Japanese Journal of Gastroenterology and Hepatology

Review Article ISSN: 2435-1210 | Volume 8

Cancer from an Unknown Primary Source

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Received: 18 May 2022
Accepted: 02 Jun 2022
Published: 08 Jun 2022
J Short Name: JJGH

Keywords:

Immunohistochemical staining; Molecular profiling; Combination Chemotherapy; Targeted therapy

Citation:

Yadav M. Cancer of an Unknown Primary Source. J Gstro Hepato. V8(19): 1-11

1. Abstract

The diagnosis of Cancer of Unknown Primary is difficult even in the present era of modern medicine. The incidence is closed to 2-5% of all epithelial cancers. There is no concrete explanation behind the development of these cancers, however, recent studies suggested the role of chromosomal abnormalities and neoangiogenesis in the development. Overall, it carries a dismal prognosis but select group of patients may have better survival. Initially, these patients were treated on the basis on radio-logical findings but introduction of the immunohistochemical staining has revolutionized the treatment strategies. Based on the staining patterns, these cancers are subdivided and accordingly treated. Molecular profiling, a recent addition in the diagnostic work up, is helpful in selecting the targeted drugs so that site specific chemotherapy can be used instead of old chemotherapeutic regimens. Most of the patients are treated with combination chemotherapy and target therapy in used in selected cases. Currently, there is emphasis on using targeted drugs detected by molecular profiling techniques, rather than a detailed exhaustive process to find a primary.

2. Introduction

Cancer of an Unknown Primary (CUP) is an important oncological entity, observed in approximately 2.3-5% of the patients with malignancy. It is a biopsy proven metastatic cancer where detailed evaluation is unable to detect the primary site [1]. It is an aggressive disease with early dissemination, and the patient presents with metastatic disease. They are characterized by the slow development of their primary lesion which nevertheless has a high potential for spreading.

NICE (National Institute of Clinical Excellence) guidelines have classified the definition of CUP according to the different phases of investigations:

A) Malignancy of undefined primary origin - when only limited tests are done, and they show metastatic cancer with no primary

B) Provisional CUP - when specialised investigations are done in addition, but specialist evaluation is awaited

C) Confirmed CUP - after specialist evaluation is conducted in addition to specialised investigations.

Earlier, CUP was defined only based on imaging, but from 2000 onwards various sub-types have been identified according to the findings of immunohistochemistry and the treatment is directed according to these specific subtypes [2]. These tumours are now assessed by Immunohistochemical (IHC) stains and Molecular profiling techniques which have expedited the relatively cumbersome evaluation protocols used earlier, to the more specific and directed therapy.

This review will aim to discuss the progression of these new developments - IHC stains and molecular profiling techniques - in the evaluation and treatment of CUP. First, it will explore the theories regarding the development of CUP, along with the extent of the consequences, prognosis, patterns of metastases and clinical presentation of the problem. Second, it will explore the evolution of diagnostic evaluations, which will include a discussion on the IHC staining, tumour markers and molecular profiling techniques. The radiological assessment will discuss the role of Computed Tomographic (CT) scans, Magnetic Resonance Imaging (MRI), and nuclear medicine examinations. Finally, it will discuss the shift of treatment patterns from empirical chemotherapy to specific targeted drugs.

3. Theories Behind the Development

Various hypotheses have been proposed behind the development of

metastases in CUP. The proposed theories are that: A) the immune system of the host has eliminated the primary lesion and only the secondaries are detected on detailed examination, B) the metastases grow fast while the primary tumour remains small and is thus not detected after evaluation, C) the metastases continue to grow after the primary tumour has disappeared and D) the biological characteristics of these tumours are unique as the secondaries can develop due to a high metastatic potential of the cancer cells.

The recent literature has evaluated the role of chromosomal or molecular abnormalities in the development of this disease. The most common site for chromosomal abnormalities with advanced cancers is on chromosome 1, in the form of deletion or duplication. There is active angiogenesis in about 50 to 80%, overexpression of oncogenes in about 30%, and hypoxia related proteins in 25% of the patients [3-6]. Aneuploidy or chromosomal instability are the common abnormalities and are the most probable reason for the aggressive behaviour, resistance to available drugs and poor outcome in CUP [7]. Neoangiogenesis is a phenomenon through which a tumour acquires multiple new vessels from the surrounding vicinity for its rapid growth, survival, and ability to invade. The genes for two proteins, Vascular Endothelial Growth Factor (the protein responsible for neoangiogenesis) and Matrix Metalloproteinase (enzyme responsible for degrading the stroma) are universally expressed in theses cancers and are responsible for angiogenesis [8]. The extent of angiogenesis or micro vessel density has been evaluated between secondaries from known and unknown primaries and found to be associated with poor survival. Several oncogenes have been linked to the CUP in past studies like Ras, her 2 neu, Bcl-2, and the tumour suppressor gene p53, but none have a reasonable influence on the treatment response or overall survival [9].

Heavy smoking and increased waist circumference are shown to have a significant risk for the development of CUP [10]. Human papilloma virus infection has been described as a high-risk factor for the development of head and neck cancers [11]. Older age and lower educational standards are associated with an advanced stage at the time of diagnosis [12].

4. The Extent of the Problem and its Prognosis

CUP is the seventh to eighth most common malignancy and the fourth most common cause of death due to cancer in both sexes [13]. It occurs mainly in the sixth to eighth decades and tends to affect men slightly more frequently than women [14, 15]. Few studies have suggested that 2.8% of cases have a familial inheritance and it has been seen with renal, lung and colorectal malignancies [16, 17]. This indicates that there may be some genetic basis behind these familial cancers and the associated organs may be the site of the primary disease.

Autopsy clarifies the natural history, and detection of the primary is possible in about 73-75% of the patients. The most common sites found in the autopsies are lung (27%), pancreas (24%), kidney or adrenal (8%), liver or bile duct (8%) genital system (7%), colon or rectum (7%), and stomach (6%) [18]. The ovary, breast and prostate are fewer common sources for primaries [18, 19].

CUP has a poor prognosis, and the median survival is short. The prognosis depends upon numerous factors including sex, histology and number and type of organs involved.

The primary site can be predicted in approximately 15% of the patients, and they are treated with site-specific treatment. This group has a better outcome compared with the other 85%, where no probable primary is found and site-specific treatment is not given [20, 21]. Better survival is reported in patients with nodal involvement, Neuro Endocrine Tumours (NET), metastatic adenocarcinoma with an IHC pattern of colonic cancer, midline tumours with poorly differentiated carcinoma, osteoblastic secondaries, and patients with a surgically resectable single small lesion [22-24]. These patients have survival rates comparable with the metastatic carcinoma from known primary sources [13, 25-29]. Disease limited to the lymph nodes, pleura or peritoneum has a relatively better survival rate of 14-16 months, in comparison with visceral metastatic disease where the survival is only 6-9 months [2].

A poorer outcome is found in men, patients with multiple sites of metastasis, non-papillary histology with malignant ascites, squamous cell carcinoma of the abdominopelvic area, multiple lytic bony and brain lesions, visceral metastases, and low albumin and lymphocyte counts [30, 31].

The clinicopathological status and raised leukocyte counts have been suggested to be independent prognostic markers [32]. The Modified Glasgow Prognostic Score and neutrophil-lymphocyte ratio are also related to prognosis and survival [33].

5. Patterns of Metastases

CUP is a diversified group of diseases with varied presentations. The pattern of spread can guide us to locate the primary, either above or below the diaphragm. Lung involvement indicates that the probable primary is likely to be above the diaphragm, while involvement of the liver indicates that a primary lays below the diaphragm. Nodal secondaries in the neck indicate probable primary in the head and neck, while nodes in the inguinal area suggest a primary in the pelvic organs. The pattern of metastases in CUP may be different from the usual presentations of the primary tumour, as bony metastases are more common in pancreatic cancers presenting as CUP. The pattern of metastases should not be the sole criterion for detecting the primary lesion as the occult cancer can go to any site.

6. Presentation

Clinical presentation depends upon the organ involved and extent of the disease. The clinical course is aggressive and constitutional symptoms like lethargy, weakness, malaise, loss of weight and appetite are usually present in most cases. Multiple sites are involved in majority of the patients at the time of presentation. The most common

presentation is with lymphadenopathy followed by involvement of the lung, liver, and bones [30, 34]. The most common site for nodal metastases is the mediastinum followed by the supraclavicular area, retroperitoneum, neck, and axilla, in decreasing order of frequency [30]. There are certain presentations which can guide us to find the probable primary site (Table 1).

Table 1: Common Presentation to Detect the Probable Primary Site in Cup

METASTATIC PRESENTATION	PROBABLE AREA OF PRIMARY IN CUP
Females with nodes in the axilla	Breast
Nodal enlargement in the neck	Ear, Nose or Throat
Liver metastases	GIT, Pancreaticobiliary, Breast, Lung
Lung metastases	Head & Neck, Thyroid, Kidney, Testes, Skin, Bone, Stomach, Breast, Pancreas, Rectum
Ascites	Ovarian or Gastrointestinal malignancy
Brain metastases	Lung, breast, or kidney
Bone metastases	Prostate, Breast, Lung, Kidney, Thyroid
Testicular involvement	Prostate, Lung, Melanoma, Colon, Bladder

7. Diagnostic Evaluation

Evaluation is aimed at: A) detecting the primary, B) minimizing the spectrum of detectable primaries, or C) identifying the specific groups of CUPs which are treatable [19]. There is no universal consensus about how and how much these patients should be investigated, but certain tests should be done universally.

7.1. Pathological Evaluation

The pathological examination is aimed at classifying the tumour based on its type, subtype, and site of origin. Histological diagnosis supported by the pattern of metastasis is sometimes helpful in the detecting the primary. Detailed Hematoxylin & Eosin (H&E) and immunohistochemical staining should be done in all cases [35, 36]. In select cases 'where tissue of origin remains unclear after histology, IHC staining and molecular assays' electron microscopy has been suggested [37].

CUP is categorized into different varieties according to its histology. The most common is adenocarcinoma constituting about 60% of the cases. The common sites of involvement are the lymph nodes, liver, lungs, and bones [19]. The second most common is poorly differentiated carcinoma, which constitutes about 29% to 30% of all the cases; the most common variety in this group is the non-Hodgkin's lymphoma (in about 35-65% of cases) [19]. The rest include Squamous Cell Carcinoma (SCC), which is found in about 5% patients; Neuroendocrine Carcinomas (NET), found in nearly 5% cases [38]; tumours with mixed histology of an adeno-squamous, neuroendocrine or sarcomatous component; and other related cancers like mesothelioma and germ cell cancer which may be like carcinoma in appearance.

7.1.1. Immunohistochemistry: This is a less expensive, reliable, and widely available investigation, which allows fast and precise identification of the primary lesion in many patients with CUP. There are a wide range of the already available and some recently introduced IHC markers [20]. The site of the primary is usually suggested by the various staining patterns rather than an individual IHC marker and the primary is detected in about one fourth of the cases [2].

A stepwise pattern of IHC staining should be adopted to detect the tumour type (carcinoma, melanoma, lymphoma, or sarcoma) first, followed by subtype (subdivide carcinoma into various subtypes: adeno, squamous, neuroendocrine, germ cell tumour or melanoma), and then the site of origin. The following flow chart depicts a systematic approach for evaluation of a patient with CUP. (Flow chart 1)

In adenocarcinoma, these stains sometimes suggest the tissue of origin like Prostate Specific Antigen (PSA) specific staining in metastatic prostatic cancers. Prediction of the primary is also possible in neuroendocrine tumours. There are no established biomarkers which can predict the primary site in squamous cell carcinomas. Well differentiated cancers retain better tissue-specific gene expression and better IHC staining than poorly differentiated ones, hence the diagnosis is more difficult in the latter. It can be easily performed on the paraffin blocks even if only a few malignant cells are present. The stains are also helpful in the characterization of poorly differentiated or undifferentiated cancers, identification of their cell type, and for final pathological diagnosis [36, 37, 39].

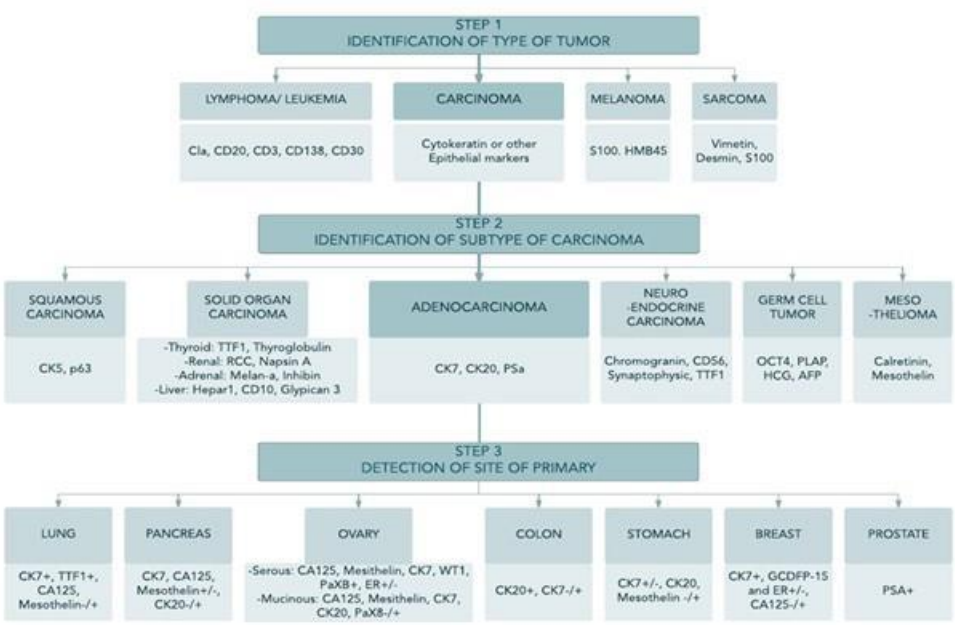
All markers need not be used in all cases. These stains are site-specific and should be used judiciously along with the clinical and radiological presentations to choose the best therapy. Cytokeratin is a useful marker which has 20 subtypes but CK20 and CK7 are the most common and frequently used stains to differentiate the various subsets of adenocarcinoma [35, 40, 41]. Presently a mixture of cytokeratin is used to diagnose the primary site of adenocarcinoma [37, 42]. CK7 is found in the glands of the lung, ovary, endometrium, and breast, but it is not detected in the tumours of the GI tract where CK20 is mainly present. CK20 is also seen in the urothelium and Merkel cells [43]. Various combinations of cytokeratin are used to suggest the location of the primary. For instance, CK7+/CK20 is used to diagnose lung cancer and may be positive in pancreatic and biliary tract cancers. CK7-/CK20+ indicate colonic cancers and may be positive in cancers of the duodenum or ampulla of vater. CK7+/CK20+ indicates urothelial malignancy [43].

During the last decade, newer IHC markers have emerged with antibodies against lineage-specific transcription factors. They have an improved efficacy towards detection of the primary site compared to the older IHC markers used to recognize keratins, other cytoplasmic and membranous antigens. The IHC staining against lineage-specific transcription factors like CDX2, TTF-1 and many others have proven to be particularly sensitive and specific, even in cases with poorly differentiated cancers [20]. TTF-1 is specific for adenocarcinoma of the lung [44]. CK 7 is positive in about 85% of lung cancers but it can be differentiated from other CK 7 positive tumours by using TTF-1 [43, 45]. Cadherin is used for the diagnosis of pulmonary adenocarcinoma and pleural mesothelioma. E-cadherin is overly sensitive for pulmonary adenocarcinoma. TTF-1 and E-cadherin are adequate for the diagnosis of pulmonary adenocarcinoma and pleural mesothelioma in most cases, but in some with negative TTF-1 and positive E-cadherin, other stains like BerEP4, calretinin, cytokeratin 5/6, thrombomodulin, and N-cadherin are required to differentiate between the two [44]. Chromogranin and synaptophysin indicates NETs. GCDFP-15-Mammoglobin are highly specific for breast cancers but have low sensitivity. PSA and thyroglobulin are the most specific markers for prostate and thyroid cancers respectively, but none of the tests are 100% specific. PSA and PSAP may be positive in the biopsy tissues of adenocarcinoma of salivary gland origin where the serum levels of these markers are normal and there is no primary prostatic carcinoma. URO III, Thrombomodulin suggest Urothelial malignancies and CDX-2 is positive in gastrointestinal cancers.

The following table provides a tabular representation of various permutations which may arise within the vast ambit of adeno and undifferentiated carcinoma (Table 2)

There are some pitfalls of IHC markers. No stain is entirely specific to a tissue, lack of standardized staining techniques and inter-observer variation in interpretation.

Immunohistochemistry is the gold standard for diagnosis, but in selected cases with undifferentiated tumours, molecular profiling plays an important role [38]. It is helpful in achieving a better diagnosis and future treatment protocol between tumour specific or empiric chemotherapy.



Flow chart 1: Systematic approach of IHC staining for evaluation of CUP

Table 2: IHC Stains Used in Adeno and Undifferentiated Carcinomas

TYPE	COMMON IHC STAINS	Indicative of:	Further tested by:
ADENO CARCINOMA	CK7+ CK20+	Transitional cell	Uroplakin, Thrombomodulin
		Gastric	Carcinoembryonic antigen (CEA)
		Pancreatic	CA 19-9
		Ovarian, Mucinous	WT-1
		Biliary	CEA
	CK7- CK20-	Prostate	PSA
		Renal cell	gp200, Vimentin
		Hepatocellular	Hepar1
	CK7- CK20+	Colorectal	CEA, CDX2
		Merkel Cell	Chromo G, Synaptophysin
	CK7+ CK20-	Lung	TTF1
		Breast	GCDFP, OR/PR

		Endometrial	Vimentin
		Ovarian, Non-Mucinous	WT 1, BerEp4
		Thyroid	Thyroglobulin
		Cholangiocarcinoma	CEA, CA 19-9
UN DIFFERENTIATED	CK+	Germ Cell	PLAP, AFP, Beta HCG
		Malignant Mesothelioma	Calretinin, CK5/6
		Synovial Sarcoma	Bcl-2, CD99
		Epithelioid Sarcoma	CK5/6
	CD45+	Lymphoma, Hematological Cancer	B &T cell marker, EMA, CD30
	PS100+	Melanoma	HMB45, Melan A
	All three -ve	Probable Sarcoma	AML, DES, CD31, CD34

7.1.2. Serum Tumour Markers: Various tumour markers like CEA, CA 19-9, CA 15-3, and CA-125 are over expressed in CUP in a non-specific way, but it is difficult to reach a conclusion based on the findings suggested by them alone [46]. CEA is helpful in differentiating adenocarcinomas of GI or endocervical origin from other sites [47] and an elevated level suggests more advanced cancer but has no predictive value in treatment response or survival. CEA and CA19-9 levels are higher in cases of CUP with hepatobiliary involvement than with nodal disease. PSA is done in all male patients being evaluated with bony metastasis. Other important tumour markers are Beta-HCG and AFP in extragonadal germ cell tumours, Alpha-Fetoprotein (AFP) in hepatic tumours, CA 125 in papillary peritoneal adenocarcinoma in females and CA15-3 in female patients with an isolated axillary adenocarcinoma.

7.1.3.Molecular profiling: Molecular profiling or gene expression profiling has been introduced recently to guide the most appropriate treatment regimen [39, 47]. This is a relatively novel approach which relies on the fact that tissues have different proteins and so, they differ in their genetic expression. If cancer develops in any organ, it usually follows the same organ specific pattern. The abnormalities at the molecular level, like the presence of micro RNAs responsible for gene expression in the primary tissue, are detected by this technique. It is done by using various molecular assays like Reverse Transcription Polymerase Chain Reaction (RT-PCR), or gene sequencing [48-50]. They can detect the site of primary even in those, where the results of the other tests are non-specific [19].

The primary aim of this technique is either to detect the primary and allow site specific treatment or to identify specific gene mutation against which targeted drugs are used. They identify the primary tissue of origin in about 83-93% of cases [19, 51, 52] and are thus helpful in choosing appropriate site-specific target therapy [53]. A multicentre trial using microarray DNA methylation technique showed 99% specificity, 97% sensitivity, 88% positive predictive value and 99% negative predictive value. The survival was better in patients treated by molecular profiling directed site specific therapy than those treated with empiric chemotherapy [54]. The technique is more useful in poorly or undifferentiated cancers and have shown substantial advantage over the other diagnostic tests. It is helpful in patients with visceral metastases and a colonic cancer profile or bony metastases with a renal or prostatic cancer profile. Once these lines are confirmed, site specific therapy can be given in these patients [13].A few chromosomal abnormalities are specific to some tumours and can be detected by molecular profiling assays. These include gene rearrangement in lymphoma, chromosomal translocation in Ewing's and neuroectodermal tumours, fusion oncogenes (BRD4-NUT) in tumours of midline structures and the short arm of chromosome 12th in germ cell cancers [19, 55].

All the patients with CUP have one specific genomic alteration which can be detected by molecular assays. These specific genomic changes are called actionable molecular alterations because targeted drugs are available against them. Once they are identified, upfront tailored targeted therapies can be started without searching for the primary tumour site and thus, improving response rates, progression-free survival, and perhaps overall survival. A recent study showed that these alterations are present in 24% of cases [56]. The most frequent alterations found are HER2, EGFR, BRAF and BRCA2 [19]. Latest research has suggested that detecting a primary site in the CUP evaluation may be less relevant than identifying a genomic alteration through molecular profiling, which may be pivotal for deciding target therapy [57]. It also has some limitations like higher cost compared to IHC, no defined protocol, only a few directed therapies available and its prognostic benefits are still not clear.

Studies in the past have compared the diagnostic capabilities of IHC and Gene profiling assays which showed that IHC was able to diagnose the primary site in 35% while Molecular profiling was helpful in 77% cases [58, 59].

7.2. Bone Marrow Examination

Bone marrow examination by aspiration cytology/biopsy is used to diagnose haematological malignancies and is also useful in the diagnosis of bony metastasis. Bone marrow aspiration provides information regarding cellular morphology while biopsy provides information about cellularity, infiltration of the bone marrow and fibrosis. Multiple pathological fractures after a trivial fall suggests metastatic bone disease and should be investigated by bone marrow examination. The differential diagnosis in these patients is adenocarcinoma with multiple metastases and multiple myeloma. Bone is the third most common site for secondaries from adenocarcinoma, after the lung and liver. It sometimes leads to the shortest way for the diagnosis of disseminated disease [60]. Trephine biopsy has a potential

advantage over bone marrow aspiration, especially if the aspiration tap is dry, because it helps to classify the type of tumour. There are no conclusive data comparing the relative value of aspiration cytology and biopsy in cases of involvement of the bone marrow in solid tumours [61].

7.3. Radiological Evaluation

Ultrasound examination of the breast and mammography are essential in women, while MRI is reserved for patients where the mammography results are suspicious. Testicular ultrasound is performed in men with retroperitoneal or mediastinal masses. CECT of the chest and abdomen including pelvis should be done in all cases to identify the location of a primary tumour, assess the disease load and select the most appropriate site for biopsy. During the last three decades, the diagnostic accuracy of the newer generations CT scans and MRI to detect primary tumours has increased with sensitivity and specificity rates up to 85%. In a study of more than 870 patients CT scan was able to diagnose 74% to 86% cases of lung and pancreatic cancers [62].

MRI detects an occult primary in about 70% of cases and is the imaging method of choice in women with adenocarcinoma found in the axillary nodes [63]. In patients with metastatic neck nodes, PET (Positron Emission Tomography) CT and 3 Tesla MRI have an equal diagnostic accuracy. MRI is also used to examine any particular area after a positive PET scan and helps in tumour staging [64].

7.3.1. Nuclear Medicine Examination: PET CT is the investigation of choice to evaluate the whole body in one scan. It is useful for diagnosis and staging and is able to detect a primary lesion in 25-43% [19, 62, 65, 66]. It has an intermediate specificity but high sensitivity. It is suggested that a PET scan can be a useful investigation in about 30% patients presenting with cervical lymphadenopathy [67-69]. There is a reported accuracy, specificity, and sensitivity of PET to detect CUP of more than 78%, 74% and 88% respectively and it is helpful in about 27% of cases with previously undetected metastases [66].

Recently there has been an increasing role of combination PET with CT/MRI scans in the diagnosis of CUP. Some neoplastic tissues have a very low radiotracer uptake of 18F fluorodeoxyglucose, hence the yield of PET scan is low. These patients are benefitted with a combination PET with either CT or MRI. Combination PET/CT is considered a better diagnostic tool than fluorodeoxyglucose (FDG) PET (55% vs. 31%) for detecting a primary in patients with cervical lymphadenopathy [70]. A meta-analysis on the combined use of PET/CT showed an identification rate of the primary up to 37%, and the most common sites were the lung (33%), head and neck (27%), pancreas (5%), colon (4%) and breast (4%) [71]. Somatostatin receptor scintigraphy or octreoscan is helpful in evaluating secondaries from neuroendocrine tumours. A special substance called octreotide bound with indium-111 is used in this test which has an affinity towards the tumour cells of various NETs. Technetium 99 labelled radioisotope scanning is the gold standard for detection of bony secondaries. It is highly sensitive but it lacks specificity because apart from the tumour, tracer accumulation can occur at the site of elevated bone resorption seen in cases of infection, trauma and arthropathy [72]. Improved methods like Single Photon Emission Computer Tomography (SPECT) for detecting bony metastasis are now available. The sensitivity and specificity of this test is extremely high.

There have been conflicting reports comparing the efficacy of PET versus bone scans. One study on patients with known metastases from prostate, lung and thyroid primaries showed FDG-PET to be more sensitive and specific [73].

7.4. Endoscopy

The use of upper and lower GI endoscopy should be based on the clinical presentation but the chance of finding a primary lesion is low [74]. Endosonographic FNAC is useful in selected cases where the suspected focus is not accessible. Colonoscopy is helpful in patients having CK7-, CK20+ or CDX2 and bronchoscopy in TTF1 positive patients or patients with enlarged hilar and mediastinal lymphadenopathy. A patient with cervical lymphadenopathy and squamous cell histology needs an endoscopic examination apart from a radiological workup. Tonsillectomy is preferred over tonsillar biopsy to search for the primary mucosal lesion in a patient presenting with CUP with squamous cell histology from the cervical nodes [75-76].

8. Treatment

CUP may relate to many different cancers; hence no standard management strategy is recommended for all forms of the disease. Most patients are refractory to currently available treatment options, but certain clinical subsets have a better survival. Therefore, the clinical and detailed pathological findings in each subset should be considered for selection of the most appropriate treatment regimen. Initially, the treatment of the patients was mainly based on the most probable site of primary cancer, but now other factors are also considered while choosing the most appropriate regimen. Treatment is usually tailored on an individual basis depending upon the clinical presentation, pathological factors, the result of immunohistochemistry and more recently, on molecular profiling in select cases. The main aim of treatment is palliation, as the cancer is unlikely to be cured. Both aspects of the treatment i.e., the potential benefits and the possible side effects should be considered while selecting any form of therapy. Chemotherapy is the mainstay of treatment with a combination of drugs being preferred over a single agent. There are multiple guidelines suggesting combination regimens [77]. Other modalities of treatment like radiotherapy, hormone therapy and surgery may be used either alone or in combination depending upon the situation.

Patients with CUP are divided into two categories for treatment, favourable and unfavourable subsets, with a better prognosis in favourable subgroup.

8.1. Favourable Subsets

In the favourable subset of patients, specific treatment with locore-

gional radiotherapy or platinum-based chemotherapy, is offered. The treatment response and the expected survival in this group is almost the same as in the patients with a known primary. Patients with metastases to the nodes, pleura or peritoneum respond better with a combination of carboplatin and paclitaxel than those with visceral disease [78]. Women with axillary lymph node involvement are treated along the lines of breast cancer and those with neck nodes are treated like head and neck cancer. Histology plays a key role in cases where the site of origin is unknown or undiscovered. Adenocarcinoma and undifferentiated cancers are treated by a combination of drugs, squamous cell carcinoma is treated as head and neck tumours of primary origin and NETs are treated according to specific protocols [79]. Patients with peritoneal carcinomatosis presenting as primary peritoneal disease are treated on the lines of stage III ovarian cancer and they respond to debulking surgery followed by adjuvant taxane or platinum-based chemotherapy. A median survival of 7 months without disease progression and overall survival of 15 months were reported in patients treated with debulking surgery and chemotherapy [80].

8.2. Unfavourable Subsets

These patients have a poor prognosis and constitute about three fourths of the patients of CUP. The histological diagnosis in most of them is either adenocarcinoma or poorly differentiated carcinoma which is resistant to the available treatment options. They are treated with empirical combination chemotherapy using various drugs like platinum-based compounds, taxane, gemcitabine and targeted therapy. Survival of nine months and response rate of 15 to 20% have been noted [81]. Cure rates are very low and the tumour regresses only in one third of the cases. A recent study has suggested that patients treated by taxane-based regimens had a prolonged median survival time of 1.52 months and a higher 1-year survival rate of 6.25% but, the benefit did not sustain for 2 years [82]. Even if the primary tumour is not detected, accurate prediction of the possible primary is important in the management of this group of patients [19].

The table below depicts the common strategies used for treating these patients (Table 3).

Table 3: Common Strategy Used to Treat Cup Patients

A	FAVOURABLE	Axilla	Women	Lymph Nodal Enlargement	Adenocarcinoma or carcinoma	Treated like stage II or III breast cancer
		Midline - mediastinum supraclavicular area, retroperitoneum [Extragonadal Germ Cell Tumour]	Men	Lymph nodal enlargement, Testicular involvement	Poorly differentiated or undifferentiated carcinoma	Treated like extragonadal germ cell tumours with platinum-based drugs
		Peritoneum	Women	Carcinomatosis	Adenocarcinoma - papillary serous type	Treated like stage III ovarian cancer with debulking surgery and adjuvant chemotherapy
		NET - Small		Local symptoms	Well differentiated or low grade	Somatostatin alone or Local therapy – Resection, Cryotherapy, RFA, TACE
		NET - Large		Systemic presentation	Poorly differentiated or high grade	Chemotherapy – platinum based, etoposide or taxanes
		Cervical nodes		Lymph nodal enlargement	Squamous cell	Treated as locally advanced head and neck cancers with concomitant chemoradiation or radical nodal dissection in select cases
		Single metastatic focus in liver, lung, nodes or brain				Neoadjuvant chemo or chemoradiation with surgery depending on situation
		Liver or peritoneal		Multiple metastatic deposits	Histology of GI Adenocarcinoma- CK20 +/CK7 – or CDX2 +	Chemotherapy for metastatic cancers – First or second line
		Inguinal area			Squamous cell carcinoma	Inguinal lymphadenectomy or radiotherapy along with combination chemotherapy
		Bone	Men	Blastic bony lesions		Treated as advanced prostate cancer
B	UN -FAVORABLE	Peritoneum		Malignant ascites	Adenocarcinoma - non-papillary type	Combination chemotherapy
		Brain		Multiple cerebral lesions	Adeno or squamous	
		Thorax		Multiple lesions - lung/pleural	Adenocarcinoma	
		Bone		Multiple bony lytic lesions		

8.3. Targeted Therapy

This is a newer modality of treatment, based on the interpretations of molecular profiling. It is more effective than conventional chemotherapy and acts either against a specific abnormality at the molecular level like gene mutation, or on the surrounding tissue environment which augments the cancer growth. It is more selective and less toxic as it acts only on the abnormal cells. Recent literature suggests an improving role of molecular profiling directed targeted therapy over empiric treatment. The median survival of 12.5 months has been reported with the use of targeted therapy, which was better than the survival noted with empiric therapy in the past [83].

8.4. Drugs Used in Treatment of CUP

Earlier, 5 FU and Cisplatin based regimens were used, but the response rate was poor [84]. Platinum compounds, taxane, gemcitabine and recently targeted agents are the various drugs used in the treatment of CUP. Gemcitabine has a synergistic action with platinum compounds, and it enhances the activity of fluoropyrimidines. Gemcitabine and oxaliplatin were well tolerated and had been used as a first line therapy in these patients [85]. A chemotherapy regimen with either two or three drugs is used for treatment in patients with suspected lung cancer. In patients with liver involvement and the primary tumour suspected to be below the diaphragm, combination of gemcitabine, carboplatin and capecitabine is preferred [86]. A meta-analysis of currently used treatments for CUP showed no significant benefit for any one treatment group over the others [87].

A taxane based combination regimen has been shown to be superior with less toxicity and a combination of paclitaxel, carboplatin and etoposide has been used with a complete response rate of 13% and a major response rate of 47%. A median survival of about 13 months was observed and the combination was almost equally effective irrespective of the histology being well or poorly differentiated adenocarcinoma.

Targeted agents like Epidermal Growth Factor Receptor (EGFR) inhibitors and, Vascular Epithelial Growth Factor (VEGF) inhibitors are a new class of drugs. They have been used as first- or second-line therapy in a few studies. Bevacizumab and erlotinib, which are used in the treatment of solid tumours, are also considered for treatment in these patients. Bevacizumab is a monoclonal antibody which acts against VEGF and prevents neoangiogenesis. It is used as a single agent in renal cell malignancies, and as one of the drugs in advanced cancers of the lung, colon, and breast [88-91]. The other agent erlotinib, which is an EGFR inhibitor, is used as a single agent in refractory non-small cell cancer of the lung and used in combination regimens in pancreatic cancers. The efficacy of the regimen increases when both these drugs are used in combination rather than being used alone. Targeted therapy with crizotinib against “actionable molecular alterations” is used in patients with predictable non-small cell lung cancer [92]. Data suggests that targeted therapy can improve survival in patients with non–small-cell lung cancers [93]. Recent research has suggested newer treatment possibilities with targeted drugs, but further clinical trials are required.

8.5. Radiotherapy

This has a selective application in the treatment of CUP. It is used for localized cancers in patients who have undergone nodal dissection in the axilla or inguinal region. It is also used for bony metastatic lesions and non-germ cell retroperitoneal tumours. Short-course radiation therapy is used for palliation of squamous cell carcinoma of an unknown primary in the head and neck [94]. Patients with advanced disease of the head and neck may have a surprising durability of response with even a short course of palliative radiation therapy. It is helpful in patient having intractable pain or vertebral collapse due to bony metastases.

The role of definitive radiation therapy has been studied in the abdomen and pelvis where the disease was considered incurable by chemotherapy alone. Despite radiation toxicity in up to 40% of cases, the progression free and overall survival was better in patients treated with radiotherapy. The use of definitive radiation therapy should be considered in selected patients with CUP in the soft tissues or nodal basins of the abdomen and pelvis [95].

Chemo embolization, or radiofrequency ablation are the other alternative therapeutic options for unresectable lesions in the liver.

9. Conclusion

CUP is an aggressive disease with a dismal prognosis, which is difficult to manage despite the advances in our diagnostic and treatment modalities. IHC and molecular profiling plays an important role in achieving a diagnosis, which is essential for designing a management protocol. Immunochemical stains should be used judiciously, and a step wise pattern is recommended for their use. Molecular profiling is a comparatively new investigative tool and helps in deciding the basis for tailormade targeted therapies in these difficult situations. Contrast-enhanced CT scans and MRI are useful adjunct but there is a growing role of PET CT in the evaluation and a combination of PET with CT/MRI is more helpful in some difficult cases. Primary site is predicted only in minority of patients, who are best treated with site directed therapy. There is a growing role of finding genomic alterations by molecular profiling, rather than following a time consuming and costly evaluation protocol to find the primary site, which can form a basis for goal directed target therapy, but further trials are needed.

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