NICE National Institute for Health and Care Excellence

NICE guideline

Metastatic malignant disease of unknown primary origin in adults: diagnosis and management

Clinical guideline
Published: 26 July 2010
Last updated: 26 April 2023

www.nice.org.uk/guidance/cg104

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Overview

This guideline covers diagnosing and managing secondary cancer in people aged 18 and over when the site of the primary cancer is unknown. This includes people who have had treatment for cancer before. It aims to improve quality of life by offering advice on tests for identifying the site of the primary cancer and options for managing the person's condition.

This guideline covers carcinomas only and does not cover, for example, lymphoma, melanoma and sarcoma. For other NICE guidelines on cancer, see the cancer topic page.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- Adults with cancer of unknown primary origin, their families and carers

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Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

1.1 Organisation of services and support

1.1.1 The CUP team and its functions

1.1.1.1 Every hospital with a cancer centre or unit should establish a carcinoma of unknown primary (CUP) team, and ensure that patients have access to the team when a malignancy of undefined primary origin (MUO) is diagnosed. The team should:

- consist of an oncologist, a palliative care physician and a CUP specialist nurse or key worker as a minimum
- have administrative support and sufficient designated time in their job plans for this specialist role **and**
- have a named lead clinician.

1.1.1.2 The CUP team's named lead clinician should:

- take managerial responsibility for the CUP service within the cancer centre or unit

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- ensure there is a clinical system for the appropriate care of MUO and CUP patients
- ensure that each patient has an identified CUP specialist nurse or key worker
- ensure there is cover for all members of the CUP team during periods of absence
- ensure that senior clinical input is available to inform decision making and treat patients as necessary
- ensure that there is a single point of contact for the patient to access the CUP team
- implement the care pathway and help to educate other healthcare professionals in diagnosing and managing MUO and CUP
- ensure timely and effective communication between all healthcare professionals involved in the care of patients with MUO or CUP, including primary and palliative care
- represent the cancer centre or unit at the CUP network site-specific group and CUP network MDT **and**
- contribute to regular local and network audits of the management of MUO or CUP.

1.1.1.3 Every hospital with a cancer centre or unit should assign a CUP specialist nurse or key worker to patients diagnosed with MUO or CUP. The CUP specialist nurse or key worker should:

- take a major role in coordinating the patient's care in line with this guideline
- liaise with the patient's GP and other community support services
- ensure that the patient and their carers can get information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial concerns
- meet with the patient in the early stages of the pathway **and** keep in close contact with the patient regularly by mutual agreement and
- be an advocate for the patient at CUP team meetings.

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1.1.1.4 Refer outpatients with MUO to the CUP team immediately using the rapid referral pathway for cancer, so that all patients are assessed within 2 weeks of referral. A member of the CUP team should assess inpatients with MUO by the end of the next working day after referral. The CUP team should take responsibility for ensuring that a management plan exists which includes:

- appropriate investigations
- symptom control
- access to psychological support **and**
- providing information.

1.1.1.5 The CUP team should actively review the outcome of all investigations with a nominated pathologist and radiologist as appropriate.

1.1.1.6 A CUP network MDT should be set up to review the treatment and care of patients with confirmed CUP, or with MUO or provisional CUP and complex diagnostic or treatment issues. This team should carry out established specialist MDT responsibilities.

1.1.1.7 The CUP team should be involved in the patient's care until the patient is:

- referred to a site-specialist consultant **or**
- referred for palliative care alone **or**
- diagnosed with a non-malignant condition.

If CUP is confirmed, the CUP team should continue managing the patient's care.

1.1.1.8 Every hospital with a cancer centre or unit should ensure that patients are upgraded to the existing cancer waiting times pathway when MUO is suspected or first diagnosed.

1.1.1.9 Every hospital with a cancer centre or unit undertaking diagnostic investigations of patients with MUO should ensure that services are set up for rapid and appropriate investigation of patients according to this

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guideline, and staff are appropriately trained.

1.1.2 Organisation of CUP services at network and national level

1.1.2.1 Every cancer network should establish a network site-specific group to define and oversee policies for managing CUP. The group should:

- ensure that every CUP team in the network is properly set up (see recommendation 1.1.1.1)
- ensure that the local care pathway for diagnosing and managing CUP is in line with this guideline
- be aware of the variety of routes by which newly diagnosed patients present
- advise the cancer network on all matters related to CUP, recognising that many healthcare professionals have limited experience of CUP
- maintain a network-wide audit of the incidence of CUP, its timely management and patient outcomes
- arrange and hold regular meetings for the group to report patient outcomes and review the local care pathway.

1.1.3 Definitions and data collection for MUO and CUP

1.1.3.1 Data and coding definitions for MUO and CUP should be developed and routine statistics should use these definitions.

1.1.3.2 A minimum data set for MUO and CUP should be agreed nationally. The data set should be collected by clinicians seeing MUO and CUP patients and reviewed at network level.

1.1.3.3 A national audit should be established for MUO and CUP patients based on the agreed minimum data set.

1.1.3.4 The National Cancer Intelligence Network should analyse current data on the epidemiology of MUO and CUP and use of the NHS by MUO and CUP patients.

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1.2 Diagnosis

For patients presenting with MUO, diagnosis can be divided into two phases. The aim of the initial diagnostic phase is to perform the most appropriate investigations efficiently, to identify:

- a primary site, which will guide treatment decisions **or**
- non-epithelial malignancy, which can be treated regardless of primary site (for example, lymphoma, other haematological malignancies, melanoma, sarcoma, and germ-cell tumours) **or**
- metastatic epithelial or neuro-endocrine malignancy without an identifiable primary site (a diagnosis of provisional CUP).

  If further investigation is appropriate, a second phase of special investigations may be offered to patients with provisional CUP. When these are complete and if a primary site has still not been identified, a diagnosis of confirmed CUP can be made.

  In current practice the nature and extent of initial diagnostic tests are not universally agreed, and evidence to support the use of special tests is lacking. The approach used in this guideline has been to:

- define the core initial tests for patients in whom investigation is clinically relevant
- examine the contribution of special tests
- define the best histological assessment of tissue samples
- examine the best approach for specific presentations or difficult diagnoses.

1.2.1 Initial diagnostic phase

1.2.1.1 Offer the following investigations to patients with MUO, as clinically appropriate, guided by the patient's symptoms:

- comprehensive history and physical examination including breast, nodal areas, skin, genital, rectal and pelvic examination

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- full blood count; urea, electrolytes and creatinine; liver function tests; calcium; urinalysis; lactate dehydrogenase
- chest X-ray
- myeloma screen (when there are isolated or multiple lytic bone lesions)
- symptom-directed endoscopy
- computed tomography (CT) scan of the chest, abdomen and pelvis
- prostate-specific antigen (PSA) in men (see recommendation 1.2.2.1)
- cancer antigen 125 (CA125) in women with peritoneal malignancy or ascites (see recommendation 1.2.2.1)
- alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) (particularly in the presence of midline nodal disease) (see recommendation 1.2.2.1)
- testicular ultrasound in men with presentations compatible with germ-cell tumours
- biopsy and standard histological examination, with immunohistochemistry where necessary, to distinguish carcinoma from other malignant diagnoses.

1.2.2 Second diagnostic phase – special investigations

Tumour markers

1.2.2.1 Do not measure tumour markers during diagnosis except for:

- AFP and hCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men).
- AFP in patients with presentations compatible with hepatocellular cancer.
- PSA in men with presentations compatible with prostate cancer.

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- CA125 in women with presentations compatible with ovarian cancer (including those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.

Upper and lower gastrointestinal endoscopy

1.2.2.2 Do not carry out upper or lower gastrointestinal (GI) endoscopy in patients with MUO unless the symptoms, histology or radiology suggest a GI primary tumour.

Mammography

1.2.2.3 Do not offer mammography routinely to women presenting with MUO, unless clinical or pathological features are compatible with breast cancer.

Breast magnetic resonance imaging

1.2.2.4 Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider dynamic contrast-enhanced breast magnetic resonance imaging (MRI) to identify lesions suitable for targeted biopsy.

Positron emission tomography–computed tomography

1.2.2.5 Offer positron emission tomography–computed tomography (18F-FDG PET-CT) to patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panendoscopy if radical treatment is considered to be an option.

1.2.2.6 Consider 18F-FDG PET-CT in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team or CUP network MDT.

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Molecular diagnostic tests

1.2.2.7 Use a panel of antibodies comprising cytokeratin 7 (CK7), CK20, thyroid transcription factor-1 (TTF-1), placental alkaline phosphatase (PLAP), oestrogen receptor (ER; women only) and PSA (men only) in all patients with adenocarcinoma of unknown origin.

1.2.2.8 Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies in recommendation 1.2.2.7 and the clinical picture.

1.2.2.9 This recommendation has been withdrawn.

For information on genomic diagnostic tests to identify primary tumours in patients with provisional CUP, see the NHS Genomic Medicine Service's national genomic test directory for cancer.

1.2.3 Investigation of specific clinical presentations

Intrapulmonary nodules without evidence of endobronchial disease

1.2.3.1 Offer flexible bronchoscopy with biopsy, brushings and washings to patients presenting with intrapulmonary nodules of probable metastatic origin that are unsuitable for percutaneous biopsy, even in the absence of endobronchial or central nodal disease on imaging.

1.2.3.2 Offer video-assisted thoracoscopic surgery (VATS) exploration to patients only after a negative bronchoscopic procedure and where percutaneous biopsy is considered inappropriate.

Investigation of malignant peritoneal disease

1.2.3.3 Obtain a tissue sample for histological examination in patients with MUO who present with ascites, if technically possible.

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1.3 Factors influencing management decisions

1.3.1 When to stop investigations

1.3.1.1 Do not offer further investigations to identify the primary site of origin of the malignancy to patients who are unfit for treatment.

1.3.1.2 Perform investigations only if:

- the results are likely to affect a treatment decision
- the patient understands why the investigations are being carried out
- the patient understands the potential benefits and risks of investigation and treatment **and**
- the patient is prepared to accept treatment.

1.3.1.3 Explain to patients and carers if further investigations will not alter treatment options. Provide appropriate emotional and psychological support, information about CUP, treatment options and palliative care.

1.3.2 Selecting optimal treatment

1.3.2.1 Take account of prognostic factors, in particular performance status, presence of liver metastases, lactate dehydrogenase levels and serum albumin, when making decisions about further diagnostic investigations and treatment.

1.3.2.2 Discuss the patient's prognostic factors with the patient and their relatives or carers, if appropriate, to help them make informed decisions about treatment.

1.3.2.3 Include the patient's prognostic factors in decision aids and other information for patients and their relatives or carers about treatment options.

1.3.2.4 This recommendation has been withdrawn.

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1.4 Managing specific presentations

1.4.1 Presentations that may benefit from radical treatment

Squamous carcinoma involving upper- or mid-neck nodes

1.4.1.1 Refer patients presenting with upper- or mid-neck squamous cell carcinoma and an unidentified primary tumour to a head and neck MDT for evaluation and treatment.

Adenocarcinoma involving the axillary nodes

1.4.1.2 Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment.

Squamous carcinoma involving the inguinal nodes

1.4.1.3 Refer patients with squamous carcinoma confined to the inguinal nodes to a specialist surgeon in an appropriate MDT to consider treatment with curative intent.

1.4.1.4 Offer patients with operable disease either:

- superficial lymphadenectomy and consider post-lymphadenectomy radiotherapy (for patients with risk factors for residual disease, for example multiple involved nodes or extracapsular spread) **or**
- simple excision of clinically involved nodes, followed by radiotherapy.

Solitary metastases

1.4.1.5 Do not investigate a tumour inappropriately because this may make radical treatment ineffective. For example, biopsy of a primary bone tumour may mean that the patient needs more extensive surgery than usual. Percutaneous biopsy of a potentially resectable liver metastasis may compromise outcome. Consider that an apparent metastasis could be an unusual primary tumour.

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1.4.1.6 Refer patients with a solitary tumour in the liver, brain, bone, skin or lung to the appropriate MDT to consider radical local treatment.

1.4.2 Presentations with a poor prognosis

Multiple metastases including brain involvement

1.4.2.1 Refer patients presenting with apparent brain metastases as the only sign of malignant disease after initial and special investigations to a neuro-oncology MDT for evaluation and treatment.

1.4.2.2 Do not offer chemotherapy to patients with brain metastases of unknown primary origin except as part of a controlled clinical trial.

1.4.2.3 Inform patients with brain metastases of unknown primary origin and their carers that there is no evidence that any treatment offers improved survival and there is limited evidence of improvement in neurological symptoms with surgery and/or whole brain radiotherapy.

1.5 Systemic treatment

1.5.1 Chemotherapy in patients with confirmed CUP

1.5.1.1 If chemotherapy is being considered for patients with confirmed CUP, with no clinical features suggesting a specific treatable syndrome, inform patients about the potential benefits and risks of treatment.

1.5.1.2 Offer patients with confirmed CUP the opportunity to enter clinical trials.

1.5.1.3 If chemotherapy is offered outside clinical trials, take into account the clinical and pathological characteristics of the tumour, the toxicity profile of the drugs, their ease of administration and response rate when choosing which treatment to use.

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1.5.2 Chemotherapy for recognised treatable syndromes

1.5.2.1 Offer patients chemotherapy directed at a specific treatable syndrome if they have:

- confirmed CUP with clinical and/or laboratory features of a specific treatable syndrome **and**
- adequate performance status.

1.5.2.2 Offer patients the opportunity to enter clinical trials.

Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline. For other definitions, see the NICE glossary and the Think Local, Act Personal Care and Support Jargon Buster.

Malignancy of undefined primary origin (MUO)

Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.

Provisional carcinoma of unknown primary origin (provisional CUP)

Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology or cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.

Confirmed carcinoma of unknown primary origin (confirmed CUP)

Metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.

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Recommendations for research

The guideline development group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The guideline development group's full set of recommendations for research is detailed in the full guideline.

1 Clinical studies group for CUP

A clinical studies group should be established at National Cancer Research Network (NCRN) level for CUP, to coordinate and direct a broad portfolio of research examining basic science, clinical studies, organisational processes and patient-centred topics

Why this is important

The existence of a national organisation to guide and facilitate research has revolutionised cancer care in the UK. High-quality, rapidly accruing trials have resulted in improved outcomes for patients with all common cancers. Patients with CUP cannot benefit from similar advances because there is no national research strategy addressing their needs. Establishing an NCRN clinical studies group for CUP with a comprehensive portfolio of relevant trials would redress this inequality.

2 Use of PET-CT in the MUO diagnostic pathway

Further research is needed to determine whether the use of 18F-FDG PET-CT early in the CUP management pathway reduces the number of investigations that the patient is subjected to.

Why this is important

Tests early in the diagnostic pathway of patients with MUO are selected on the basis of clinical factors (suspicion about a possible primary site) and test-related factors (expected yield, ease of access, ease of use, cost). Investigation is an iterative process in which the results of one round of tests inform the selection of subsequent tests. 18F-FDG PET-CT may reveal a primary tumour that would either not be detected using standard tests, or

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that would have been detected only after a protracted and costly series of other tests. Using 18F-FDG PET-CT early in the diagnostic pathway may reveal useful clinical information more quickly and more cost effectively than current diagnostic strategies. Comparison of established methods of investigation with early use of 18F-FDG PET-CT is therefore warranted.

3 Decision aids

Decision aids should be developed and research carried out to evaluate their benefit.

Why this is important

Decision aids have been shown to help breast cancer patients when they face difficult choices. Such aids could be of even greater value to patients with CUP. Research to evaluate the benefits, ease of use and acceptability of such tools to both clinicians and patients should be conducted. Such studies could be an adjunct to larger trials of chemotherapy.

4 Gene-expression-based profiling

Prospective randomised trials should be undertaken in patients with confirmed CUP to evaluate whether chemotherapy guided by gene-expression-based profiling is superior to treatment guided by conventional clinical and pathological factors.

Why this is important

Selection of optimal chemotherapy for patients with cancer is largely based on knowing the organ of origin of the tumour. For patients with CUP this is not known and decisions are therefore based on the likely organ of origin, as determined by tests such as histology. The limited benefit of treatment selected on this basis highlights the ineffectiveness of current tests in guiding treatment. If the likely organ of origin were more accurately defined there may be a greater chance that treatment would be more effective. Gene-expression-based profiling reliably defines the organ of origin of tumour samples, and the information this test provides in cases of CUP may translate into superior outcomes. Comparing the outcome of chemotherapy selected using conventional factors with the outcome of chemotherapy based on a putative organ of origin defined by gene-expression-based profiling would determine whether this technique could be a beneficial

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addition to standard management in CUP.

5 Defining optimal systemic therapy

Randomised controlled clinical trials should be undertaken in patients with confirmed CUP to define optimal systemic therapy.

Why this is important

The evidence currently used to guide selection of systemic treatment for patients with CUP is very limited, and mainly based on phase II non-comparative studies. In the majority of patients it is uncertain whether systemic treatment offers any advantages over supportive care alone. Randomised controlled trials comparing different interventions should be conducted in well-defined groups of patients with CUP to define optimal treatment. Such trials should include in their design methods to assess cost-effectiveness and patient-centred factors such as quality of life.

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Context

Patients with 'cancer of unknown primary origin' have metastatic malignant disease without an identifiable primary site. For patients with this condition the type of tumour, the extent of its spread, and the outcome of treatment all vary widely. Most patients have malignancy that appears to derive from epithelial cells, that is, 'carcinoma of unknown primary origin' (CUP). Patients with tumours of non-epithelial lineage (melanoma, sarcoma, lymphoma, germ cell) are not considered in this guideline because their care is covered in existing guidelines for their specific tumour type. They form a distinct minority because their tumours can often be managed satisfactorily even without an identifiable primary site.

CUP is currently an inexact term because it is often applied to patients who have had only limited investigations. In this guideline a patient who presents with metastatic malignancy (in the form of tumour masses or effusions) identified on clinical examination or by imaging, without an obvious primary site, is regarded as having 'malignancy of undefined primary origin' (MUO). 'Provisional carcinoma of unknown primary origin' (provisional CUP) is used to refer to patients with metastatic malignancy of proven epithelial, neuro-endocrine or undifferentiated lineage, after initial, but not exhaustive investigations. Although a primary site will be found in most of these patients, or a non-epithelial malignancy diagnosed, in some patients a primary site will not be found and a diagnosis of 'provisional CUP' will change to a diagnosis of 'confirmed CUP' after the results of all tests are complete. Definitions of MUO and CUP are given in the section on terms used in this guideline.

In England and Wales, over 10,000 cases of CUP occur annually and it is the fourth most common cause of cancer death. Patients presenting with MUO and those who are ultimately diagnosed with confirmed CUP are disadvantaged in many ways. The following problems in current practice have been identified:

Lack of agreed definitions of the clinical entity.

No referral guidelines for suspected cancer relevant to patients without an obvious or strongly suspected primary.

No system to rapidly identify patients and to ensure early specialist involvement.

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Lack of efficient arrangements to manage the initial diagnostic phase.

Uncertainty about appropriate diagnostic tests, including the use of new technologies.

Lack of a team structure to efficiently care for newly presenting patients.

Insufficient specialist oncology expertise.

Lack of dedicated key workers or specialist nurses.

Referral to inappropriate site-specific cancer teams.

Lack of support and information for patients.

Delays in involvement of specialist palliative care.

Lack of an overall organisational structure to ensure high-quality care.

Uncertainty about optimal treatment.

Lack of adequate epidemiology data.

No research organisation.

The aim of this guideline is to address the needs of patients with CUP, which are not covered by current NICE cancer service guidance.

There is important overlap between the developments necessary for optimal management of MUO and CUP and the acute oncology initiatives in the National Chemotherapy Advisory Group (NCAG) report on Chemotherapy Services in England: Ensuring quality and safety. This guideline complements and supports the relevant recommendations in the NCAG report.

The guideline requires the development of a CUP specialist role for oncologists, multidisciplinary team (MDT) functioning, and site-specific group organisation in line with practice for cancers with identified primary sites. It is expected that many consultant oncologists who develop a specialist interest in CUP will also be involved in organising and delivering aspects of the acute oncology service for newly presenting patients with

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previously undiagnosed cancer.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

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Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on metastases.

For full details of the evidence and the guideline committee's discussions, see the full guideline and evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

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Update information

April 2023: We withdrew recommendations 1.2.2.9 and 1.3.2.4 on gene-expression-based profiling and added a link to the NHS Genomic Medicine Service's national genomic test directory. For more information see the surveillance decision.

ISBN: 978-1-4731-5173-4

Accreditation

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