomies can thus be avoided.

Many of the radiologically proven non metastatic tumours with positive peritoneal cytology may need laparotomy for palliative cause. Apart from these palliative reasons, many unnecessary laparotomies are performed in most of the centers as routine pre-operative laparoscopy and peritoneal wash cytology are not practiced. So a prospective cohort study to quantify the incidence of visible peritoneal deposits and positive peritoneal wash cytology in clinically and radiologically proven non-metastatic gastric adenocarcinoma, may add valuable input to decide whether preoperative laparoscopy and peritoneal wash cytology are mandatory for staging work up.

AIMS AND OBJECTIVES: To find out the incidence of positive peritoneal wash cytology (presence of intra peritoneal free tumour cells) in clinically and radiologically proven non metastatic adenocarcinoma stomach.

MATERIALS AND METHODS:

Study Design: Prospective Cohort study.

Duration: 18 months (1st march 2013 to 31st august 2014)

Sample size: 60.

Setting: Dept. of General Surgery and surgical gastroenterology, Govt. Medical College, Kozhikode.

Inclusion Criteria: Patients with adenocarcinoma stomach (confirmed by endoscopic tissue biopsy) without clinical and radiological evidence of distant metastasis.

Exclusion Criteria:

- Adenocarcinoma with clinical or radiological evidence of distant metastasis.
- Those who had undergone neoadjuvant chemo/radiotherapy after the last CECT study.

PROCEDURE: All 60 patients with histopathologically proven adenocarcinoma stomach, clinically and radiologically proved as non-metastatic disease who were planned to have curative resection in Govt. Medical College, Kozhikode during the period from 1st March 2013 to 31st August, 2014 (18 months) were selected randomly and followed up. All clinical and radiological details including any neoadjuvant treatment details were recorded. After enrolling the subjects in the study, some of them developed features suggestive of metastasis and hence were eliminated from the study cohort. At the time of surgery, after laparoscopic port placement, thorough search for peritoneal or other organ metastasis were done, after that 300 ml of normal saline was instilled into the peritoneal cavity and all the peritoneal surfaces were flushed and 75 ml of the same was transferred to a sterile bottle and sent for cytology analysis immediately. The sample was cytocentrifuged and a slide was prepared with Papanicolaou staining. If the cytology was positive for intra peritoneal free tumour cells, the tumour was classified as CY1. If there were peritoneal deposits found at laparotomy or the tumour was CY1at cytology analysis, it is restaged as M1 and became stage IV disease, which implies the staging evaluation with CECT alone is not adequate in carcinoma stomach. Statistical analysis was done using SPSS software version 18.1 and p-value <.05 was considered as significant.

RESULTS AND OBSERVATIONS:

Sex Distribution: Incidence was more in males (61%).

Age Distribution: Mean age at diagnosis was 57±12.8. 55% of the patients belongs to 51-70-year age group.

Risk Factors: Habit of smoking was present in 47% and alcohol in 35% cases. Family history of intra-abdominal malignancy was present in 15%.

Clinical Features: Most common presenting symptom was abdominal pain, present in 78.3%. History of weight loss was present in 61.7%, early satiety in 31% and melena in 15%. On examination, anaemia was there in 41.7% cases and palpable abdominal mass in 36.7% cases.

Stage of Disease: In CECT study, no T1 disease was reported. 6.7%(4) was T2, 40%(24) was T3, and 53.3%(32) T4 diseases. (Fig 1. Pie Chart).

Laparoscopic Inspection: Number of cases with intra-peritoneal macrometastasis found at pre-operative laparoscopy was 14(23.3%).

CECT stage v/s. macrometastasis:

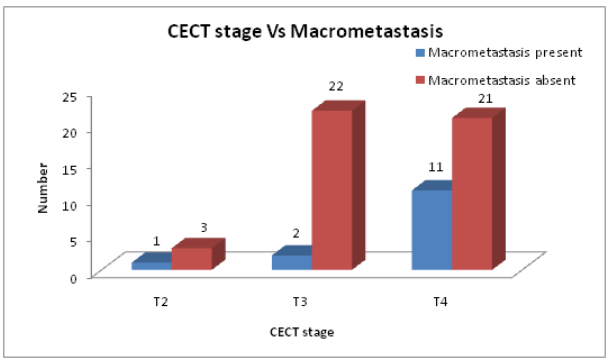


Fig. 1

One out of 4(25%) T2 diseases, 2 out of 24(8.33%) T3 diseases and 11 out of 32(34.38%) T4 disease had visible peritoneal macrometastasis.

Peritoneal wash cytology*

		Macrometastasis		Total
		Present	**Absent**	
Peritoneal wash cytology	Positive	10	5	15
	Negative	4	41	45
Total		**14**	**46**	**60**

Table 1: Peritoneal wash cytology vs. macrometastasis

Total number of positive peritoneal wash cytology was 15(25%). Of them, 10 cases had peritoneal macrometastasis. Out of 46 cases without peritoneal macrometastasis, 5(10.86%) had positive peritoneal wash cytology for intra peritoneal free cancer cells.

Peritoneal Wash Cytology v/s. CECT Stage in Cases without Macrometastasis

CECT stage			Macrometastasis		Total
			Present	**Absent**	
T2	Peritoneal wash cytology	Positive	1	0	1
		Negative	0	3	3
	Total		**1**	**3**	**4**
T3	Peritoneal wash cytology	Positive	1	1	2
		Negative	1	21	22
	Total		**2**	**22**	**24**
T4	Peritoneal wash cytology	Positive	8	4	12
		Negative	3	17	20
	Total		**11**	**21**	**32**

Table 2: Peritoneal wash cytology v/s. macrometastasis v/s. CECT stage

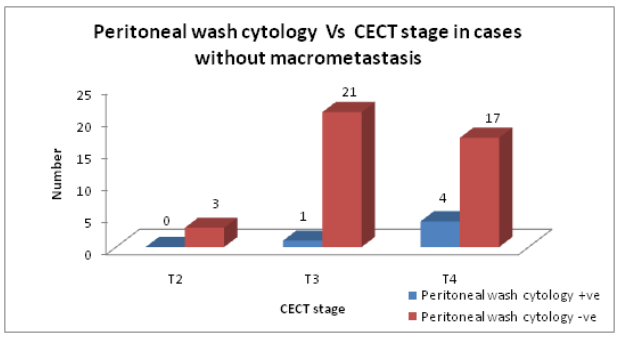


Fig. 2

Among cases without peritoneal macrometastasis, the incidence of positive peritoneal wash cytology for specific stages were:

- Out of 3 T2 cases, none were positive.
- Out of 22 T3 cases, 1(4.54%) was positive.
- Out of 21 T4 cases, 4(19.05%) were positive.

CECT stage v/s. Postoperative HPR: One out of 4 T2 cases (CECT stage) was unresectable due to peritoneal metastasis (M1) and one was upstaged as T3 in post-operative histopathology report (HPR). Two out of 24 T3 cases had peritoneal metastasis (M1) and 12 were upstaged as T4 in post-operative HPR. 11 out of 32 T4 cases had peritoneal macrometastasis (M1) and 1 was down staged to T3 in post-operative HPR.

DISCUSSION: 60 cases of adenocarcinoma stomach without clinical or radiological evidence of metastasis, admitted in Dept. of general Surgery and Dept. of Surgical Gastroenterology in MCH, Calicut were randomly selected and followed up.

Of the total, 61% were male patients. The average age at diagnosis was 57 yrs. (SD±12). 9 patients (15%) had a first degree relative with history of an intra-abdominal malignancy. 47% of patients had a habit of smoking and 36% had a habit of alcohol consumption. On examination, only 37% had a palpable intra-abdominal mass.

All the cases were enrolled in the study, only after obtaining endoscopic biopsy as adenocarcinoma and CECT confirmation of respectability of the tumour. Apart from the above mentioned 60 cases, another 4 cases were enrolled in the study initially, but later excluded from the study group as they developed clinical evidence of distant metastasis, during the hospital stay, before being taken up for definitive surgery.

Among the 60 cases studied nobody was diagnosed as T1 stage disease in CECT. Only 4 cases (6.7%) were diagnosed at T2 stage, 24 cases (40%) at T3 stage and remaining 32 cases (54%) were diagnosed only at T4 stage. Those patients who were diagnosed as metastatic disease were not included in the study, so the incidence of that particular group is not available. Of the patients enrolled in the study, only 2 patients had a history of prior upper G.I. endoscopy before being included in the study. These observations emphasize the need for a population screening program to pick the disease in its early stage, as the stage at diagnosis has the biggest prognostic significance. The

incidence of early stage cancer outweighs the advanced disease in Japan where radiologic and endoscopic screening are part of the routine.[1]

Of the 60 cases who were taken for surgery, 14 (23.3%) had visible intra peritoneal or hepatic metastasis and the definitive surgery was abandoned. These are the group of patients, in whom pre-operative laparoscopic inspection was helpful to avoid a non-beneficial laparotomy. None of these patients had features of gastric outlet obstruction, perforation or profuse bleeding which would have otherwise warranted a laparotomy. The observation that 23.3% of the laparotomies were avoided due to peritoneal metastasis, is significant considering the morbidity of the surgery, the cost and the hospital stay. The observation was comparable to the other major studies, conducted by other groups[4,5,6] in this field.

Author	Percentage
Muntean V et al[5]	37.8%
Mahadevan D et al[6]	20%
Lowy AM et al[7]	37%
deGraaf GW et al[8]	23%
Present study	23.3%
Table 3: Comparing studies on pre-operative laparoscopy	

Peritoneal wash was done for cytological analysis to pick intraperitoneal free tumour cells. It was positive (CY1) in 15 cases (25%). Among these, 10 cases were having visible peritoneal or hepatic metastasis, which were found intra operatively, but not in CECT study. The remaining 5 patients with positive peritoneal wash cytology, were not having macroscopic peritoneal metastasis. These 5 cases belong to the previously labelled 'curable' group (46 out of 60) based on the absence of macroscopic peritoneal metastasis. Still they are staged as M1 (stage 4) disease according to the 7th edition AJCC TNM staging and there is no role for curative resection in them. But these 5 patients would not have been picked by mere laparoscopic inspection, as they would need peritoneal wash cytology analysis as well. This accounts for 10.86% of the total (5 out of 46) cases, which might have been labelled as 'curable' even after laparoscopic staging, and were found to be incurable only after peritoneal wash cytology. These observations were also comparable to other major studies which are mentioned.[9,10,11]

Author	Percentage
Brito AM et al[9]	11.1%
Wang Zhen-ning et al[10]	10.2%
Boku T et al[11]	4.5%
Present study	10.86%
Table 4. comparing studies on peritoneal wash cytology	

Of the 14 cases with macroscopic peritoneal metastasis found at laparoscopic inspection, 10 were positive for malignant cells in peritoneal wash cytology, which indicates a good sensitivity (71.42%) for cytology analysis to find intra peritoneal free cancer cells whereas its high specificity has also been well documented in literature.[12] The patients were not followed up to find the peritoneal recurrence, so the predictive value of cytology analysis could not be assessed from this study.

The dismal prognosis of CY1 disease has been well documented.[13,14] Several researchers have reported that the chance of survival of CY1 patients is equivalent to that of patients with macroscopic peritoneal deposits.[15] For patients who present with distant metastatic disease, long-term survival is only 4%.[16] The accuracy of cytologic examination may be an issue for debate, as it has been questioned by Leake et al. in their review article.[17] This study featured several investigators who adopted immunostaining and RT-PCR techniques, in addition to the conventional cytologic examination, to more sensitively detect minimal cancer cells. It is apparent that the weakness in the conventional cytologic examination lies in its relatively low sensitivity, an area where techniques such as RT-PCR could do better.[18] Given its high specificity, however, conventional cytologic examination remains useful in identifying patients for whom some fundamental considerations are necessary to establish the treatment strategy, such as delivering highly toxic treatments or making serious decisions such as ruling out surgery.

It was observed in the study that 25% of T2 disease, 8.33% of T3 disease and 34.58% of T4 disease had macroscopic intra peritoneal metastasis. Of the remaining 46 cases which did not have intraperitoneal macrometastasis, none of them had T2 disease, 4.54% of T3 disease and 19.05% of T4 disease were positive for intraperitoneal free cancer cells (CY1). So deeper the tissue invasion more will be the chance of peritoneal macro or micro metastasis. Still the early stages are not immune to the possibility of having metastasis. So, all cases of radiologically proven carcinoma stomach are candidates for pre-operative laparoscopic peritoneal wash cytology.

From this study, it is well understood that among the total 60 radio logically proven cases of carcinoma stomach, 19 cases (14 cases with macro metastasis and 5 cases with positive IFCC without macro metastasis) became M1 disease after peritoneal inspection and peritoneal wash cytology analysis. That accounts for 31.66% of the study population. In this 31.6% cases, curative resection does not have any role and will not give any survival advantage and only adds to the surgical morbidity. This considerable amount signifies the mandatory role of pre- operative laparoscopic peritoneal wash cytology in carcinoma stomach patients in whom curative resections were planned.

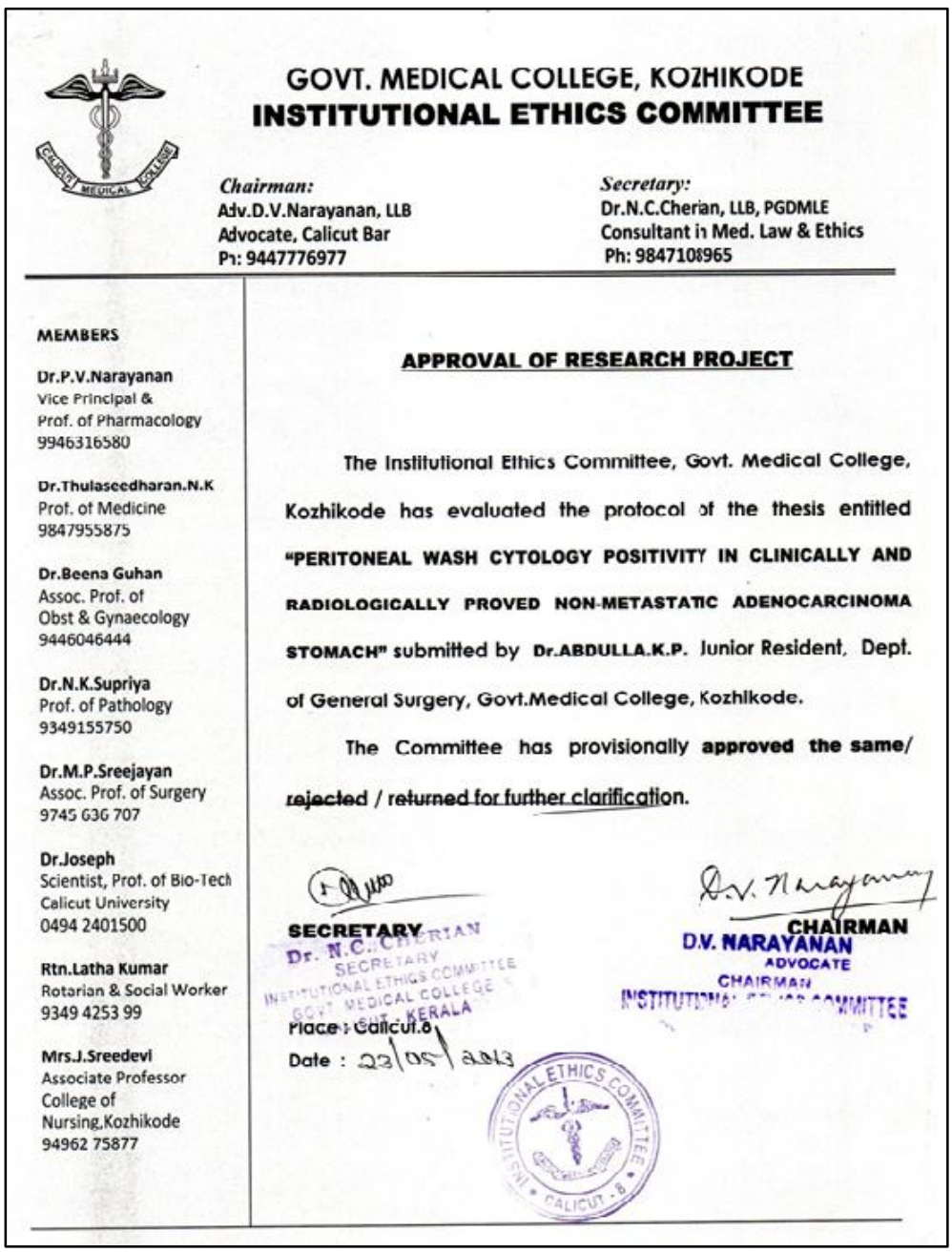
The ideal treatment option for CY1 disease is still a controversial issue. According to AJCC guideline, the only treatment option is palliative chemotherapy[19,20,21] But trials are still in progress on neoadjuvant chemo therapy, resection and intra peritoneal chemotherapeutic agent instillation[22,23] for CY1 disease.

SUMMARY AND CONCLUSIONS: Sixty cases of carcinoma stomach without clinical and radiological evidence of metastasis were enrolled in the study to find the incidence of undetected (in pre-operative staging CECT study) peritoneal macro metastasis and positive peritoneal wash cytology.

14 out of 60 had peritoneal macrometastasis. Of the remaining 46 cases 5 had positive peritoneal wash cytology. These 19 cases were restaged as M1 (which was M0 in pre-operative CECT study). So CECT study alone is not adequate for pre-operative staging work up in adenocarcinoma stomach.

Pre-operative laparoscopic staging and peritoneal wash cytology analysis should be made mandatory before planning curative resection in patients with adenocarcinoma stomach. If routine pre-operative laparoscopic staging and peritoneal wash cytology analysis for adenocarcinoma stomach are practiced, around one third of the resections done today can be avoided, as it is done in undetected M1 disease. These unwanted resections only add significant morbidity to the already ill patient and also delays the appropriate further management.

Further, the proposed laparoscopic peritoneal cytology study does not add any morbidity or risk to the procedure and causes no further delay in administering appropriate care to the patient.



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APPROVAL OF RESEARCH PROJECT

The Institutional Ethics Committee, Govt. Medical College, Kozhikode has evaluated the protocol of the thesis entitled **"PERITONEAL WASH CYTOLOGY POSITIVITY IN CLINICALLY AND RADIOLOGICALLY PROVED NON-METASTATIC ADENOCARCINOMA STOMACH"** submitted by **Dr.ABDULLA.K.P.** Junior Resident, Dept. of General Surgery, Govt.Medical College, Kozhikode.

The Committee has provisionally **approved the same**/ ~~rejected~~ / ~~returned for further clarification~~.

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