

## THE ROLE OF DIAGNOSTIC OESOPHAGO-GASTRODUODENOSCOPY (OGD) AND COLONOSCOPY IN CANCER OF UNKNOWN PRIMARY

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### ABSTRACT

**Objective:** To study the role of gastrointestinal procedures, namely oesophago-gastroduodenoscopy (OGD) and colonoscopy, in helping to establish a definitive primary tumour site in cancer of unknown primary.

**Study Design:** Prospective observational study.

**Place and Duration of Study:** Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore Pakistan, from Jan 2018 to Jan 2019.

**Methodology:** A total of 115 patients included in the study were those, who underwent OGD and a colonoscopy for the diagnosis of a cancer of unknown primary. Data collected included demographics, baseline clinical characteristics, definitive diagnosis, tissue diagnosis and immune-histochemical stains. Primary outcome was the attainment of a definitive diagnosis via OGD and/or colonoscopy.

**Results:** A total of 115 patients underwent a diagnostic gastrointestinal procedure. Of these 70 (61%) were males. Mean age was  $63 \pm 12.6$  years (range 22-88 years). Abdominal pain comprised the most common presenting complaint, found in 61 (53%). The most common tissue diagnosis of the metastatic sites was adenocarcinoma 81 (70.45%). Tumour markers including carcinoembryonic antigen, alpha-fetoprotein and carbohydrate antigen 19-9 were checked in 90 (78.2%), 46 (40%) and 69 (60%) patients respectively. No patient reached a definitive diagnosis by means of OGD and/or colonoscopy.

**Conclusion:** OGD and colonoscopy when done collectively as diagnostic procedures to look for a primary tumour, have no value in the evaluation of patients with cancer of unknown primary.

**Keywords:** Cancer of unknown primary (CUP), Colonoscopy, Oesophago-gastroduodenoscopy (OGD).

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### INTRODUCTION

Carcinoma of unknown primary site (CUP) is the 10<sup>th</sup> most common presentation of cancers seen globally, accounting for 3-5% of all malignancies.<sup>1</sup> It is defined as a heterogeneous group of cancers in which one or more metastatic sites are found but the primary site of origin cannot be identified.<sup>2,4</sup> It is broadly classified into adenocarcinoma, squamous cell carcinoma, poorly differentiated malignant neoplasm, neuroendocrine carcinoma and lymphoma.<sup>5</sup> The most common of these is adenocarcinoma and it often has a poor prognosis.<sup>2,6</sup>

The detection of the primary site of a tumour requires a thorough history and clinical examination, followed by investigation, usually with radiological techniques, often supplemented by endoscopic procedures. Biopsy with additional immunohisto-chemistry studies and tumour markers is usually performed.<sup>6-9</sup> Finding the primary site of a tumour has both therapeutic and prognostic implications<sup>2</sup> and so an appropriate

diagnostic workup is an important aspect of patient care.<sup>10</sup>

Endoscopy has a low specificity and sensitivity in diagnosing primary tumour in patients with CUP<sup>6</sup> and its use should therefore be guided by appropriate signs and symptoms.<sup>10</sup> Limited studies are available to date regarding the yield of upper and lower GI endoscopic procedures in reaching a definitive diagnosis in patients with CUP. We therefore aimed to ascertain the role of endoscopic procedures, namely OGD and colonoscopy, in establishing a definitive diagnosis in CUP.

### METHODOLOGY

This was a prospective observational study evaluating patients seen at Shaukat Khanum Memorial Hospital and Research Centre Lahore, from January 2018 and January 2019. Approval from the hospital's institutional review board (IRB approval no. 02-01-18-01) was obtained prior to commencing data collection. We recorded patient demographics including age, gender, clinical presentation, imaging studies, immunohistochemical staining, and tissue diagnosis of malignancy. We also recorded the definitive diagnosis, if

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achieved. We included all the patients from January 2018 to January 2019 through convenient sampling technique.

**Inclusion Criteria:** Patients who had a tissue diagnosis of a metastatic malignancy, without a definitive primary site were included.

**Exclusion Criteria:** Patients, who were less than 18 years of age, were excluded.

Based on these criteria, a total of 115 patients fulfilled the inclusion criteria. These patients had a clinical history, imaging studies, or immunohistochemistry suggestive of a possible gastrointestinal (GI) primary site.

All the patients included in the study underwent both an OGD and a colonoscopy. The procedures were done by or under the direct supervision of a consultant gastroenterologist, under conscious sedation, with monitoring of pulse, blood pressure, oxygen saturation at five-minute intervals throughout the procedure. The various endoscopic findings were recorded and any lesion/area considered to be suspicious was subjected to biopsy. The primary outcome of our study was the attainment of a definitive diagnosis in patients with CUP by the use of OGD and colonoscopy.

Detailed demographics, history and physical examination were carried for all patients prior to their endoscopic procedures. Qualitative and quantitative variables, including age, gender, symptoms and imaging characteristics were recorded. Mean, median, frequencies and standard deviations values were calculated where applicable. The proportion of tissue diagnoses obtained by OGD and colonoscopy was also recorded as a quantitative variable. All the data were collected and analyzed on the Statistical Package for the Social Sciences (SPSS) version 20 (International Business Machines, IBM corporation).

**RESULTS**

A total of 115 patients were included in the study, each of whom had an OGD and a colonoscopy. Thus a total of 230 procedures were performed. Out of 115 patients, 70 (61%) were males. The mean age at presentation was 63 ± 12.6 years (range, 22-88 yrs) and 87/115 patients had gastrointestinal symptoms. Abdominal pain comprised the most common presenting complaint, occurring in 61 (53%) of patients, while other GI symptoms included weight loss, altered bowel habit, dysphagia, anorexia, nausea and vomiting as shown in Table-I. While 28 patients had no GI symptoms, but had OGD and colonoscopy in view of either raised

tumour markers or immunohistochemical (IHC) stains and/or imaging features suggestive of a GI tract primary. The various imaging modalities that were used in our patients included computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound scan and positron emission tomography (PET) scan. Among these, CT was the most commonly employed imaging modality, being used in 107 (93%) of patients. The most common site of metastases was liver 40 (34.8%), followed by metastases in multiple sites in 19 (16.5%), Out of 115 patients, 58 (50.4%) patients had imaging findings suggestive of a GI primary. The tumour markers were checked in a total of 96 (83.5%) out of 115 patients. These included carcino-embryonic antigen (CEA), alpha fetoprotein (AFP), carbohydrate antigen (CA-19.9) and cancer antigen (CA 125). The CEA levels were checked in 90/ 115 (78.2%), and found to be raised in 62 (53.9), AFP was checked in a total of 46 (40%), and was found to be elevated in 15 (13%) Similarly, CA 19.9 was checked in 69 (60%) of the total patients and was found to be high in 38 (33%), The most common histological diagnoses with which patients were referred for endoscopy included adenocarcinoma 81 (70.4%), followed by poorly differentiated metastatic carcinoma 16 (13.9%), malignant fluid (ascites, pleural fluid) cytology in 9 (7.8%), neuroendocrine tumor 3 (2.6%), miscellaneous 4 (3.4%) and squamous cell carcinoma 2 (1.7%), as shown in Table-II.

These diagnoses were obtained by various means, as elaborated in Figure-1. Immunohistochemical stains, including cytokeratin (CK) 7 and CK 20, were checked in 21 patients. Of these, 10 (47.6%) patients were positive for both CK 7 and CK 20, 8 (38.1%) were positive for CK 20 only and 3 (14.3%) were negative for both CK7 and CK 20.

Of these 115 patients, 75 (66%) patients had a normal OGD, 17 (14.8%) had gastropathy, 8 (6.9%) had

**Table-I: Baseline clinical characteristics.**

Variables	n (%)
Mean ± SD	63 ± 12.6 years
Range	22-88 years
<b>Gender</b>	
Male	70 (61%)
Female	45 (39%)
GI symptoms present	87 (75.6%)
Abdominal pain	61 (53%)
Weight loss	17 (14.7%)
Altered bowel habit	5 (4.3%)
Dysphagia	2 (1.8%)
Anorexia	1 (0.9%)
Vomiting	1 (0.9%)
Without GI symptoms	28 (24.4%)

changes of portal hypertension and 7 (6.1%), patients had evidence of extrinsic compression. Similarly, 84 out of 115 (73%) patients had a normal colonoscopy, 13 (11.3%) had hemorrhoids only, whereas 8 (7%) had polyps, histopathology of which showed no evidence of malignancy, 5 (4.3%) of these patients had external colonic compression as shown in Table-III. In none of the patients included in the study, a definitive diagnosis of primary GI tumour obtained from OGD and/or colonoscopy.

**Table-II: Details of various investigative modalities used.**

Investigative Modalities Suggesting GI Primary	n (%)
<b>Imaging Findings</b>	
Metastases	66 (57.4%)
Liver	40 (34.8)
Multiple sites	19 (16.5)
Pulmonary	5 (4.3)
Brain	2 (0.9)
Bone	2 (0.9)
Lymphadenopathy	10 (7)
Peritoneal thickening	15 (13)
Ascites	7 (6.1)
Gastric wall thickening	3 (2.6)
<b>Tumour Markers</b>	
Carcinoembryonic antigen Median (IQR)	7 (1-3)
Alpha fetoprotein Median (IQR)	2.69 (1-1761)
Carbohydrate antigen-19.9 Median (IQR)	86 (2-100,000)
<b>Histopathological Diagnoses</b>	
Adenocarcinoma	81 (70.4)
Poorly diff metastatic carcinoma	16 (13.9)
Neuroendocrine tumour	3 (2.6)
Squamous cell carcinoma	2 (1.7)
Miscellaneous	4 (3.4)
Papillary carcinoma	2 (1.7)
Epitheloid tumour	2 (1.8)
Malignant cytology	9 (7.8)

**Table-III: Endoscopic findings.**

Endoscopic findings	n (%)
<b>Oesophago-Gastroduodenoscopy (OGD)</b>	
Normal	75 (66)
Gastrpathy	12 (14.8)
Portal hypertension	8 (6.9)
Extrinsic compression	7 (6.1)
<b>Colonoscopy</b>	
Normal	84 (73)
Hemorrhoids	13 (11.3)
Polyps	8 (7)
Extrinsic compression	5 (4.3)

## DISCUSSION

According to the European Society for Medical Oncology (ESMO), the National Comprehensive

Cancer Network (NCCN) and the National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis of CUP, OGD and colonoscopy should be performed only in patients who either have gastrointestinal (GI) symptoms or in those with imaging characteristics or immunohistochemical stains favoring the gastrointestinal tract as a source of primary tumour.<sup>10-12</sup>

In our study, we found that CUP is a cancer of elderly patients, most commonly occurring in the 6<sup>th</sup> decade of life and is also more common in men (60.9% vs. 39.9%) than in women, as opposed to the figures stated in a population-based study done in Sweden,<sup>13</sup> who reported a male to female proportion of 44.8 vs. 55.2% respectively. In another study by Saliminejad *et al*,<sup>14</sup> The male to female proportion was equal. The mean age of presentation in our cohort was 63.3 years. In comparison, Abbruzzese *et al*,<sup>15</sup> reported a median age of 59 years, while Levi *et al*,<sup>16</sup> reported a median age of 70 years.

Most of our patients had abdominal pain (53%, n: 61) as a presenting complaint, while 24.3% (n=28) had no GI symptoms. The proportion of abdominal pain in our study group was similar to a study conducted by Usmani *et al*,<sup>2</sup> (50%) however, they reported a higher proportion of non-GI symptoms (45%).

The most common tissue diagnoses of the metastatic site seen in our cohort was adenocarcinoma in 70.4% of patients, while 13.9% had poorly differentiated metastatic carcinoma, followed by malignant cytology in 7.8%, neuroendocrine tumour in 3 (2.6%), and squamous cell carcinoma in 2 (1.7%). The commonest of the two tissue types are comparable to the study done by Abbruzzese *et al*,<sup>15</sup> with their figures of adenocarcinoma and metastatic carcinoma of 58.1 and 29.4% respectively. However, the other study from our own country, by Usmani *et al*,<sup>2</sup> revealed somewhat different results, apart from adenocarcinoma being the most common tissue type (75.5%). Their second most common tissue type was neuroendocrine tumour, being a mere 3.4% of the total cohort (n=86). In one study, by Petrović *et al*,<sup>17</sup> histopathology review of biopsy specimens revealed adenocarcinoma to be 70%, poorly differentiated carcinoma 20%, squamous cell carcinoma 10%, and poorly differentiated neoplasm 5%.

Looking at the primary end point, our study did not demonstrate a single case of a primary tumour being detected by OGD and colonoscopy. In comparison, Usmani *et al*,<sup>2</sup> reported a primary cancer detection rate of 7%, or 3.5% each with OGD and colonoscopy.

Saliminejad *et al*,<sup>14</sup> analyzed the yield and cost of colonoscopy in patients with metastatic cancer of unknown primary. They reported primary cancer detection rates of only 1% and concluded that colonoscopy is not cost-effective in seeking a primary in CUP. Overall, the data on primary tumour detection is quite scarce and no other studies could be found to support these figures. Additionally, the guidelines also advocate using OGD and colonoscopy based on symptoms or imaging findings. Nevertheless, these recommendations are largely anecdotal and require further studies to confirm this strategy.<sup>10-12</sup>

Bayrak *et al*,<sup>18</sup> reported an immunohistochemical stain pattern of CK 7/20, showing CK7-/CK20+ being found in 64% of colorectal cancers and 5% of gastric cancers. Similarly CK7+/CK20+ was seen in 20% of colorectal and 48% of gastric cancers, while a CK7+/CK20- pattern was seen in 2% of colorectal cancers. Keeping this in view, our study does raise some important questions. Imaging characteristics, raised tumour markers and immunohistochemical stains are all considered to be good predictors of a possible primary tumour in the GI tract. In our study, 62/115 (53.9%) of patients had raised CEA levels, 58/115 (50.4%) of our patients had imaging characteristics suggestive of a GI primary, and positive immune stains (both CK7 and CK20) were seen in 10/115 (8.6%).

**LIMITATION OF STUDY**

In this relatively small and specific study population sample in a cancer specialized center, where patients are referred from peripheries after extensive work up, we were not able to find a GI primary in any of these patients, suggesting that the value of these investigations when referring for GI work up may need further discussion and review.

**CONCLUSION**

Our results concluded that OGD and colonoscopy, when done collectively as diagnostic procedures to look for a primary tumour, have no role in the evaluation of patients with CUP. Our results are largely in concordance with similar studies done on the subject under discussion and in light of these results, it is recommended that larger prospective studies be carried out, to help decide whether the guidelines for the use of OGD and colonoscopy in detecting CUP should be revised.

**Conflict of Interest:** None.

**Authors' Contribution**

MI: Conception, design, data analysis & intellectual collection, RSAK: Conception, design, data analysis & intellectual collection, FS: Conception, design, data analysis

& intellectual collection, MAY: Conception, design, data analysis & intellectual collection.

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