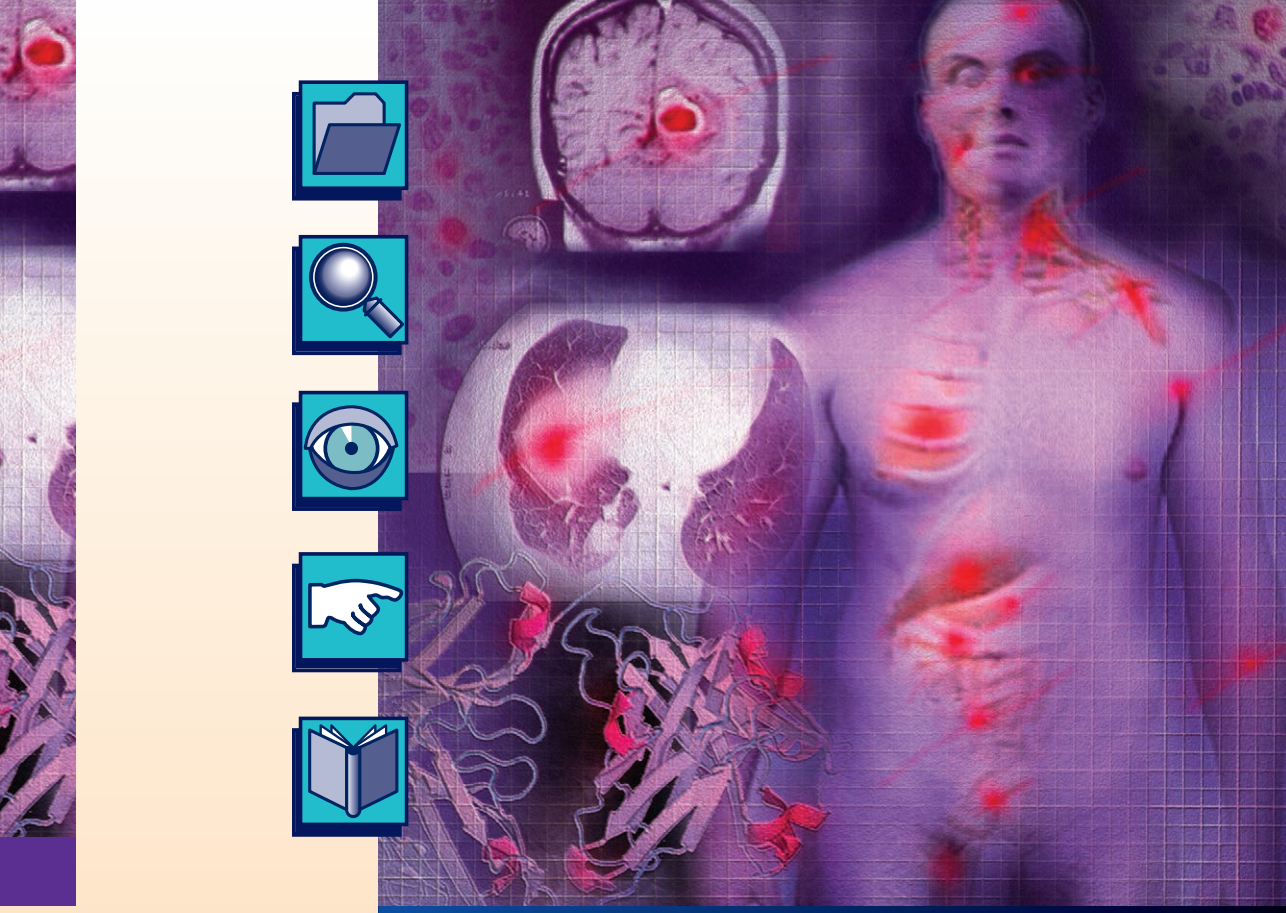

Problem Solving in Acute Oncology

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Contributor e print

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Acute Oncology

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Foreword

The Importance of Acute Oncology to Cancer Patients

We have made considerable progress to improve the services provided in the NHS for cancer patients. Multidisciplinary specialized care has been developed throughout the NHS, and cancer services have been reconfigured to ensure that patients move to the appropriate place so that their care can be provided by teams with the right specialized expertise. Facilities have been improved and there have been substantial increases in workforce and training. These developments have not completed the task. We have much to do to maintain and continue to improve the excellence of care and to ensure that patients can quickly and appropriately gain access to that care. Although cancer outcomes in the UK are getting better, there is room for further improvement.

Emergency presentation as the route to diagnosis for cancer is common. In England, 24% of all cancers present in this way and the proportion is greater in patients over 70 years of age. For all cancers emergency presentation is associated with a poorer outcome and patients are less likely to survive the next year following presentation.

The development of acute oncology will improve the care of cancer patients, the management of acute complications of cancer, and of its treatment, and our approaches to diagnosing patients who present with cancer and have no obvious primary site. This will address the needs of patients who present acutely to the healthcare system with findings that suggest the possibility of a malignancy, ensure that patients who develop acute complications of their cancer or their treatment are seen, evaluated and managed promptly by clinicians with the right skills and facilities, and provide a supportive acute cancer care service for patients throughout their journey. Key appointments in acute oncology, many at consultant and nurse practitioner level, are being made across the NHS.

There remains a need to ensure that practitioners are fully informed and kept up to date with the appropriate clinical care to be provided in the setting of acute oncology. It is also necessary to ensure a continuing developmental dialogue on the best way to deliver acute oncology services in a hard-pressed healthcare service. For these reasons, this text on acute oncology is particularly helpful and timely. It will serve as a valuable resource for those who have to continue to develop an excellent acute oncology service, as well as providing a source of training and updates for clinicians working in this challenging clinical area. The Association of Cancer Physicians is to be congratulated on bringing about this valuable additional resource, which is the first of its kind, and we can look forward to further contributions in future.

Michael Richards, Sean Duffy

Preface

Michael Richards and Sean Duffy, who lead the development of cancer care in the UK, have drawn attention to the importance of acute oncology in providing high-quality cancer care for our patients. We have prepared this book in the format of the *Problem Solving* series in order to present the issues surrounding the development of acute oncology services, both in the UK and internationally, in a patient-centred format. We have illustrated most of the problems that will present to an oncologist who is part of the acute oncology services. These cover the perspective of service development, but also many aspects of acute general medical and acute oncological care that will arise, this includes the care of patients with cancer of unknown primary site, the major complications of systemic therapy (especially febrile neutropenia), the complications of radiotherapy, the major acute complications of cancer itself and some considerations of patients in clinical trials presenting acutely. Palliative care and pain control can be critically important challenges to oncology services, and key aspects of these are set out in the context of patient related-problems.

Our purpose is to provide a highly patient-centred, readable text, that will support acute oncologists both in training and in practice. We hope that it will provide a valuable resource for all acute oncology services to those who are charged with developing acute oncology services in the future across the world, and be helpful for the individual oncologist, whether in training or established as consultants and staff physicians. Acute oncology has been developing rapidly, bringing improvements in services and benefits to patients. We hope this book will help this process and add to its momentum.

Ernie Marshall, Alison Young, Peter Clark and Peter Selby

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Abbreviations

ACE	angiotensin-converting enzyme
ADLs	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALF	acute liver failure
ALP	alkaline phosphatase
ALT	alanine transaminase
AOS	acute oncology service(s)
AOT	acute oncology team
AR	adverse reaction
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
bpm	beats per minute
BCNU	bis-chloroethylnitrosourea (carmustine)
CA125	cancer antigen 125 (MUC16, mucin 16)
CCC	Clatterbridge Cancer Centre
CEA	carcinoembryonic antigen
CFS	cerebrospinal fluid
CHF	congestive heart failure
CID	chemotherapy-induced diarrhoea
CKD	chronic kidney disease
CNS	central nervous system
CONcePT	Comparison of Oxaliplatin vs Conventional Methods with Calcium/Magnesium in First-Line Metastatic Colorectal Cancer (NCT00129870)
COPD	chronic obstructive pulmonary disease
COSA	Clinical Oncology Society of Australia
CPAP	continuous positive airway pressure
Cr	creatinine
CRF	case record form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUP	cancer of unknown primary
CVP	central venous pressure
DGH	district general hospital
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase 4
DPYD	dihydropyrimidine dehydrogenase
DVT	deep vein thrombosis
EC	epirubicin and cyclophosphamide
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	emergency department
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
FBC	full blood count
FEC	fluorouracil, epirubicin and cyclophosphamide
5-FU	fluorouracil
FNA	fine-needle aspiration
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GEBP	gene expression-based profiling
GFR	glomerular filtration rate
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
GLP-1	glucagon-like peptide-1
GP	general practitioner
Hb	haemoglobin concentration
HbA1c	glycosylated haemoglobin
HBcAg	core antigen of hepatitis B virus
HBeAg	core antigen of hepatitis B virus, extracellular form
HBsAg	surface antigen of hepatitis B virus
HBV	hepatitis B virus
HER2	human epidermal growth factor receptor 2
HFS	hand-foot syndrome
HSCT	haematopoietic stem cell transplantation
IB	Investigator Brochure
IDSA	Infectious Diseases Society of America
IgE	immunoglobulin E
IMRT	intensity-modulated radiation therapy
INR	international normalized ratio

IV	intravenous
IVC	inferior vena cava
LEVF	left ventricular ejection fraction
LMWH	low-molecular-weight heparin
LN	lymph node
MASCC	Multinational Association of Supportive Care in Cancer
MCCN	Merseyside and Cheshire Cancer Network
MdG	modified de Gramont regimen
MDT	multi disciplinary team
MOSAIC	Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer
MRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSCC	metastatic spinal cord compression
MUO	malignancy of undefined primary origin
NCAG	National Cancer Action Group
NCCTG	North Central Cancer Treatment Group
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCIN	National Cancer Intelligence Network
NCQA	National Committee for Quality Assurance
NEWS	national early warning score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNH	number needed to harm
NNT	number needed to treat
NS	neutropenic sepsis
NYHA	New York Heart Association
OPD	outpatient department
PCD	paraneoplastic cerebellar degeneration
PCN	percutaneous nephrostomy
PDGF	platelet-derived growth factor
PDGFR	PDGF receptor
PE	pulmonary embolus
PET	positron emission tomography
PICC	peripherally inserted central catheter
PIS	patient information sheet
P_{O_2}	oxygen tension (partial pressure)
PPI	proton pump inhibitor
PQRI	Physician Quality Reporting Initiative
PRES	posterior reversible encephalopathy syndrome
PSA	prostate-specific antigen
PTHrP	parathyroid hormone-related protein
QOPI	Quality of Oncology Practice Initiative
RCP	Royal College of Physicians
RPA	recursive partitioning analysis
RTK	receptor tyrosine kinase
RTOG	Radiation Therapy Oncology Group
RUL	right upper lobe
SAAG	serum-ascites albumin gradient
SACT	systemic anticancer therapy
SAE	serious adverse event
SAR	serious adverse reaction
SCF	supraclavicular fossa
SCLC	small-cell lung cancer
SIADH	syndrome of inappropriate antidiuretic hormone
SJIO	St James's Institute of Oncology
Sp_{O_2}	arterial oxygen saturation measured by pulse oximetry
SpR	specialist registrar
SRS	stereotactic radiosurgery
SSG	site-specific group
SUSAR	suspected unexpected serious adverse reaction
SVCO	superior vena cava obstruction
T4	levothyroxine
TKI	tyrosine kinase inhibitor
TLS	tumour lysis syndrome
U&Es	blood test for urea and electrolytes (sodium and potassium)
UGT	uridine diphosphate-glucuronosyltransferase
UK	United Kingdom
Ur	supraclavicular fossa
US	United States (of America)
VATS	video-assisted thoracic surgery
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor
VRE	vancomycin-resistant *Enterococcus*
VTE	venous thromboembolism
WBC	white blood cell count
WBRT	whole-brain radiotherapy
WHO	World Health Organization

PROBLEM

03 Cancer of Unknown Primary (CUP)

Richard Osborne

Case History

A 68-year-old man attended the emergency department at the weekend with sudden onset of pain in his right arm after minor trauma. He had a number of other non-specific symptoms including general malaise and weight loss. X-rays revealed an undisplaced pathological fracture of the right humerus and other bone metastases. A set of routine blood tests was requested, though not reviewed. The patient was discharged home the same day with a sling by a junior member of the orthopaedic team who also arranged referral to a multidisciplinary team (MDT).

How can this patient's cancer be categorized for appropriate referral and ongoing care?

What organizational shortcomings might exist that would prevent this patient receiving optimal care?

What system of immediate care should established for patients such as this?

How should the subsequent care of patients on the MUO/CUP spectrum be organized (see Table 3.1)?

How has the paradigm for treatment of CUP changed recently?

Background

How should this patient's cancer be categorized for appropriate referral and ongoing care?

This patient provides an example of a common dilemma. He almost certainly has cancer, but in current practice there is uncertainty about how he should be further investigated, who should be responsible for this task, and who should coordinate delivery of services for his ancillary needs of information, support and symptom control.

He has features of metastatic bone disease, but has not undergone any subsequent tests designed to characterize the disease more precisely. The differential diagnosis is broad, ranging from a primary bone tumour (with metastases), to myeloma, to the most common scenario of bone metastases from a recognized primary such as kidney, stomach or lung. Ultimately, if carcinoma is confirmed but all other investigations are completed without a primary site being identified, the patient would be classified as having cancer of unknown primary (CUP). In terms of initial care, a similar dilemma is frequently encountered when patients present *de novo* with other common manifestations of metastatic cancer, such as malignant liver disease, malignant ascites, malignant pleural effusions, brain metastases, malignant nodes or other malignant masses.

One factor which has blocked developments in this setting is the lack of specific

language to delineate the clinical entity, and hence to allow appropriate focus on service development. This has been rectified recently by standard definitions provided in the NICE Clinical Guideline for 'Metastatic malignant disease of unknown primary origin (CG104)', summarized in Table 3.1.[1]

Table 3.1 Definitions following NICE Clinical Guidelines CG104.

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, pCUP) Metastatic epithelial or neuroendocrine 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 specialized investigations.
Confirmed carcinoma of unknown primary origin (confirmed CUP, cCUP) Metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialized investigations as appropriate.

The concept of metastatic malignancy of undefined primary origin (metastatic MUO) is now embedded among acute oncology practitioners, with beneficial consequences. It is becoming possible to collect reliable data on incidence rate, allowing workforce planning. Agreement on the existence of MUO and its wide recognition should now permit appropriate management to be introduced in a more timely and uniform fashion.

What organizational shortcomings might exist that would prevent a patient with MUO receiving optimal care?

Although cancer services for patients with an established primary site are well developed, this system of care does not efficiently serve those in whom the origin of metastatic cancer is unknown. The relatively rigid and compartmentalized nature of site-specific cancer management has actually resulted in a deterioration in skills and facilities for generic diagnosis and care.

Compared with a patient in whom a site-specific cancer diagnosis is clear, the patient with MUO faces numerous significant, *immediate* problems:

- The lack of an explicit, efficient, formal system to manage the initial diagnostic phase
- Inadequate information about their illness
- Uncertainty about the nature and organization of clinical plans
- Insufficient symptom control and delayed access to specialist palliative care
- No cancer nurse specialist support
- Referral to an inappropriate site-specific cancer team using a process which does not provide necessary information for decision making, leading to delays in investigation and treatment.

Additionally, as seen with the patient described above, the current vogue for ambulatory care and rapid discharge means that formal arrangements for management of outstanding clinical problems are often neglected. In this case, the lack of continuity of care meant that serious problems due to metastatic malignancy involving bones (e.g. hypercalcaemia, uncontrolled pain, other fractures, spinal cord compression, myeloma complications) could have been present or developed subsequently, leading to additional yet avoidable morbidity.

The list of deficiencies in current care arrangements can be further expanded when other clinical scenarios are considered. For MUO patients identified in primary care there are no specific referral guidelines to assist timely expert assessment. Currently, oncological and palliative care advice is only accessed after significant delay, with adverse consequences in terms of speed and quality of decision making, efficiency (in terms of length of stay) and patient satisfaction. The latter point warrants reinforcement. The debilitating uncertainty experienced by patients and carers is a direct consequence of a lack of specialist services in this area, meaning the development of dedicated expert care for this very common scenario is an urgent priority.

The main purpose of this chapter is therefore to provide guidance on the organization of services for optimal acute care of MUO and CUP, rather than to act as a didactic tool for investigation and management of the specific clinical problems seen in this group. Information about modern strategies for investigation of MUO and treatment for common acute complications of malignant disease is easily found elsewhere.[1–4]

Recent Developments

What system of immediate care should be established for patients with MUO?

The appropriate organization of care for patients with MUO/CUP is defined in detail in the National Cancer Peer Review Programme Manual for Cancer Services Cancer of Unknown Primary Measures.[5] The key principle is that the NICE CUP Guideline:

> *"… recognizes the validity for MUO/CUP of the same basic service infrastructure which underpins that for site specific cancers, as outlined in the various Improving Outcomes Guidance publications and The Manual for Cancer Services. That is, multidisciplinary teams, network site specific groups, various related hospital services and the cancer network."*

Accordingly, the main components required are:

1. ***A "CUP Team"*** *to advise on, and supervise appropriate investigation and subsequent management, according to the guidelines in NICE CG104.*[1]

   The team should comprise a consultant oncologist with expertise in MUO/CUP, a palliative medicine consultant, and a designated cancer nurse specialist. The CUP team will, with other colleagues in radiology and pathology, along with necessary administrative support, undertake traditional MDT functions. The team will meet weekly to review all new patients and to ensure the necessary input is available to deliver comprehensive care for each individual.

   An important concept is that the newly presenting patient with MUO will usually remain under the care of the admitting (non-oncology) consultant initially, with the

CUP team exercising an advisory role. This arrangement is necessary where patients are admitted to hospitals without resident oncologists or oncology beds.

2. ***A system for rapid review*** *of inpatients, or access to rapid, dedicated outpatient specialist oncologist assessment when MUO is diagnosed but admission is not required.*
   The necessity for prompt expert oncological advice, attention to symptomatic needs, and holistic support cannot be overemphasized. Equally, with this new approach, the ability to enter a generic process for investigation is expected to significantly benefit patients who would otherwise spend unacceptable amounts of time being investigated inappropriately by site-specific clinicians. It is important to recognize that these developments place novel demands on some oncologists whose proficiency in front-line diagnosis may not be fully developed. It is anticipated that the emergence of acute oncology as a subspecialty in oncology will largely overcome this problem.

3. ***A full range of network-level functions*** *(in common with the arrangements for known-site cancers) to underpin high quality care.*
   The CUP site-specific group (SSG) is essential to ensuring that this relatively common condition is accorded appropriate investment in terms of clinical and support resources. Additionally, for this neglected disease complex, the establishment and maintenance of explicit management guidelines and the delivery of ancillary functions, such as audit and research, is an obvious need.

   The precise arrangements for SSG working can be organized to suit the requirements of different networks. So long as the essential duties are conducted, it may be that some organizations will link the CUP SSG with another established SSG. Consideration should, however, be given to ensuring the highest-quality CUP service is delivered, in full compliance with the National Cancer Peer Review measures. There will be some configurations (for instance amalgamation within the acute oncology SSG) which may superficially appear logical, but which run the risk of neglecting aspects of CUP care (see below).

How should the subsequent care of patients on the MUO/CUP spectrum be organized?

Approaches developed for rapid problem solving in the acute phase after presentation with MUO must be complemented by suitable organization of care in the much longer phase of management and treatment that follows this. It is certainly reasonable to design and implement services for immediate care of newly presenting MUO within the context of emerging Acute Oncology Services (AOS), since the benefits arising from a rapid-response approach are well suited to the problems of this group. However, continuing care beyond the initial phase requires that 'disease-specific' structures, analogous to those for patients with known-site cancer, are put in place for those in whom a primary site is not rapidly identified.

For this sizeable cohort with 'provisional CUP', post-acute care remains compromised by:

- A lack of dedicated and specialist oncology expertise
- Uncertainty about appropriate advanced diagnostic tests, including the use of new technologies such as positron emission tomography (PET) and molecular profiling

- Lack of an overall organizational structure to ensure high-quality care through the whole patient journey
- Uncertainty about optimal treatment
- Lack of adequate epidemiology data
- No research organization.

Existing acute oncology models designed around the National Cancer Peer Review measures do not deliver these facilities. Recognition of the requirement for later, 'site-specific' arrangements for CUP is needed, analogous to those routinely provided for other major cancers. This has consequences when designing an overarching structure for MUO/CUP care. Simply concentrating on acute needs, based on an acute oncology SSG approach, cannot provide the necessary expertise and facilities to comprehensively address identified shortcomings in long-term care. Figure 3.1 demonstrates the distinction between overall MUO/CUP care and the acute oncology remit.

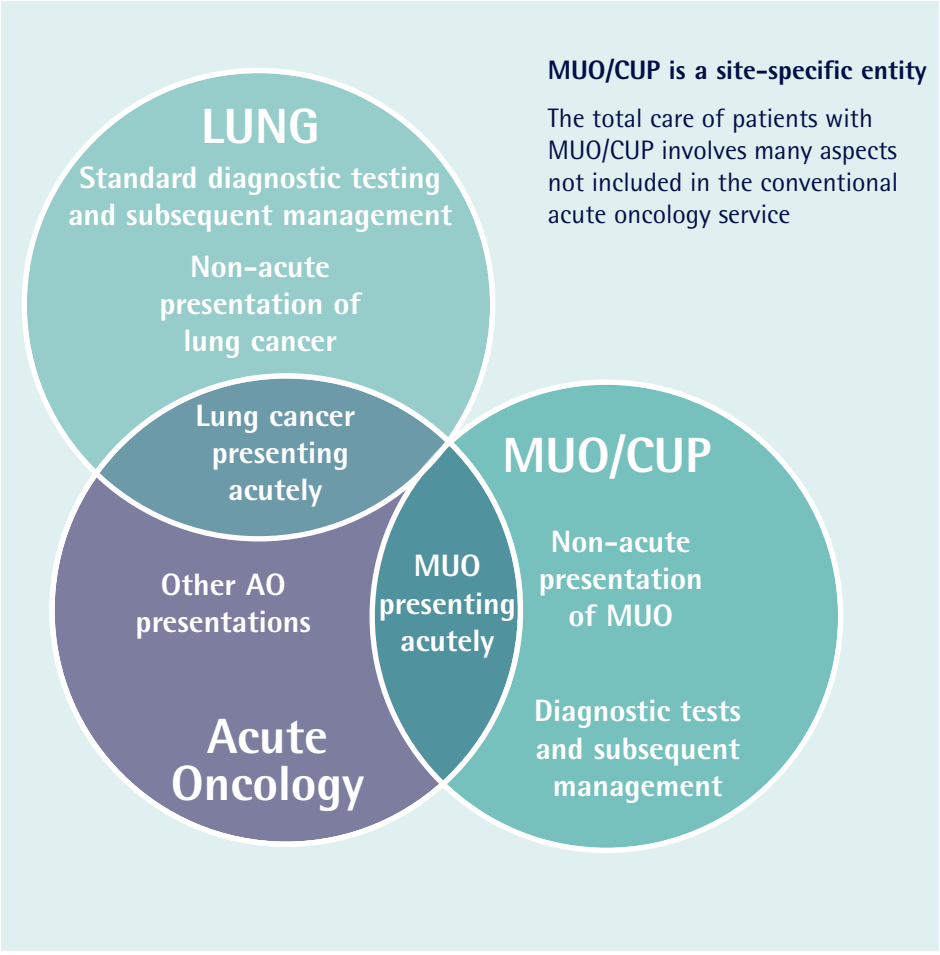

Figure 3.1 MUO/CUP is a site-specific entity. AO, acute oncology; CUP, carcinoma of unknown primary origin; MUO, malignancy of undefined primary origin.

How has the paradigm for treatment of CUP changed recently?

Having defined the desirable architecture for the comprehensive management of patients with MUO/CUP, it is important to consider actual therapeutic advances which can further improve care.

The past history of therapeutic nihilism surrounding CUP is, in a way, understandable, because the outcomes from treatment are very limited for the majority of patients. Lack of engagement with investigating and managing the condition has compounded the limitations of medical interventions such that this patient group has been uniquely disadvantaged.

This whole picture is now undergoing radical change. Oncologists are recognizing that management of MUO/CUP offers significant intellectual challenges which render the condition worthy of interest. The ability (and now the requirement)[5] to radically improve care through proper organization, aided by the introduction of AOS, means that this is a satisfying area of work. At the same time, tantalizing developments in treatment are emerging which have the ability to bring outcomes for CUP patients up towards the standards achieved in other common metastatic malignancies. Gene expression-based profiling (GEBP) has been investigated for many years in patients with confirmed CUP, and the weight of data now supports the potential of this approach to characterize patients as having a 'primary-like' genotype. When treated along site-specific lines, based on these results relating to tissue of origin, outcomes are beginning to match those expected in patients with known-site disease.[6,7] The policy of explicitly managing confirmed CUP patients along these lines is now achieving credence among experts in the field, though access to the necessary GEBP test is limited by cost at present.

Conclusions

In summary, it is anticipated that implementation of new organizational structures and services for MUO will radically improve many aspects of the patient journey. The growing acceptance of treatment of confirmed CUP along 'primary-like' lines will have a beneficial impact on the equally important outcomes of response and survival for this challenging condition.

Further reading

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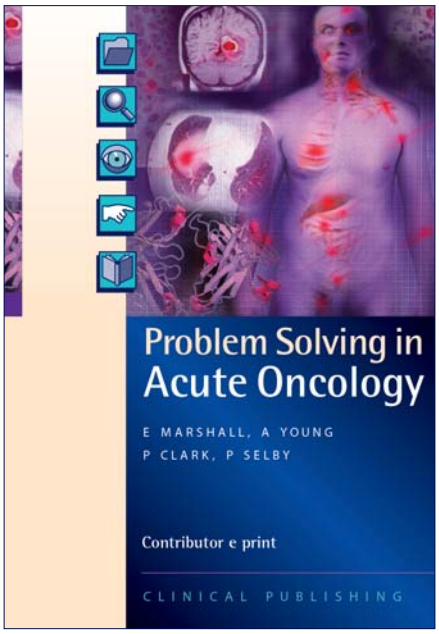

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