METASTASIS OF UNKNOWN ORIGIN: AN ENIGMA IN CLINICAL ONCOLOGY

Anil Kumar Dhull[1], Rajeev Atri[2], Vivek Kaushal[3], Narayan P. Patel[4], N. Balasubramanian[5], Rakesh Dhankhar[6], Ashok K. Chauhan[7], Kamal Nain Rattan[8]

[1]Radiation Oncologist, HCMS-I, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[2]Associate Professor, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[3]Senior Professor & HOD, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[4]Associate Professor, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[5]Assistant Professor, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[6]Professor, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[7]Senior Professor & Unit Head, Department of Radiation Oncology, Pt. B. D. Sharma, PGIMS, Rohtak.
[8]Senior Professor & HOD, Department of Paediatric Surgery, Pt. B. D. Sharma, PGIMS, Rohtak.

ABSTRACT

INTRODUCTION

Metastasis of unknown origin (MUO) represents a heterogeneous group of malignancies presenting with lymph nodes or distant metastases, for which diagnostic workup fails to identify the site of origin. Management of MUO with undetermined primary remains unclear because of the heterogeneous pathological condition and the treatment for such cases is still controversial. Various therapeutic regimens are present, but no clear-cut consensus has evolved. MUO on the whole carries a very poor prognosis. To assess the outcome of patients in a real-world situation, we retrospectively reviewed the database in our department to determine patterns of presentation and to analyse the response of various treatment modalities.

MATERIAL AND METHODS

The patients of metastasis of unknown origin who presented in the Department of Radiotherapy, PGIMS Rohtak from Jan 1st, 2008 to December 31st, 2010 were retrospectively analysed to determine patterns of presentation and to elucidate the outcome of various treatment modalities like radiation, surgery and chemotherapy.

RESULTS

Total 349 patients of metastasis of unknown origin were identified in the Department of Radiotherapy, PGIMS Rohtak, which constituted 4.9% of the total cancer patients. The median age at presentation was 56 years. Most of the patients presented in advanced stage (stage III-93% & stage IV-7%). In this retrospective analysis, the presenting site was lymph nodal in 68% and visceral in 32%. Out of total 349 patients of metastasis of unknown origin, 77 patients (22%) did not report for treatment after initial investigations. Out of the remaining 272 patients who took treatment, 185(68%) patients underwent radiotherapy and 137 patients (50%) received different chemotherapy protocols. 20% were given radical treatment and 58% were treated with palliative intent. Primary site was found in 13(5%) patients and were treated accordingly.

CONCLUSION

The overall prognosis in patients with MUO is generally very poor with a mean survival of 5-10 months. The most common site of presentation observed was cervical lymphadenopathy. Most of the patients presented in advanced stage and accordingly were treated with palliative intent. Evaluation of patients with metastasis of unknown origin should be structured to quickly identify treatable tumours or the need for palliation. Radiation therapy, chemotherapy and surgery were used alone or in combination to treat these patients to prolong survival and improve the quality of life.

KEYWORDS

MUO, Metastasis of Unknown Origin, Lymphadenopathy, Cancer of Unknown Primary, CUP, Palliative treatment, Review.

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INTRODUCTION: Metastasis of unknown origin (MUO) represents a heterogeneous group of malignancies presenting with lymph nodes or distant metastases, for which diagnostic workup fails to identify the site of origin. Patients are considered to have MUO if no anatomical primary site is identified after clinical evaluation.[1] Two major groups of MUO can be defined as MUO to lymph nodes only (N1-3) and MUO to visceral sites. The authors believe a more realistic estimate of the incidence of MUO patients as 5% of all invasive cancers as evident from our study, incidence of MUO is 4.9% of the total cancer patients and this is consistent with similar studies reported in the literature.[1-5] Management of MUO with undetermined primary remains unclear because of the heterogeneous pathological condition and the treatment for such cases is still controversial. Various therapeutic regimens are present, but no clear-cut

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Corresponding Author:
Dr. Anil Kumar Dhull,
Radiation Oncologist, Department of Radiation Oncology,
Regional Cancer Centre,
Pt. B. D. Sharma Post Graduate Institute of Medical Sciences,
P. O. Box: 100, Rohtak-124001, Haryana, India.
E-mail: anilkdhull@gmail.com
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consensus has evolved. MUO on the whole carries a very poor prognosis and 5-year overall survival rate is only about 11%.[1-3] To assess the outcome of patients in a real-world situation, we retrospectively reviewed the database in our department to determine patterns of presentation and to analyse the response of various treatment modalities.

MATERIAL AND METHODS: The patients of metastasis of unknown origin who presented in the Department of Radiotherapy, PGIMS Rohtak from January 1st, 2008 to December 31st, 2010 were retrospectively analysed to determine patterns of presentation and to elucidate the outcome of various treatment modalities like radiation, surgery and chemotherapy (alone or in combination) in various stages of the disease. A total of 349 patients with tumours of various histological types were recorded in the database. Patients included in the study were those having positive biopsy for different histological subtypes of MUO with normal blood biochemistry, liver and kidney function tests. The patients having prior radiation, surgery or chemotherapy for the disease; pregnant or lactating patients; associated medical conditions were excluded from the study. Data was analysed using IBM SPSS Statistics version 15.0 software (SPSS Inc., Chicago, IL) and Microsoft® Excel® 2013 (version 15.0.4805.1001).

RESULTS: Patients Demography: Total 349 patients of metastasis of unknown origin were identified in the Department of Radiotherapy, PGIMS Rohtak, which constituted 4.9% of the total cancer patients. The median age at presentation was 56 years (Range: 6-94) Table 1. Sixth decade of life was the commonest presentation, 87% patients presented between 31-70 year age group, 4% presented with <30 year of age while the remaining 9% presented in >71 year of age group. The male to female ratio was 11:3. Eighty six percent patients had a history of tobacco intake in some form or the other. Mean duration of symptoms was three months. Most common presentation was lymphadenopathy (68%) and dysphagia (42%).

Site of Presentation: The most common metastatic site of presentation was lymph nodes in 239 patients (68%), out of which 203 patients (58%) had cervical lymph nodes. 53 patients (15%) had liver metastasis and 30 patients (9%) presented with bone metastasis. In patients with multiple lymph nodes, the site of lymph node mentioned was the one first noted by the patient out of all.

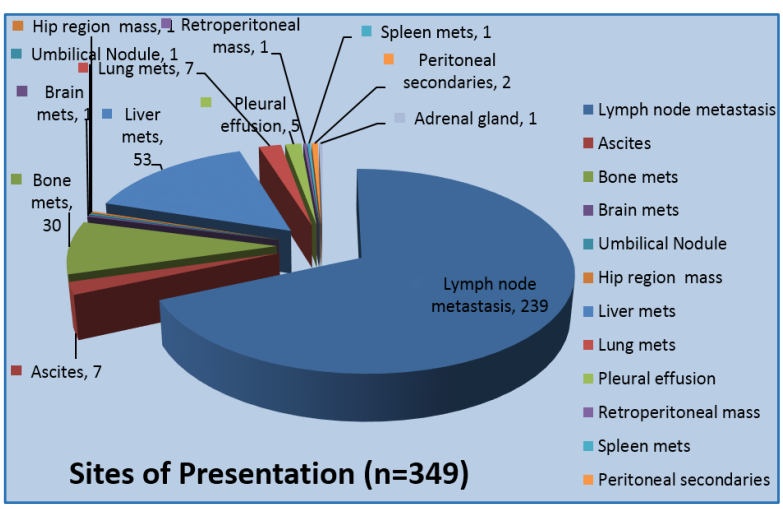

Fig. 1

Histopathological Distribution: 237 patients (68%) presented with squamous cell carcinoma while 14% each presented with adenocarcinoma and carcinoma of unspecified type.

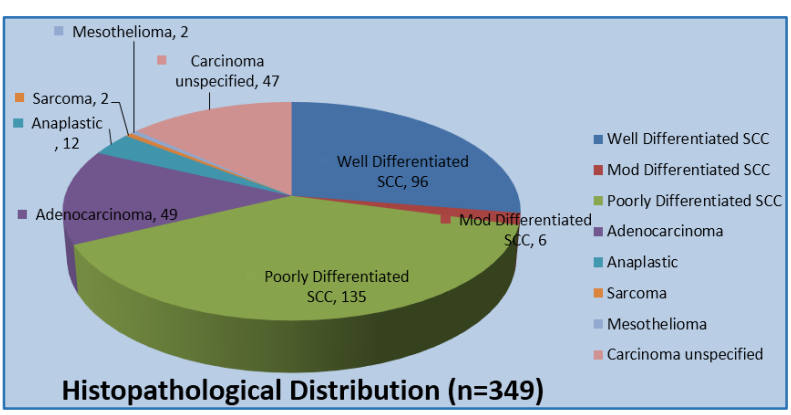

Fig. 2

Presenting Sites of Lymph Nodes: All patients were staged according to the AJCC classification. The most common site of presentation was cervical lymphadenopathy (203 patients, 58%) followed by supraclavicular, axillary, mediastinal and inguinal lymphadenopathy. Majority of the patients i.e. 326 patients (93%) presented with stage IV, while only 23 patients (7%) presented with stage III. The nodal (N) status at presentation was N1 - 26, N2 - 82 and N3 - 131 patients.

Treatment: Out of total 349 patients of metastasis of unknown origin, 77 patients (22%) did not report for treatment after initial investigations because of the following reasons:

- Poor general condition of the patient.
- Prognosis was explained and subsequently family decided to discontinue further treatment.
- Poor patients, could not afford further cost of treatment in third world country.
- Progressive disease.
- Sought alternative treatment/alternative hospital.

Multiple modality treatment types including external beam radiotherapy (EBRT), different protocols of chemotherapy i.e. neo-adjuvant chemotherapy/NACT, concomitant chemoradiation/CCT, salvage chemotherapy and surgery were tried according to the general condition and feasibility of the treatment.

The intent of treatment given was curative 20%, palliative 58%, while 22% patients received no treatment. Eventually, only 272 patients out of 349(78%) patients who received treatment were found eligible for this analysis and were finally evaluated for response.

Radiation Therapy: All the patients were planned and proper field placement and verification were done on the Simulix HP Simulator with Digital Therapy Imaging (DTI) facility. The treatment was individualised according to the site and extent of the disease. Involved region and/or metastatic lymph nodes as well as other sites of metastasis were treated in all patients. In patients with extensive skeletal metastasis, hemibody irradiation was given.

External Beam Radiotherapy/EBRT: Out of the total 272 patients who took treatment, 185(68%) patients underwent radiotherapy. Radical radiotherapy was given in 33 patients (18%), palliative radiotherapy in 153 patients (82%), and supplementary radiotherapy was given in 25 patients because of good initial response after the initial short course palliative radiotherapy or for high palliation.

Radiotherapy Schedules: The median dose for radical radiotherapy was 64 Gy/32#/6.2 weeks. Out of total 185 patients who underwent radiotherapy, 33 patients (18%) received radical radiotherapy, 77 patients (42%) received 8 Gy single session of palliative radiotherapy, 67 patients (36%) received palliative radiotherapy dose of 20 Gy/5#/5 days and 8 patients (4%) received palliative radiotherapy dose of 30 Gy/10#/10 days.

Surgery: Out of the total 272 patients who were finally evaluated, 16 patients (6%) underwent different types of surgical procedure.

Chemotherapy: Out of the remaining 272 patients who took treatment, 137 patients (50%) received different chemotherapy protocols. 93 patients (34%) received neoadjuvant chemotherapy, 8 patients (3%) received concomitant chemoradiation, while different salvage chemotherapy regimens were tried in 36 patients (13%). Majority of the patients i.e. 75 patients (28%) received taxanes based combination chemotherapy. Most commonly used combination chemotherapy regimens were paclitaxel, carboplatin & 5-fluorouracil; docetaxel, carboplatin & 5-fluorouracil; various combination of taxanes and platinum along with etoposide, gemcitabine etc. were used depending upon the site, type and aggressiveness of the tumour.

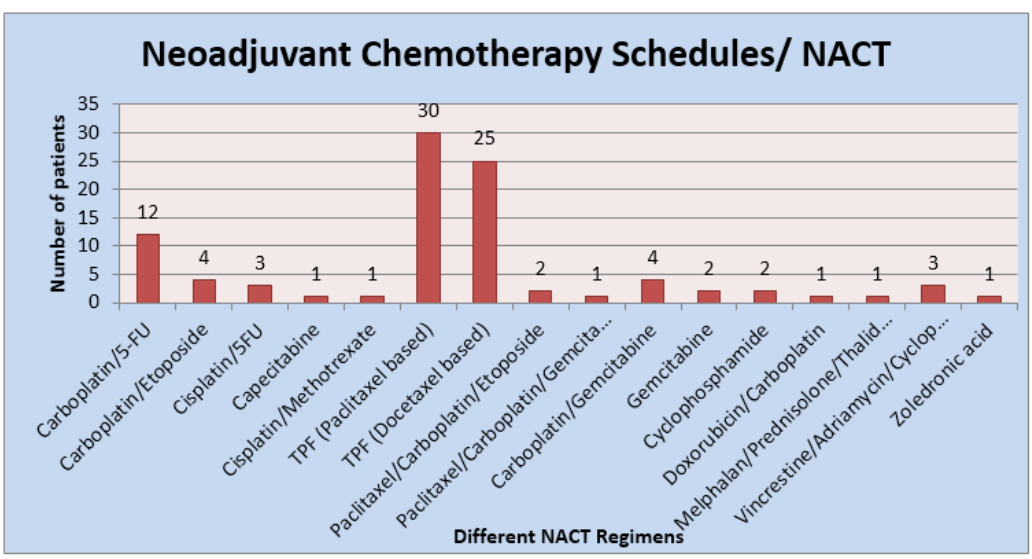

Fig. 3

Salvage Chemotherapy: Different salvage chemotherapy regimens were tried in 36 patients (13%), out of which 20 patients received TPF based chemotherapy, 6 patients received PF based chemotherapy, 3 patients received carboplatin+etoposide while in some other patients combination chemotherapy used were carboplatin+gemcitabine; oxaliplatin+5-fluorouracil; carboplatin+doxorubicin. In some patients, single agent chemotherapy with cyclophosphamide, 5-fluorouracil and melphalan were also tried. In none of the patients, results of any chemotherapy regimen were found promising.

Detection of Primary Site: Primary site was found in 13(5%) patients and were treated accordingly. The most frequent site of primary tumour as detected in our retrospective analysis was carcinoma oropharynx (6 patients) and carcinoma lung (4 patients), carcinoma nasopharynx (2 patients) and one patient of carcinoma hypopharynx.

Clinical Response (n=272): Disease Status at Completion of Treatment: Median followup was 5-years (Range: 1 month to 5 years).

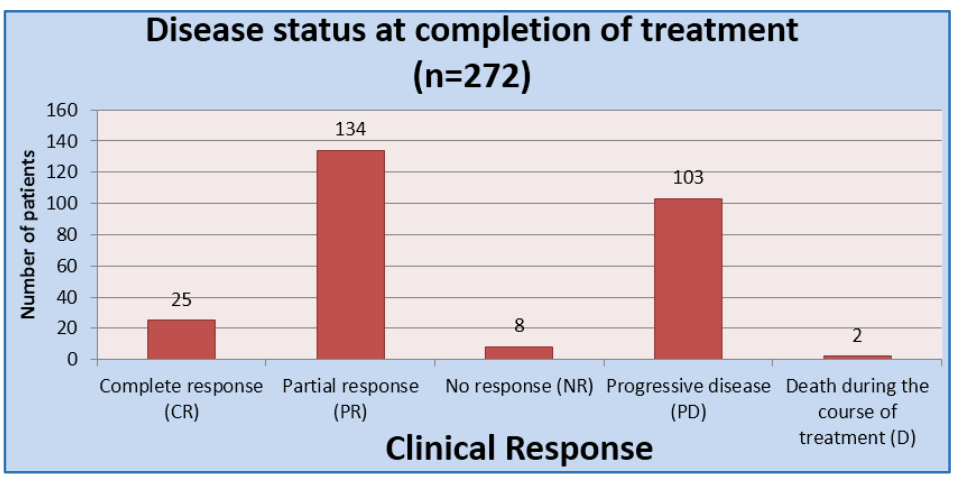

Fig. 4

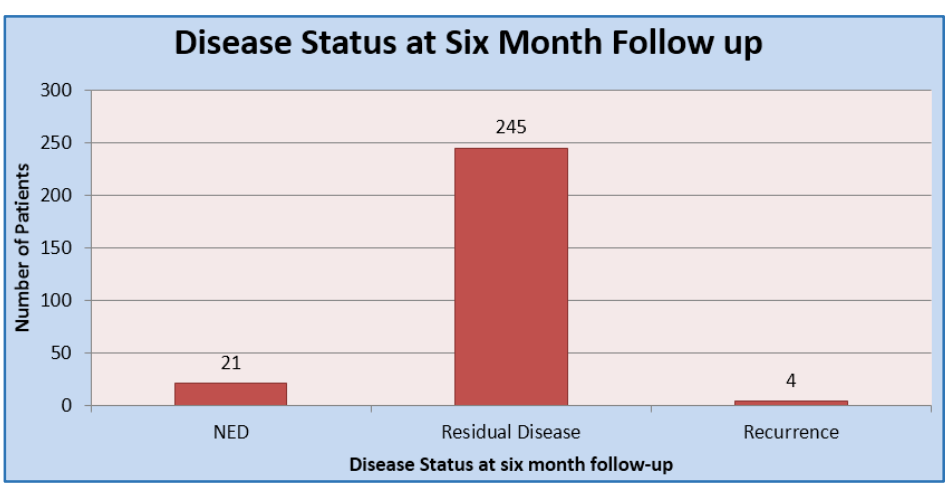

Fig. 5: Disease status at six month follow-up

Disease status at 5 years out of the evaluated 272 MUO patients, only 15 patients (6%) were found disease-free at five years of followup which further confirms the aggressiveness of the disease and lack of effectiveness of different therapeutic approaches.

DISCUSSION: Metastasis of unknown origin (MUO) is a clinical syndrome that includes many types of advanced cancers. Patients are considered to have MUO if no anatomical primary site is identified after clinical evaluation. International registries from seven countries have reported incidences ranging from 2.3% to 7.8%.[1-5] The authors believe a more realistic estimate of the incidence of these patients as 5% of all invasive cancers as evident from our study also, incidence of MUO is 4.9% of the total cancer patients and this is consistent with similar studies reported in the literature. The five-year overall survival rate is about 11%. The median age on presentation for both men and women in our study was 56 years which has varied in other series from 55 to 69 years, likewise, the male preponderance in our study (11:3) is very well consistent with that reported in previous studies.[6]

Biological Features: Regardless of their heterogeneity, MUO have common biological features having the main characteristics as: Early dissemination in clinical absence of

primary tumour; unpredictable metastatic pattern; aggressive biological and clinical behaviour.[6]

Hypothetically, primary tumour remains of microscopic size or escapes clinical detection or disappears after the appearance of metastases.

MUO are divided into four major histopathological subtypes[6,7] which are:

- Adenocarcinomas well-to-moderately differentiated.
- Poorly differentiated carcinomas.
- Squamous cell carcinomas.
- Undifferentiated neoplasms.
- Neuroendocrine tumours.

It is not always possible to identify a primary site of tumour origin by using histopathology alone. Most patients (60%) have more than two sites affected at presentation[8] with lymph nodes being the most frequently involved. Liver, lung, bone, and pleura constitute common metastatic sites, whereas relatively high frequencies of odd localisations of metastases have been observed.[9] In order to know a MUO staging, one has to know the site of presentation when it is started. Since the type of cancer is not known, it is not possible to accurately stage MUO, nonetheless, to be considered a MUO, the cancer must have spread beyond the primary site and most of them are locally advanced and are at least of stage II.

As suggested by International Guidelines, all MUO patients should have an accurate physical examination, complete biochemical/laboratory tests and a whole body imaging study (computed tomography CT-scan and Positron Emission Tomography, PET-scan).[2,3] Besides, female patients have to undergo mammography and vaginal ultrasonography scan (VUS), whereas in males, prostate ultrasonography is required. Various endoscopic procedures like laryngoscopy, bronchoscopy, gastroscopy, colonoscopy or cystoscopy should be individually selected based on several clinical factors such as signs & symptoms, physical examination findings, sites of metastases, occult blood in the stool, biochemistry findings as well as other factors which would prompt endoscopies.[2,3]

Regardless of all available diagnostic procedures, attempts to detect primary tumour mainly remains futile and the primary site of origin is identified only in 13% of these patients.[6] A recent meta-analysis showed that, overall, FDG-PET/CT is able to detect 37% of primary tumours in MUO patients, with both sensitivity and specificity of 84%.[2,10] Hence, in near future, contrast enhanced PET-CT studies in MUO can be of greater use for establishing the diagnosis.

Somatostatin receptor scintigraphy (SRS), also known as OctreoScan, can be very helpful in diagnosing neuroendocrine tumours (NETs), including neuroendocrine carcinomas. However, no screening tests have been proven to be effective in the early detection of many of the cancers that are likely to be diagnosed as cancer of unknown primary.[11]

Since the exact type of cancer is not known, it is hard to identify factors that might affect risk for cancer of unknown primary. Smoking, alcohol and dietary factors are probably the important risk factor for MUO.[12-16] More than half of patients with MUO have a history of smoking and alcohol.[12-16]

Surgery may be an option if the cancer is found only in the lymph nodes or in one organ, where the surgeon may be able to remove it all.[17,18] If surgery is used, it may be followed by radiation therapy and possibly chemotherapy to take care of the residual disease.[1-4,12-19] In our study, also 6% patients underwent different types of surgical procedure.

Radiation therapy is used as an individual modality or in adjuvant or neo-adjuvant setting along with surgery. Radiation therapy can be given as EBRT alone or brachytherapy alone or combination of both. In our present retrospective review, 68% patients underwent different radiotherapy schedules out of which 18% underwent radical and 82% underwent palliative radiotherapy.

Chemotherapy may be the main treatment for MUO that are clearly advanced and are unlikely to be helped by local treatments such as surgery or radiation therapy. In some cases, like germ cell tumours or certain types of lymphomas, chemotherapy has much better survival advantage. In other cases, it may be used as palliative chemotherapy. Chemotherapeutic drugs are often given in combinations, which are more likely to be effective than giving a single drug alone. In our present review also, half of the enrolled patients received different chemotherapy protocols including 34% with neoadjuvant chemotherapy, 3% received concomitant chemoradiation, while 13% patients were subjected to different salvage chemotherapy regimens. Taxanes based combination chemotherapy (18%) was the most commonly used chemotherapy in our study which is in concurrence with the available literature. Taxanes based chemotherapy have proven an overall response rate of 35-40%.[17-20] Besides, growing evidence sustains that rationale for personalised targeted therapies is inside the tumour's genome rather than in their tissue of origin. This idea of personalised oncology has not been reached for most patients and the clinical reality at this time is that at least some MUO may be more effectively treated by recognising their tissue of origin.[1-4,12-14]

Adenocarcinoma and Poorly Differentiated Carcinoma: For a MUO that is an adenocarcinoma or a poorly differentiated carcinoma, a number of chemotherapy combinations may be used, including taxanes plus carboplatin, with or without etoposide; gemcitabine plus cisplatin, gemcitabine plus docetaxel, oxaliplatin plus 5-fluorouracil and leucovorin; and oxaliplatin plus capecitabine etc.[1-4,12-14] In multiple studies, taxanes based chemotherapy have proven an overall response rate of 35-40% but contrary to that in our study, the overall response was lesser as compared to available literature which further confirm the aggressiveness of the disease.[17-22]

Squamous Cell Carcinoma: If chemotherapy is to be used for MUO of squamous cell type, the options includes cisplatin or carboplatin plus a taxane (paclitaxel or docetaxel); TPF (docetaxel/ paclitaxel, carboplatin/cisplatin and 5-

fluorouracil (5-FU) and gemcitabine plus carboplatin/ cisplatin.[1-4,12-14]

Neuroendocrine Tumour (NET): The chemotherapy of choice in NET that are poorly differentiated carcinoma is platinum and etoposide with a response rate of 73%. Well-differentiated neuroendocrine cancers are not often the cause of MUO, but may present with liver metastasis and an occult primary. These patients are treated like patients with well differentiated carcinoid tumour, with drugs combinations such as doxorubicin and streptozocin; temozolomide plus capecitabine, etc.[1-4,11-14]

Squamous Cell Carcinoma in Lymph Nodes in the Neck: Often these cancers belong to head & neck cancer and are usually treated with surgery and/or radiation therapy.

In our present retrospective study, the most frequent site of primary tumour observed was the oropharynx, lung, nasopharynx and hypopharynx which are in consistence with the studies reported in the literature.[3] The proposed treatment options for MUO include surgery alone, radiotherapy alone or postoperative radiotherapy or chemotherapy alone or in combinations. In our analysis, 185 patients (68%) of total MUO patients received radiotherapy at some point during the course of treatment while chemotherapy and surgery was given in 39% and 5% patients respectively.

Significant prognostic factors recognised in MUO are: histopathology, organs involved, patient's age, gender, tumour burden, weight loss, Karnofsky performance status (KPS) and number of metastatic sites; as well as serum biomarkers. In addition, the French Group (GEFCAPI) developed a simple prognostic index for patients with MUO, in which favourable prognostic factors included a KPS< 2 and normal serum LDH levels.[22]

The overall prognosis in patients with MUO is generally very poor, with a mean survival of five to ten months with about 50% of patients alive at 1-year and about 10% at 5 years from diagnosis, but survival differs among clinicohistopathological subgroups.[1,2,4,23] In our retrospective study also, only 6% patients were found disease free at five years of followup. This further confirms that metastasis of unknown origin is still a challenge in clinical oncology in advanced as well as developing countries. Use of advanced diagnostic tools like PET-CT, extensive immunohistochemical profiling, OctreoScan etc., individualised approach for every patient, use of clinical trials, combining targeted therapies along with standard treatment can be the future era of medicine in metastasis of unknown origin.

SUMMARY & CONCLUSIONS: MUO identifies as a very aggressive pathology which at present is still lacking for appropriate management strategies. In this retrospective analysis, MUO constituted 4.9% of all reported cases. The most common metastatic site of presentation was lymph nodes in 239 patients (68%), out of which 203 patients (58%) had cervical lymph nodes. 53 patients (15%) had liver metastasis and 30 patients (9%) presented with bone metastasis. Twenty percent were given radical treatment and 58% were given palliative treatment. Evaluation of patients with metastasis of unknown origin should be structured to quickly identify treatable tumours or the need for palliation. Use of advanced diagnostic tools, individualised approach for every patient, clinical trials, targeted therapies can be the future era of medicine in metastasis of unknown origin.

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