World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Original Article

Carcinoma of the Unknown Primary (CUPS) - Knowing the Unknown

Pathak A[1], Gupta A[2], Rathore A[1], Vishwanath S[3]

[1]Asst. Prof. and [3]Professor, Dept. of Medical Oncology Army Hospital Research & Referral
[2]Asst Prof, Dept of Pathology, Base Hospital Delhi Cantt, India

Received: 10-10-2017 / Revised Accepted: 05-01-2018 / Published: 10-01-2018

ABSTRACT

Introduction: Cancers of unknown primary site (CUPs) account for approximately 3% of all malignant neoplasms and it is the ninth commonest type of cancer. Indian data with CUPs comprises of very few publications except for isolated case reports. **Methodology**: Cross sectional study of 100 patients, reporting to a tertiary care centre was carried out. Detailed history, examination and relevant investigations were done. Data tabulated and analysed for demographic and histopathological aspects. **Results:** The median age of presentation was 49 yrs in the patients who presented with nodal metastasis while in extra nodal disease the median age of presentation was 59 yrs. Majority of patients 40% c/o neck swelling, whereas 10% patients also had enlarged inguinal nodes Hepatomegaly was found in 17% of cases and splenomegaly in 9% patients. 28% of patients had peripheral lymphadenopathy. The most common histopathology was adenocarcinoma followed by poorly differentiated carcinoma. The liver, pleura and bone were the most commonly involved metastatic sites. **Conclusion**: The molecular tumor profiling is important for faster diagnosis and improved treatment options. However, till the time the newer modalities are validated and used in clinical practice, conventional diagnostic modalities and clinical examination remain to be the main stay.

Keywords: CUPs, Hepatomegaly, Metastatic

Address for Correspondence: Dr Alpana Gupta, MD Pathology, Dept Of Pathology, Base Hospital Delhi Cantt, New Delhi, India; E-mail: alpana.dr@gmail.com

How to Cite this Article: Carcinoma of the Unknown Primary- Knowing the unknown facts. Pathak A, Gupta A, Rathore A, Vishwanath S. World J Pharm Sci 2018; 6(1): 40-46.

INTRODUCTION

Cancers of unknown primary site (CUPs) account for approximately 3% of all malignant neoplasms and it is the ninth commonest type of cancer. CUPs are defined as a heterogeneous group with metastatic disease for which the site of origin cannot be identified at the time of diagnosis despite careful clinical and laboratory examination. Background research for Indian data with CUPs have revealed no publications apart from isolated case reports. Majority of the data is from western literature. Hence there is an urgent need to study the disease entity in detail and also there is a widespread misconception that CUPs is an inability to diagnose the underlying malignancy and not a separate disease in itself. As there are no clear-cut diagnostic and treatment protocol for these patients it is an endeavour to study the various modalities of investigation and treatment and to see response to treatment of various management protocols.

The aim of the syudy is to Clinico-epidemiological profile of CUPS patients and response to treatment
The objectives of present study to collecting the data on epidemiological profile of patients of CUPS, to elucidation of favourable and unfavourable subsets, to treatment free interval and progression free survival and Prognostic markers

MATERIALS AND METHODS

Inclusion Criteria

1. Patient to be considered CUPS if no primary site is detected after standard clinical and pathological evaluation.
2. Both genders to be included
3. All age groups to be included

Total of 100 patients of CUPS who reported to a tertiary care center were included in our study. This is a descriptive, cross sectional study. Details of treatment would be elaborated in the Performa(Annexure 1). Total duration of study was for 2 yrs.

Method: Complete clinical examination as per the protocol was carried out for all patients.

1. Complete pathological and radiological evaluation was carried out as per protocol.
2. Response to standard therapy was done by Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
3. Data Collection Methods: As per Performa (Annexure 1)

Baseline Assessment: Study was descriptive, cross sectional study of 100 patients who were under treatment at Army Hospital (R&R) including serving and ex-serviceman and their dependents.

The patients were selected for study as per inclusion criteria mentioned above.

Written informed consent was taken from patients or relatives. All patients were screened and diagnosis of CUPS were established based upon biopsy reports and immunohistochemistry(IHC).

Staging procedure included-

(1) Detailed history & thorough clinical examination.
(2) Complete blood counts and serum biochemistry including serum lactate dehydrogenase (LDH) & bone marrow examination for metastasis.
(3) Computed tomography (CT) scan of chest, abdomen, and pelvis
(4) Upper gastrointestinal (GI) endoscopy.

Statistical Analysis: Statistical analysis was done using appropriate analytical software. Data was reported as a number (percentages) of patients for categorical variables. It was a cross sectional study and obtained data was analyzed using appropriate statistical method.

RESULTS

A total of hundred (100) patients who were admitted or attended the outpatient department of medical oncology at Army Hospital Research & Referral, New Delhi were included in the study. A total of one hundred (100) patients were diagnosed as CUPS during the study period, of them 56(56%) were male and 44(44%) were female and male: female ratio was 1.27. Mean and median age of presentation was 45 years and 49 years respectively. 4(4%) patients gave family history of malignancy in first degree relatives. However, in 28(28%) there was history of malignancy in some family member.

CLINICAL PRESENTATION

Symptoms: A total of 100 patients were interviewed for the various symptoms. 34(34%) patients gave h/o bony pain, 10(10 %) patients gave h/o diarrhea whereas 40 (40%) patients complained of fatigue at the time of presentation to the hospital. 40 (40%) patients had c/o neck swelling at the onset whereas 20 (20%) patients also had enlarged inguinal nodes and the rest had axillary lymphadenopathy. 30(30%) patients had significant weight loss of >10% of body weight. 12 patients had features of ascites whereas 10 patients had hemoptysis. 4 patients presented with diffuse pain abdomen. Pallor was present in 25 (25%) patients. Hepatomegaly was found in 17(17%) of cases and splenomegaly was detected in 9 (9%) patients. 44(44%) of patients were found to have peripheral

lymphadenopathy. Ascites was detected in 8 (8%) patients.

Investigations: Anemia (Criteria considered in this study is Hb of < 10 gm/dl for females and <12 gm/dl in males) was found in a total of 18(18%) patients. Out of these 18 patients, 11 were males and 7 were females. Mean hemoglobin in the study group was 10.56 gm/dl. Deranged liver function tests were found in 17(17%) patients, most of these comprised of raised Bilirubin and AST levels (S.Bil> 1.2 mg/dl; AST>30 IU/L). Deranged renal parameters were seen in 8(8%) of cases. (Creatinine> 1.2 mg/dl and BUN> 20 mg/dl). Elevated levels of Serum Lactic dehydrogenase levels were found above the normal laboratory value (>200IU/L) in 57 (57%) patients.

Distribution of histological subtypes CUPS: A total of 100 patients in whom the diagnosis was established on the basis of clinical features, immunohistochemistry (IHC), and molecular tumor profiling.

Table 1:

Histological Subtype	Cases	%
Adenocarcinoma	64	64
Poorly differentiated carcinoma	20	20
Squamous cell carcinoma	14	14
Neuroendocrine differentiation	2	2

Nodal Involvement Only: There were 60 cases of 100 cases which presented only with lymphadenopathy as their main presentation. Lymphnode metastases to cervical and axillary region were the most common (40). .Lymphnode metastasis to cervical group was relatively more common in males than in females. Other sites of nodal involvement were lymph nodes in inguinal region (20), Intrathoracic lymphnodes (6), intraabdominal lyphnodes (4), generalized lymphadenopathy (10).

Histopathology of Lymphnodes: The most common histopathology in the lymphnodes were adenocarcinoma (40) followed by poorly differentiated carcinoma (12) and then Squamous cell carcinoma (8).

Progression Free survival among different histological subgroups: On plotting Kaplanmeyer curve to calculate the event free survival among various subgroups it was seen the among the nodal subgroups Squamous Cell carcinoma subgroup had the worst out come and adenocarcinoma subgroups had the best Event Free Survival.

EXTRANODAL INVOVEMENT

The total number of patients who were diagnosed as CUPs with predominant extranodal involvement were 20 cases. The liver, pleura and bone were the most commonly involved metastatic sites. Skin and retroperitoneal sites were involved in females.

Table 2:

SITE	NO
LIVER	10
PLEURA	3
BONE	2
RETROPERITONEUM	2
SKIN	1

Histopathology of Extranodal sites

The most common histopathology was adenocarcinoma (15), 2 patients had neuroendocrine differentiation and in 3 patients the histopathology was poorly differentiated carcinoma.

Progression Free survival among different histological subgroups: On plotting Kaplan meyer curve to calculate the event free survival among various subgroups it was seen the among the extra nodal subgroups poorly differentiated carcinoma subgroup had the worst out come and adenocarcinoma subgroups had the best Event free survival.

DISCUSSION

Cancer of unknown primary site (CUP) is a relatively common clinical entity, accounting for 4 to 5 percent of all invasive cancers (1,2). Within this category, tumours from many primary sites with varying biology are represented. This heterogeneity has made the design and interpretation of clinical studies difficult (3,4). A total of fifty patients (100) patients were diagnosed as CUPS during the study period, of them 56(56%) were male and 44(44%) were female and male female ratio was 1.27:1.Compared to other studies in the west where the ratio of male and female were more or less equal (5,6) Among the females they presented with metastatic deposits of axillary lymph nodes, whereas in males head and neck related CUPS were common.

The median age of presentation was 49 yrs in the patients who presented with nodal metastasis where as in patients with extra nodal disease the median age of presentation was 59 years.(7) The presentation of nodal disease was approximately 10 years before the presentation in extranodal presentation. Study conducted by Hemmiki et al revealed a difference of around 5 years in the presentation between the nodal and extranodal groups. Most of the patients i.e.50 patients (50 %)

patients have presented beyond 5th decade. This is concordance with most of the studies conducted elsewhere in the world.(8,9,10).

The family history was important as 4(4%) patients gave family history of malignancy in first degree relatives. Whereas 28(28%) gave history of malignancy in some family member. However, in 68(68%) there was no contributory family history. CUP occurred more commonly in patients with family history of malignancy.(11,12) The common associations were cancers with lung, colorectal, , liver ,ovary and kidney. Family clustering of these cancers suggested a genetic basis which could reveal joint mechanism for metastasis.(13)

Figure 1:

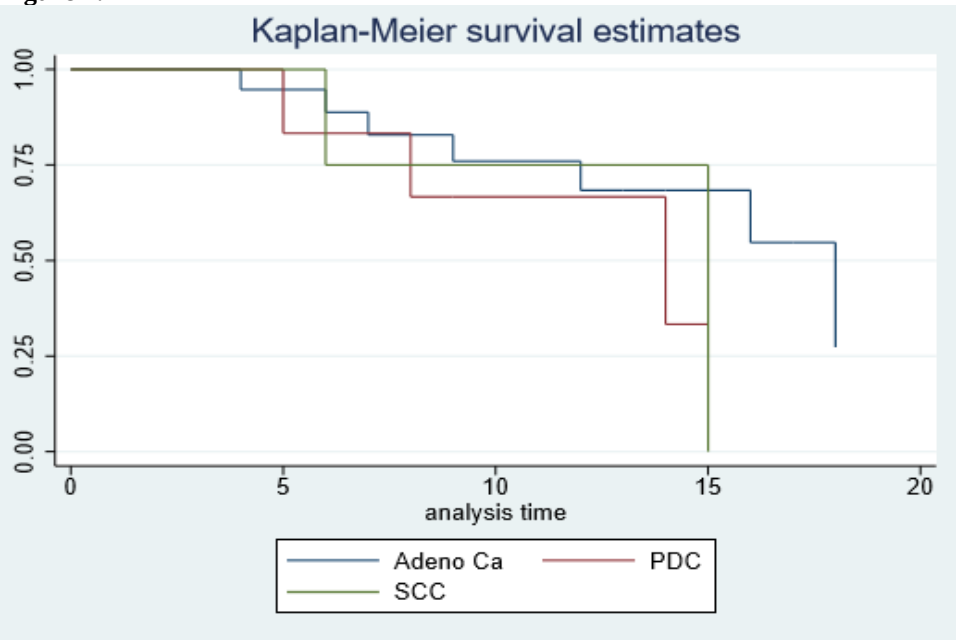
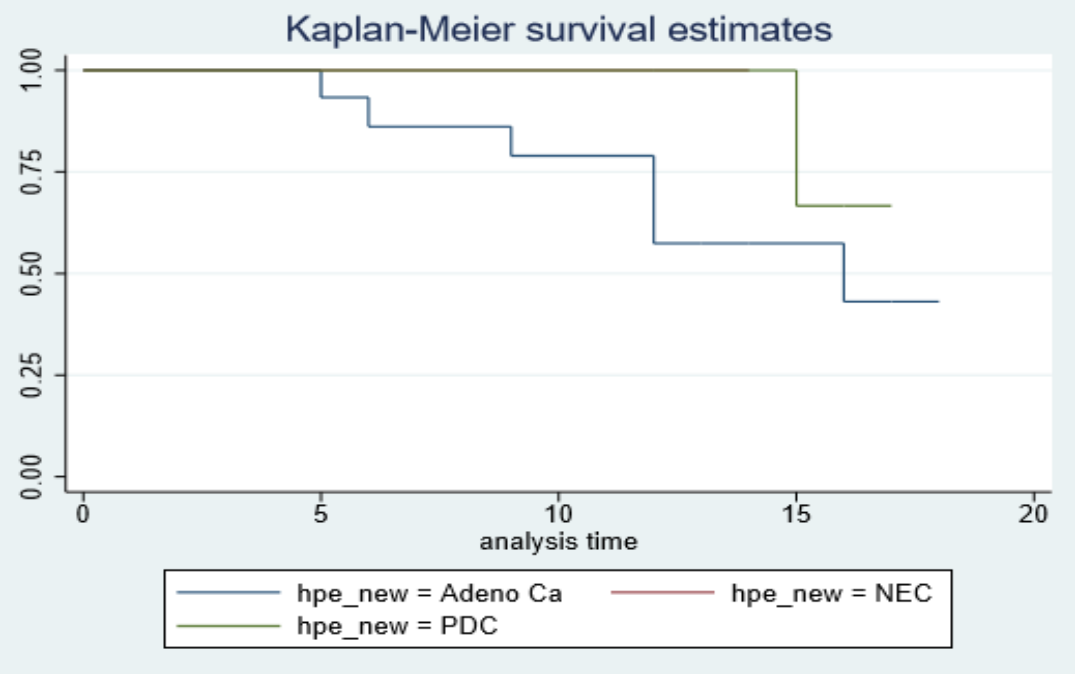


Figure 2:



A total of 100 patients were interviewed for the various symptoms. 34(34%) patients gave h/o bony pain , 10(10 %) patients gave h/o diarrhea whereas 40 (40%) of patients complained of fatigue at the time of presentation to the hospital.

40(40%) patients had c/o neck swelling at the onset whereas 20 (20%) patients also had enlarged inguinal nodes most of these patients had head and neck as suspected primary presenting with cervical lymphadenopathy were as axillary lymphadenopathy was presented in females with suspected breast cancer.(14)

30(30%) patients had significant weight loss of >10% of body weight. Most of the patients had weight loss as part of the B symptoms which involved greater than 10% of weight. 12 had features of ascites whereas 10 patients had hemoptysis. 2 patients presented with diffuse pain abdomen.

Hepatomegaly was found in 17(17%) of cases and splenomegaly was detected in 9 (9%) patients. 56(56%) of patients were found to have peripheral lymphadenopathy. Ascites was detected in 8 (8%) patients.

Anemia which was defined as Hb of < 10 gm/dl for females and <12 gm/dl in males was found in a total of 36(36 %) patients. Out of these 36 patients, 22 were males and 14 were females. Anemia in these were multifactorial and mostly it was due to anemia of chronic disease and iron deficiency anemia. Mean hemoglobin in this study group was 10.56 gm/dl. Deranged liver function tests were found in 17(17%) patients, most of these comprised of raised Bilirubin and AST levels (S.Bil> 1.2 mg/dl ; AST>30 IU/L).(14,15) Deranged renal parameters were seen in 8(8%) of cases. (Creatinine> 1.2 mg/dl and BUN> 20 mg/dl).Elevated levels of Serum Lactic dehydrogenase levels were found above the normal laboratory value (>200IU/L) in 57 (57%) patients. Serum LDH gives us a idea of the tumor load in patients and it has been found to be of prognostic importance.(16)

The diagnosis was established on the basis of clinical features, immunohistochemistry (IHC), and molecular tumor profiling.

NODAL INVOLVEMENT ONLY

There were 60 cases of 100 cases which presented only with lymphadenopathy as their main presentation. Lymphnode metastases of head and neck and of axilla were the most common (20 patients) .Lymphnode metastasis to cervical group was more common in males where as lymphnode metastasis to axilla (14 patients) was common in females. Other sites of nodal involvement were lymph nodes in inguinal region (20 patients) .Intrathoracic lymphnodes (12 patients), intraabdominal lyphnodes (4 patients), generalized lymphadenopathy (10 patients).

The most common histopathology in the lymphnodes were adenocarcinoma (40) followed by poorly differentiated carcinoma (12) Squamous cell carcinoma were seen in 8 cases. With regard to the histology, patients with adenocarcinoma and undifferentiated histologies had the worst prognoses. This applied even to lymph nodes associated with a more favorable prognosis. Clear exceptions were lymph nodes of the axilla, for which adenocarcinoma signaled a favorable prognosis, compatible with the primary being in the breast. One hypothesis for the poor prognosis of patients with intrapelvic and intraabdominal nodal involvement of possible ovarian origin relates to immunology. This perhaps was the reason for the better outcome of patients in our study as well. Regulatory T cells are strongly suppressive of immune reactions and are known to be present in high numbers in ovarian cancer.[i]

Progression Free survival among different histological subgroups: On plotting Kaplanmeyer curve to calculate the event free survival among various subgroups it was seen the among the nodal subgroups Squamous Cell carcinoma subgroup had the worst out come and adenocarcinoma subgroups had the best Event Free Survival.

EXTRANODAL INVOLVEMENT

The total number of patients who were diagnosed as CUP with predominant extranodal involvement were 20 cases. The liver, pleura and bone were the most commonly involved metastatic sites. Skin and retroperitoneal sites were involved in females.
The most common histopathology was adenocarcinoma (15), 2 patients had neuroendocrine differentiation and in three patients the histopathology was poorly differentiated carcinoma.

The selected patient populations in hospital-based studies are probably the reason why even expert reviewers cite survival figures for CUP of ≥6 months and refer to histological distributions enriched in those subtypes commensurate with favorable survival. Frailty of patients is recognized in the prognostic evaluation of CUP because performance status is a favorable prognostic sign[ii] . Similar to the data which can be seen in our study as the majority of the patients were of performance status 3 and 4 in our study as well.

Other data showed that the two most common histologies, adenocarcinoma and undifferentiated

cancer, which respectively accounted for 70.0% and 20.7% of the present CUP cases, were associated with the poorest prognoses (12month survival rates of 17% and 16%, respectively, and a median survival time of 3 months) and had almost superimposable survival curves. however, in our study. The similarity between the curves does not imply deviations in pathological evaluations but rather reflects the limited overall variation in patient survival between the two histologies and various metastatic sites. According to a hospital-based study on 47 CUP patients with brain metastasis, the median survival was 4.8 months [27]. The relatively favorable 12-month survival of patients with mediastinal cancers (over 40%) indicates that mediastinal cancer should be included in the list of prognostic indicators. Although we had no data on metastases at multiple sites, we believe that CUP 199, the largest subgroup in this study, often presented with multiple affected sites.(23) The reason for this conclusion is the fact that the causes of death of these patients included cancers at diverse organ sites. In previous survival studies, patients with squamous cell carcinoma have been shown to have a favorable prognosis compared with those with adenocarcinoma. In a cancer registry-based study on 76 subjects, the median survival times were 3.5 months for squamous cell carcinoma and 2.5 months for adenocarcinoma [15]. In two hospital-based studies, the original articles Annals of Oncology Hemminki et al. Volume 23 | No. 7 | July 2012 reported differences in survival between the histologies were 9 and 4 months in one and 22 and 9 months in the other [iii]. In the present study, the median survival time for patients with squamous cell carcinoma was 6 months. However, the present data showed that squamous cell metastasis in the liver was associated with a poor prognosis, with a 12-month survival rate of 5%. Bone metastasis was also associated with a poor prognosis (12-month survival rate 15%). A recent review of the global literature on CUP melanoma identified skin involvement in 222 patients, visceral tissue involvement in 211 patients and bone involvement in 31 patients; median survival in the visceral involvement group was given as 3–16 months [iv]. The present study covered 98 cases of skin metastasis, 138 of visceral metastasis and 10 of bone metastasis, as well as 459 melanomas in unspecified sites. Median survival was 13 months. Survival was favorable in patients with skin melanoma (median time 34 months) but poor in those with liver (1 month) and brain (6 months) metastatic melanomas.

Prognostic factors

25(25%) patients were aged more than 60 years. 57 (57%) patients had Serum lactic dehydrogenase (LDH) above the normal laboratory value (>200IU/L). 74 (74%) patients presented with Performance Score of 3-4, whereas 26(26%) patients presented with a poor Performance Score of 3-4. This is in contrast to the presentation which we see elsewhere, where almost 80% of the patients present in early stage i.e. stage 0-2 and only around 20% present in late stages. This is probably due to uninformed patients and lesser degree of sensitization among young doctors.

On plotting Kaplan-meyer curve to calculate the event free survival among various subgroups it was seen the among the nodal subgroups Squamous Cell carcinoma subgroup had the worst out come and adenocarcinoma subgroups had the best Event Free Survival.

Limitation of study

Since CUPS is a rare disease and the number of cases found anywhere in the world are few, it is difficult to make a standard of care for rare diseases. There are many new diagnostic modalities which have come but they have not been validated, hence they were not used in the study. This is major limitation of the disease.

CONCLUSION

Our epidemiological results facilitate clinical decision making and encourage mechanistic studies into the biology of CUP. CUPS continues to be a difficult malignancy to treat. However, whenever possible one should make all attempt to try to look for the site of origin and treat accordingly. Predominately CUPS related to nodes have better prognosis than extranodal CUPS. The outcome of CUPS with squamous cell histology tend to have poorer prognosis. The latter might eventually translate into improved treatment options for CUP patient.There has been better understanding of disease with newer diagnostic modalities including tumor molecular profiling / Immune histo-chemistry etc. However, till the time all these newer modalities are validated and used in clinical practice, we have to resort to the clinical findings and other diagnostic modalities as used in our study. These newer diagnostic modalities may eventually translate into improved treatment options for CUP patients.

REFERENCES

1. Greco FA, Hainsworth JD. Introduction: unknown primary cancer. Semin Oncol 2009; 36:6.
2. Hemminki K, Bevier M, Hemminki A, Sundquist J. Survival in cancer of unknown primary site: population-based analysis by site and histology. Ann Oncol 2012; 23:1854.

3. Dabbs D. Diagnostic immunohistochemistry, Churchill Livingstone, 2006.
4. NCCN guidelines http://www.nccn.org/professionals /physician_gls/f_guidelines.asp (Accessed on June 26, 2014).
5. Gomez-Fernandez C, Jorda M, Delgado PI, Ganjei-Azar P. Thyroid transcription factor 1: a marker for lung adenoarinoma in body cavity fluids. Cancer 2002; 96:289.
6. Brown RW, Campagna LB, Dunn JK, Cagle PT. Immunohistochemical identification of tumor markers in metastatic adenocarcinoma. A diagnostic adjunct in the determination of primary site. Am J Clin Pathol 1997; 107:12.
7. Su AI, Welsh JB, Sapinoso LM, et al. Molecular classification of human carcinomas by use of gene expression signatures. Cancer Res 2001; 61:7388.
8. Tot T. Adenocarcinomas metastatic to the liver: the value of cytokeratins 20 and 7 in the search for unknown primary tumors. Cancer 1999; 85:171.
9. Varadhachary GR, Talantov D, Raber MN, et al. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. J Clin Oncol 2008; 26:4442.
10. Hainsworth JD, Schnabel CA, Erlander MG, et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. Clin Colorectal Cancer 2012; 11:112.
11. Møller AK, Loft A, Berthelsen AK, et al. A prospective comparison of 18F-FDG PET/CT and CT as diagnostic tools to identify the primary tumor site in patients with extracervical carcinoma of unknown primary site. Oncologist 2012; 17:1146.
12. Currow DC, Findlay M, Cox K, Harnett PR. Elevated germ cell markers in carcinoma of uncertain primary site do not predict response to platinum based chemotherapy. Eur J Cancer 1996; 32A:2357.
13. Strnad CM, Grosh WW, Baxter J, et al. Peritoneal carcinomatosis of unknown primary site in women. A distinctive subset of adenocarcinoma. Ann Intern Med 1989; 111:213.
14. Katagiri H, Takahashi M, Inagaki J, et al. Determining the site of the primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study. Cancer 1999; 86:533.
15. Tell DT, Khoury JM, Taylor HG, Veasey SP. Atypical metastasis from prostate cancer. Clinical utility of the immunoperoxidase technique for prostate-specific antigen. JAMA 1985; 253:3574.
16. Schorge JO, Muto MG, Welch WR, et al. Molecular evidence for multifocal papillary serous carcinoma of the peritoneum in patients with germline BRCA1 mutations. J Natl Cancer Inst 1998; 90:841.
17. Rades D, Kühnel G, Wildfang I, et al. Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management. Ann Oncol 2001; 12:1605
18. Salvati M, Cervoni L, Raco A. Single brain metastases from unknown primary malignancies in CT-era. J Neurooncol 1995; 23:75.
19. Greco FA, Rubin MS, Boccia RV, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients (pts) with carcinoma of unknown primary site (CUP): Results of a prospective Sarah Cannon Research Institute (SCRI) trial. J Clin Oncol 2012; 30: (suppl; abstr 10530).
20. Huebner G, Link H, Kohne CH, et al. Paclitaxel and carboplatin vs gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: a randomised prospective phase II trial. Br J Cancer 2009; 100:44.
21. Greco FA, Pavlidis N. Treatment for patients with unknown primary carcinoma and unfavorable prognostic factors. Semin Oncol 2009; 36:65.
22. van der Gaast A, Verweij J, Henzen-Logmans SC, et al. Carcinoma of unknown primary: identification of a treatable subset? Ann Oncol 1990; 1:119.