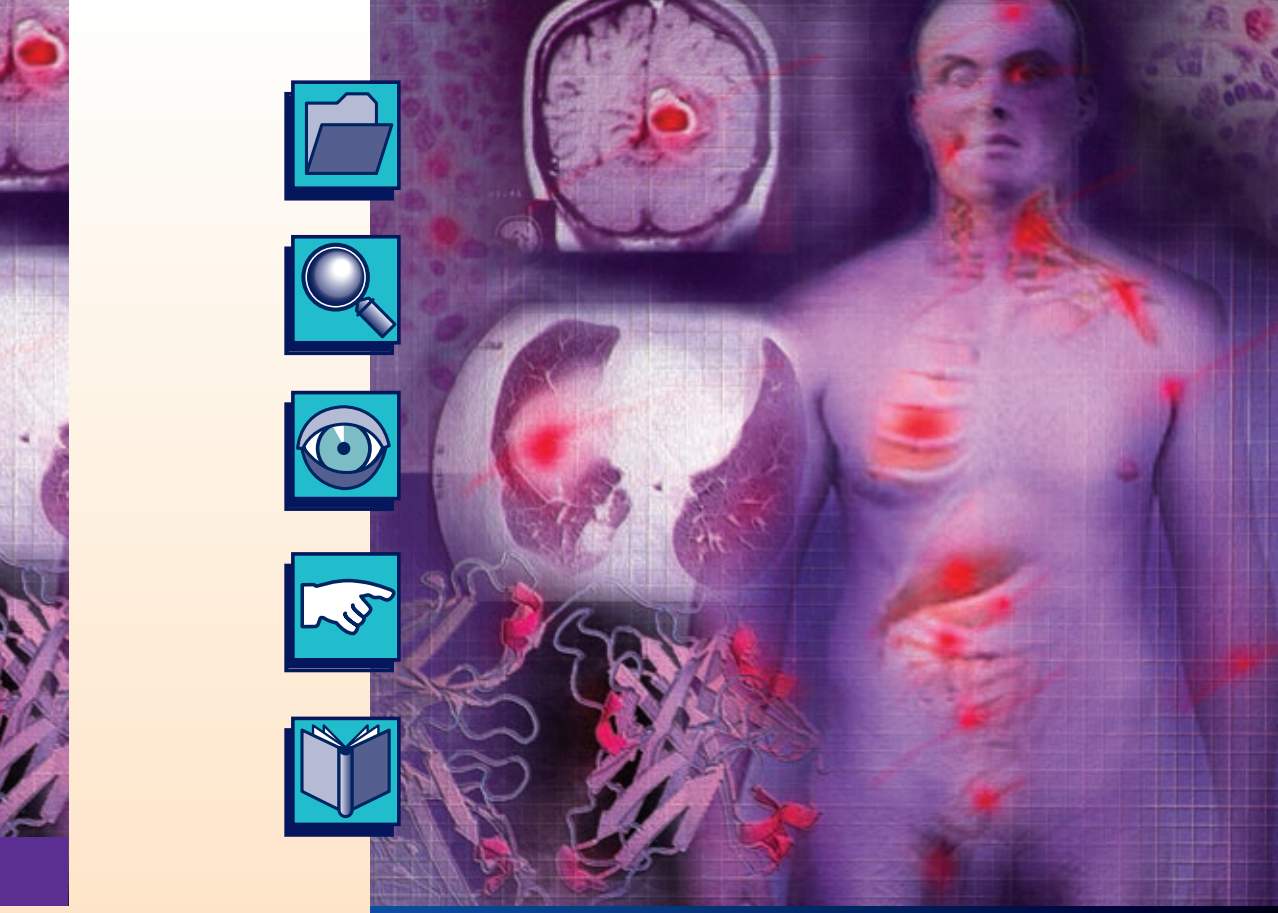

Problem Solving in Acute Oncology

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CLINICAL PUBLISHING

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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

Perspectives in the Development of Acute Oncology

PROBLEM

01 The Development of Acute Oncology: Solutions and Options

Ernie Marshall, Pauline Leonard, Alison Young

Case Histories

Patient 1: A 74-year-old man presents to primary care with a three-month history of progressive lumbar spine pain despite analgesia and physiotherapy. The patient has localizing tenderness but no neurological deficit and this leads the GP to request an MRI spine. The MRI report is faxed urgently to primary care stating that there are findings consistent with multiple metastases present throughout the spine.

Patient 2: A 54-year-old woman with Grade 3, T2 N1 breast cancer is undergoing adjuvant FEC chemotherapy and develops nausea and dizziness. The patient is

hypotensive with a temperature of 39°C and the GP requests an urgent ambulance to direct the patient to the nearest emergency department for review.

Patient 3: A 65-year-old woman, previously fit and well, presents to her local A&E department with acute abdominal pain, weight loss, anorexia, and increasing tiredness and lethargy. She is admitted acutely to the medical assessment unit and is found on CT scan to have liver metastases.

How do acute oncology models differ within and across cancer networks?

How would differing acute oncology models support the management of the above emergency presentations?

Background

Cancer is a major health issue. In the UK there are 325 000 new cases of cancer diagnosed annually. There are 157 000 deaths, contributing 28% of all deaths every year. With a wealth of possible curative and life-prolonging treatments it is estimated there are 1.7 million cancer survivors.[1]

The National Audit Office Hospital Episode Statistics estimate that the number of patients receiving systemic anticancer chemotherapy (SACT) has been increasing year on year since 2001/02, accounting for £1 billion expenditure annually.

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD),[2] published in 2008, provided uncomfortable reading regarding the quality and safety of care for patients who died within 30 days of receiving SACT. The enquiry was set up especially to understand precisely the care pathways for this group of sick cancer patients. In only 35% of patients was the care deemed to be acceptable. In the 49% of patients where care was less than optimal, factors relating to both the organization of emergency care and the specific care delivered by each institution were identified. The National Chemotherapy Advisory Group (NCAG)[3] was formed to address how care should be delivered, not only to improve the outcome of the sick cancer patient, but to also address key issues in the organization of care to improve the patient experience.

The development of an Acute Oncology Service (AOS) in every trust with an emergency department was a key recommendation of the NCEPOD report. It described an AOS as one that brings together the expertise from oncology disciplines, emergency medicine, general medicine and general surgery to ensure the rapid identification and prompt management of all patients who present with severe complications following chemotherapy or as a consequence of their cancer. Uniquely, it also described the management of patients who present as emergencies with previously undiagnosed cancer as a key responsibility of an AOS. These groups of patients who present to the emergency department with a constellation of symptoms and are subsequently found to have cancer represent 22% of all new cancers diagnosed each year in England, with lung, pancreas and brain malignant tumours forming the largest group. Data collected by the National Cancer Intelligence Network (NCIN) have shown that, apart from acute leukaemia, the survival for this group of patients is far worse than for those who are referred by their general practitioner (GP) directly to elective non-emergency services. This is because such patients are usually of poor performance status, often elderly, and with multiple comorbidities. Their median survival is short as they are frequently too

unwell to benefit from SACT or other potentially life-prolonging interventions. It was clear this group of patients needed properly coordinated pathways with early oncology and palliative care input to ensure appropriate care was given.

Against this background, the cancer patient journey not infrequently interfaces with multiple institutions and departments, and poses key challenges for patients, families and the evolving acute oncology services. In the patient population reviewed by NCEPOD, all of whom died within 30 days of receiving systemic anti-cancer therapy, 42% of them were admitted to a general medical service rather than to an oncology service. In addition 43% of all patients had either grade 3 or grade 4, life-threatening toxicity from their SACT recorded during their admission to hospital prior to their deaths. Of the NCEPOD population, 86% of patients were being treated with palliative intent and 50% of patients were on their second or subsequent line of SACT. It was notable that 15% of the NCEPOD study population, prior to their death, were admitted to a healthcare organization other than that which had actually delivered their chemotherapy, implying a lack of continuity of care. The findings suggest that factors in the deaths of these patients included toxicity from chemotherapy, often experienced by patients who were being treated with palliative intent. The admissions, sometimes to organisations other than those who were providing the SACT, and often to general medical services which were not specialized in oncology, might have resulted in some delay or inappropriate provision of treatment. Acute oncology services are charged with improving the quality of care for this and other patient populations."

Irrespective of local hospital or network solutions, acute oncology is underpinned by a number of core principles that promote education, awareness and early access to specialist oncology teams. In these models early specialist review must be combined with strong leadership and innovative service developments that will improve the safety and quality of emergency cancer care.

The number and type of acute oncology emergency admissions is highly dependent on local service configuration. This reflects the role of an individual hospital trust as an acute district general hospital, a fully integrated cancer centre or a standalone cancer centre that lacks acute medical and surgical support. For each of these services, the core acute oncology principles remain the same; however, the models of care may appear very different.

Data on acute oncology patterns and workload remain sparse. In 2006/07 there were 273 000 emergency admissions with a diagnosis of cancer, representing a 30% increase from 1997/98.[2] This is roughly equivalent to 750 emergency admissions each day across England, so that a typical trust may have five emergency admissions with cancer per day (two under general medicine, one under general surgery, one under oncology/haematology and one under 'other'). Unplanned cancer admissions may happen several times for the same patient. Average length of stay for inpatient cancer admissions between regions varied from 5.1 to 10.1 days in 2008/09. If every region had the same length of stay as the average in regions in the best performing quartile, even with no reduction in admissions, 566 000 bed-days could be saved, equivalent to £113 million each year.[1]

A one-day snapshot of inpatients at a combined acute university hospital trust and cancer centre identified that cancer patients accounted for 19% of all inpatients and that 57% of these had a known diagnosis of cancer.[4] Patients admitted under oncology had a

shorter length of stay than those admitted under general medicine or general surgery (median 7 vs 18 days).

At the wider network level, the seven Acute Oncology Teams (AOTs) in the Merseyside and Cheshire Cancer Network (MCCN) reviewed 3031 cases following their first year of establishment, with monthly referral rates reaching a plateau after six months of inception.[5] The acute oncology type is shown in Tables 1.1 and 1.2. Patients admitted with complications of cancer at a time of disease progression represent the majority, with lung cancer the most frequent primary site. Emergency presentation of malignancy of undefined primary origin (MUO) accounted for 290 'type 1' acute oncology episodes.

Data collected prospectively by the AOTs revealed an average length of stay for the MCCN network as a whole to be 9.7 days. Comparing present average length of stay with baseline average on 2005/6 (12.8 days) shows a reduction of 3.1 days for cancer patients admitted to hospital since the network-wide AOS was implemented. This equates to a total number of 9014 bed-days saved.

Table 1.1 Acute oncology subtypes across Merseyside and Cheshire Cancer Network

AO Trust	Type 1 (new cancer)		Type 2 (chemo/ radiation comps <6wks		Type 3 (know cancer complications)		Other		Not recorded		Total N
	N	%	N	%	N	%	N	%	N	%	
1	100	13%	154	21%	482	65%	0	0.0%	6	0.8%	742
2	130	23%	203	35%	239	42%	0	0.0%	2	0.3%	574
3	92	16%	248	43%	241	41%	0	0.0%	1	0.2%	582
4	121	28%	74	17%	203	47%	7	1.6%	24	5.6%	429
5	33	20%	49	30%	79	49%	0	0.0%	1	0.6%	162
6	46	12%	125	33%	200	53%	1	0.3%	6	1.6%	378
7	42	26%	42	26%	80	48%	0	0%	0	0%	164
Total	**564**		**895**		**1524**		**8**		**40**		**3031**

Table 1.2 Acute oncology referrals – top four primary sites across Merseyside and Cheshire Cancer Network

Tumour site Group	Trust 1	Trust 2	Trust 3	Trust 4	Trust 5	Trust 6	Total
Lung	207	147	139	94	39	74	700
Breast	85	89	120	52	19	77	442
Colorectal	86	37	118	28	42	58	369
UKP	52	50	86	65	16	21	290

The clinical challenges identified by the NCEPOD report and the subsequent development of acute oncology services has, in the UK, resulted in determined activity to improve the quality of care available to the patients who are at risk. The National Health Service (NHS) has provided valuable funding for the development of these services. There is, at present, no single template for an AOS. The complexity of the provision of care, the diversity of hospital configurations and the way in which hospitals cooperate in their cancer networks is such that a single template would be unworkable. However, clear principles have been

developed. We have therefore presented the options for patient care by describing the management that would be provided by three different acute oncology services in three different clinical cancer care networks. These bring out the approaches that have been used and demonstrate how the principles have been incorporated, or are in the process of being incorporated, into care patterns in the UK.

Model I: a standalone cancer centre (Merseyside and Cheshire Cancer Network)

The MCCN serves a population of 2.3 million with non-surgical oncology provision delivered via a 'hub-and-spoke' model coordinated from the Clatterbridge Cancer Centre (CCC), a single standalone cancer centre. The CCC functions as a tertiary referral service and manages approximately 10 000 new patient episodes and over 47 000 chemotherapy episodes per year. The CCC has no acute medical, surgical or intensive care facilities, and delivers the majority of elective chemotherapy via satellite chemotherapy day units situated in seven acute NHS trusts. New and follow-up patients are reviewed in defined outpatient clinic sessions that are held within the CCC and across the satellite cancer units. Subsequently, patients are prescribed chemotherapy according to a single network protocol book, and receive standardized patient information and a chemotherapy alert card. The model of care ensures that the majority of chemotherapy and outpatient services are delivered close to the patient's home via fixed outpatient sessions supported by visiting peripatetic medical and chemotherapy nursing staff. In this model, the CCC hosts a 24-hour chemotherapy triage service for all solid tumour patients who have received chemotherapy within the previous six weeks.

The MCCN has developed an acute hospital acute oncology model that consists of at least two visiting oncologists (one of whom is the acute oncology lead for the host trust), providing a 5-day service, equating to one programmed activity, equivalent to one half day of a consultant working time, of acute oncology support per day Monday to Friday. The oncologist also provides one or more site-specialized services at the same trust where they provide acute oncology support. The oncologists do not have their own beds, but are available in the hospital on a Monday-to-Friday basis to review patients as necessary. The lead acute oncology consultant also uses their acute oncology session to lead and develop the service, support cancer peer review and represent the acute trust at the level of the cancer network.

The AOT also consists of a minimum of one full-time equivalent oncology cancer nurse specialist, available Monday to Friday, 9 a.m. to 5 p.m. This is in addition to administrative support linked to the local cancer services department, which provides a focal point for referrals, clinical enquiries and data support pertaining to each patient episode referred to the AOT. The acute oncology nursing remit is pivotal to the running of the service and often represents the first point of contact for professional and patient enquires.

Emergency presentation of suspected cancer requires responsive pathways and access to fast-track clinics as a means of improving care and reducing emergency admissions. Acute oncology services are particularly well placed to coordinate management, either through direct access to acute oncology fast-track clinic slots (within established outpatient oncology sessions) or via early cross-referral pathways with existing site-specific multi-disciplinary teams (MDTs). In either scenario it is essential that AOTs work closely with expert site-specific MDTs to facilitate investigation, speedy diagnosis

and appropriate treatment. In the context of the cited MUO referral, local acute oncology services are developing direct GP referral capacity via new fast-track acute oncology slots within existing oncology outpatient clinics.

How might standalone cancer centre acute oncology services facilitate the ongoing management of these patients?

For **patient 1**, the request was identified within local district general hospital cancer services and triaged to acute oncology. The patient was contacted directly via telephone and received information and symptom management with acute oncology nursing support. Subsequently, the patient was reviewed in the outpatient department by the AOT within five days of referral, thus reducing the risk of inappropriate site-specific referral or an emergency admission. Focused investigation, including prostate-specific antigen (PSA), confirmed a diagnosis of metastatic prostatic carcinoma and the patient was transferred to the uro-oncology team for ongoing management.

For **patient 2**, central chemotherapy triage directed the patient to their local emergency department (ED) and alerted local AO services via email. Acute oncology education and pathway development can ensure that patients presenting with known complications of chemotherapy are triaged and managed along defined inpatient pathways. The development of local acute oncology pathways with ED and haematology services ensured the patient received expert timely care at the point of admission and subsequent triage to a specialist haematology ward environment. Ongoing review within 24 working hours by AOTs ensured optimal communication with the treating team at the cancer centre, liaison with central cytotoxic pharmacy, provision of patient information and support, and the development of risk-adapted early discharge policies.

For **patient 3**, the finding of metastatic cancer following a CT scan triggered an immediate acute oncology referral. This was facilitated by an increasing awareness of acute oncology services, and underpinned by a radiology flagging policy and acute oncology pathways that are placed on the hospital intranet. The patient was admitted to a general medical ward but reviewed within 24 hours by a member of the acute oncology team. In view of the patient's poor performance status, further investigations were cancelled, urgent review by the hospital palliative care team was undertaken and the case and imaging were reviewed at the weekly acute oncology MDT.

Model II: a comprehensive cancer centre (Yorkshire Cancer Network)

The Yorkshire Cancer Network (YCN) serves a population of approximately 2.6 million within the Yorkshire and Humber Strategic Health Authority. Non-surgical oncology provision is delivered via a cancer centre – the St James's Institute of Oncology (SJIO) – based in Leeds Teaching Hospitals Trust, and six additional hospital trusts providing cancer unit services with resident medical oncologists in the surrounding region. The cancer centre at Leeds functions both to provide local services for the people of Leeds and as a tertiary referral service for the YCN providing specialist cancer services for intermediate and rare cancers. The SJIO manages approximately 8000 new referrals per year, with 4500 patients receiving treatment and in excess of 22 000 chemotherapy episodes. The SJIO is a purpose-built cancer wing within a large teaching hospital providing emergency, acute medical, surgical and intensive care facilities. It also delivers all elective cancer treatment (chemotherapy and radiotherapy) within the centre. Patients living in the rest of the network are generally seen and treated by resident oncologists in

the additional cancer units so that treatment is delivered close to the patient's home wherever possible. For the purpose of this chapter, further management will be discussed assuming the patients are, or will be, treated in the cancer centre.

All patients receiving treatment for cancer at SJIO are given a contact card (credit card-sized) with the appropriate numbers to call if they develop a complication of their cancer or treatment. This is a 24-hour triage service that is designed for all patients who have received treatment within the previous six weeks. If a patient calls, appropriate triage is carried out over the phone and a decision made whether or not the patient requires admission. Within SJIO there is a 4-bed assessment unit staffed by nurse practitioners and junior doctors designed for assessment of such patients, and an acute admissions ward for direct admission where appropriate. Very few patients attend the ED routinely in the model of care at SJIO, but good links are established to enable direct admission to acute oncology from the ED when necessary.

Within the YCN, acute oncology models are being developed independently in all the trusts in the network since resident medical oncologists exist locally in all trusts. The acute oncology model being developed at Leeds will consist of 20 programmed activities (PAs) of consultant time which is the equivalent of two full time consultants, providing a five-day service with the equivalent of around two PAs of support per day, Monday to Friday. Patients admitted to the Leeds hospitals with a suspected metastatic cancer will be referred to the AOS, and all patients are reviewed within 24 hours of referral to assist with appropriate choice of investigations, ongoing symptom management and other specialist advice.

How might comprehensive cancer centre acute oncology services facilitate the ongoing management of these patients?

Patients who present with suspected metastatic MUO, as illustrated in **patient 1**, are currently managed via existing two-week cancer referral pathways to defined cancer site-specific teams and managed in the outpatient setting where possible. Once the acute oncology MUO/cancer of unknown primary (CUP) service is fully developed and available, the GP might instead make a direct fast-track outpatient referral to the AOS if the patient is ambulatory and can be managed in the outpatient setting. The MUO/CUP team could then carry out the initial work-up and investigation of the patient, including assessing whether urgent oncological intervention is required, but also undertaking well informed discussion about potential diagnoses. Once the patient had been fully investigated and a confirmed site-specific diagnosis of metastatic prostate cancer determined, the patient would be referred quickly and appropriately to the urological cancer team to take over and continue the patient's care.

For patients who are already identified as cancer patients and being managed by cancer services in Leeds within the SJIO, there are already well established pathways for management of complications of their cancer or treatment, such as the febrile neutropenia seen in **patient 2**. If patients are unwell and require assessment or admission to hospital whilst on treatment they are reviewed on the assessment unit, or admitted to the acute admissions ward within SJIO and managed by an on-call team initially, but the following morning their care will be handed over to the site-specific team which is already responsible for the delivery of their treatment. This site-specific team will continue to provide their care whilst they are an inpatient within the oncology service in SJIO.

Suspected newly diagnosed cancer patients who require admission due to ill health or for inpatient investigation are currently managed by admission to the appropriate acute medical or surgical speciality, with input from oncology as requested. With the introduction of an AOS at Leeds, oncology involvement in the management of such patients will happen much earlier in the patient's pathway. In the case of **patient 3** above, presenting acutely to the ED with a suspected underlying cancer diagnosis, early referral through to the AOT will not only allow for early specialist input regarding appropriate investigation, management and referral to the correct MDT, but will also help facilitate early discharge from hospital with appropriate support and follow-up.

Model III: An acute cancer unit model (Whittington Health)

In April 2011, the Whittington Hospital NHS Trust joined up with the NHS Haringey and Islington community health services to form an integrated care organization, called Whittington Health (WH). This alliance has enabled local NHS service providers to work together to deliver patient care. It brings services and clinicians closer together, ensuring that care is more centred on the needs of local people and allows patients to navigate more easily between the services that they need. This new organization of care has allowed traditional barriers to be overcome, thus optimizing care pathway for patients.

In April 2012 the old cancer networks of North Central and North East London merged to form London Cancer: an integrated cancer system (ICS). The ICS serves a population of 3.5 million across North London and West Essex. Care for specialist tumour types will be delivered through pathway boards with representation from each of the nine trusts that comprise the ICS. Acute oncology services across the ICS will be addressed via an expert reference group. Building on the AOS developed at the Whittington Hospital NHS Trust cancer unit, fast-track pathways for GPs have been established as well as pathways developed for acute oncology admissions via the ED.

Whittington Health has developed an acute oncology model that consists of a stand-alone Consultant Medical Oncologist sub-specializing in lung and gastrointestinal cancers, speciality doctor, in oncology, haematology consultant and two oncology clinical nurse specialists, providing a comprehensive 5-day service. The Consultant Medical Oncologist is responsible for consultancy for all inpatients admitted to a designated medical ward with an oncology-related admission. Clear admission guidelines have been approved to ensure appropriate patients are admitted under the care of the consultant. In addition, the AOT offers daily review of all acute oncology admissions in outlying wards and those housed in the medical admissions unit. The Consultant Medical Oncologist was also appointed as Lead Cancer Clinician and so used their sessions to lead and further develop the AOS, support cancer peer review, and represent the acute trust at cancer network level. The Consultant Medical Oncologist chaired the network acute oncology group for two years from 2010.

The referral pathways were built into existing electronic order communications systems so are familiar to users, are cost neutral, and have inbuilt audit trails and data collection capacity owned and managed by the existing information technology (IT) team. This has also reduced the need for specific administrative support for the AOS, as all relevant clinical data can be accessed via the electronic order communications system where referrals are held on each patient. Additional acute oncology administrative support is provided by two oncology secretaries, who will type letters, make

appointments and retrieve archived correspondence, as well as provide a telephone contact for any administrative query from a patient or healthcare professional.

How might the acute cancer centre services facilitate ongoing management of these patients?

For **patient 1**, the GP could make a direct fast-track acute oncology outpatient referral if the patient is ambulatory. This could not only avoid an unnecessary admission or presentation via the ED, but can enable prompt assessment by the expert AOT. The role of the AOT here is twofold: firstly, urgent assessment to determine if prompt oncological intervention is indicated, and secondly to communicate empathically and knowledgeably about the overall situation if this is a first presentation of a previously undiagnosed cancer. If the patient has any evidence of neurological impairment which threatens mobility the patient can be referred to the ED or the duty medical registrar, who will alert the malignant spinal cord coordinator (MSCC) within the AOT. A pathway exists that is approved by the cancer network to ensure prompt diagnosis and access to neurosurgery if indicated. All trusts have on-site chemotherapy facilities if urgent chemotherapy is the treatment of choice, and designated centres for radiotherapy have been approved. Data collected and collated from the NCIN consistently show that the prognosis and outcomes for all solid tumour cancer types that present for the first time via the ED is significantly worse than for those that present through the traditional two-week wait or urgent outpatient referrals. Acute oncology has a key role in ensuring appropriateness of further investigation, especially if the patient is of poor performance status or has multiple comorbidities.

In the second scenario, where **patient 2** is receiving a systemic anticancer chemotherapy regimen with a greater than 20% chance of febrile neutropenia, there would be an alert attached to the patient's ED file as well as a patient-specific protocol held by the relevant regional ambulance service (the London Ambulance Service in this case). In this way, as soon as a call is made to the emergency services from the patient's home an ambulance will be triggered to provide a blue-light service to ensure the patient is rapidly assessed and resuscitated if necessary before arrival in the ED. The ambulance service will also call ahead to prepare the ED team to expect a patient with suspected febrile neutropenia. This protocol has optimized the delivery of systemic antibiotics to patients within 60 minutes of arrival to the ED.

With **patient 3** the admitting medical team would have requested an inpatient AOS assessment and referred the case for discussion at the weekly MUO MDT. A separate radiology alert would have been triggered at the time of preparing the report of the CT scan. This ensures that if admitting teams delay referral to the AOS an e-mail alert is sent to a confidential and specific e-mail address by the reporting consultant radiologist.

Once assessed by the AOT within 24 hours of referral, the patient's fitness and personal wishes regarding further interventions would have been established. In view of her poor performance status, invasive investigations such as liver biopsy would not have changed her management so would not be routinely ordered. The priority for this lady's care would be to optimize symptom control and agree on the preferred place of care. Further management would be undertaken with the community palliative care team on discharge.

A follow-up alert would be placed on her ED record to direct appropriate investigations and care should she present again in the future.

Conclusion

Solutions and options for acute oncology require effective leadership and a clear understanding of cancer patient pathways within cancer networks and also within individual hospital trusts. The models described above exist within a complex and diverse cancer service configuration, but all share the common themes of triage, cancer alerts, early specialist review and defined inpatient pathways. These are all areas that have been highlighted by the NHS Improvement Transforming Inpatient Care programme.[6]

Acute oncology services are applying these principles to improve the management of patients admitted to hospital. In future it should be possible to work closely with colleagues in primary care to extend these principles to identify more precisely those patients who require admission and those who may be managed safely in the community. Improvements remain possible in the investigation of patients with suspected cancer, both to arrive more rapidly at an accurate diagnosis and to promptly ensure referral to the appropriate specialist teams. Early in a patient's journey we must take account of their fitness and their wishes about appropriate investigations and subsequent interventions.

Further reading

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Complications of Systemic Therapy

PROBLEM

12 Febrile Neutropenia

Amy Ford, Ernie Marshall

Case Histories

Two patients present directly to the oncology centre with fever. The salient features are as follows:

Patient 1: A 22-year-old man with no comorbidities has recorded a temperature of 38.0°C at home 12 days after his first cycle of adjuvant chemotherapy for testicular cancer. He feels well and has no localizing symptoms.

Vital signs for **patient 1** read: temperature 38.0°C, pulse 80 bpm, blood pressure 125/80 mmHg. A full blood count reveals: Hb 10.1 g/dl; WBC 1 $\times 10^9$/l; neutrophils 0.4 $\times$ 10^9/l; platelets 200 $\times$ 10^9/l.

Patient 2: A 63-year-old man is known to have chronic obstructive pulmonary disease (COPD). He is unwell and dehydrated seven days after his third cycle of palliative chemotherapy for bowel cancer. Vital signs: temperature 38.8°C, pulse 124 bpm, blood pressure 110/70 mmHg. Full blood count reveals: Hb 9.2 g/dl; WBC 0.5 $\times$ 10^9/l; neutrophils 0.08$\times 10^9$/l; platelets 100$\times 10^9$/l.

Subsequently, you receive a call from the local district general hospital (DGH) regarding an oncology patient who has presented with fever to the emergency department (ED), and you are asked to advise. A summary of the verbal report is as follows:

Patient 3: A 52-year-old woman, with a peripherally inserted central catheter (PICC) line *in situ* has presented with a history of rigors nine days after her fourth cycle of adjuvant chemotherapy for breast cancer. She has been receiving primary prophylaxis with pegfilgrastim after each cycle, to reduce the risk of neutropenia. Vital signs: temperature 36.8°C, pulse 112 bpm, blood pressure 90/unrecordable mmHg. A full blood count reveals: Hb 8.9 g/dl; WBC 0.7$\times 10^9$/l; neutrophils 0.1 $\times$ 10^9; platelets 120 $\times$ 10^9/l.

What is febrile neutropenia?

How do you evaluate febrile neutropenia?

How would you assess and manage each of these patients?

Background

What is febrile neutropenia?

Febrile neutropenia is defined as a temperature of greater than 38°C, with a neutrophil count $<0.5 \times 10^9$/l in a patient undergoing anticancer treatment, most commonly cytotoxic chemotherapy.[1] Newer, biological systemic anticancer treatments and radiotherapy have a much lower propensity to cause neutropenia. Haematological malignancies have a relatively high rate of febrile neutropenia. Febrile neutropenia is a significant cause of cancer-related mortality, with the number of attributable deaths doubling between 2001 and 2010, even after adjusting for the increasing number of cancers diagnosed during this time period.[1] The majority of febrile neutropenic deaths are in those aged 65–79 years. The explanation for the rising mortality is unclear, but may be related to the increasing use of chemotherapy, greater dose intensity, the treatment of patients who would previously have been considered too high risk for chemotherapy, and the increase in antibiotic resistance. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report into patient deaths within 30 days of receiving systemic anti cancer therapy also found evidence of increasing dislocation of care, and deemed the management of febrile neutropenia unsatisfactory.[2]

The pattern of causative organisms in febrile neutropenia has changed from being largely gram-negative pathogens during the early years of chemotherapy use, to predominantly gram-positive organisms since the introduction of indwelling plastic catheters in the 1980s, which promote the colonization and entry of gram-positive skin flora into the bloodstream.[3] Gram-positive cocci causing febrile neutropenia include *Staphylococcus epidermidis*, *Staph. aureus* and streptococci.[4] Drug-resistant gram-positive organisms, such as methicillin-resistant *Staph. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are increasingly prevalent. Gram-negative organisms are also implicated in febrile neutropenia, in particular *Klebsiella* species and *Escherichia coli* strains, among which antibiotic resistance due to extended-spectrum β-lactamase (ESBL) production is increasing.[3]

There is evidence that primary antibiotic prophylaxis, most commonly with a quinolone or cotrimoxazole, reduces the incidence of febrile neutropenia and short-term mortality.[5] However, this needs to be balanced against the risks of increasing antibiotic resistance and the adverse effects of antibiotic use. The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of prophylactic quinolones for the predicted duration of neutropenia only in patients being treated for acute leukaemias, stem cell transplants, or solid tumours where significant neutropenia (neutrophil count $< 0.5 \times 10^9$/l) is anticipated.[1]

The severity and duration of neutropenia can be moderated with primary prophylaxis using granulocyte colony-stimulating factor (G-CSF). Although there is no convincing evidence that prophylaxis with G-CSF reduces short-term mortality, it has been shown to reduce the rate of febrile neutropenia and shorten the length of hospital stay, which may help maintain the dose intensity of chemotherapy used with curative intent.[6] The efficacy of G-CSF may vary according to the type of cancer therapy (leukaemia, lymphoma/solid tumour, stem cell transplant), and must be weighed against the side effects of its use, such as bone pain, headache and nausea. There is some evidence that pegylated G-CSF (pegfilgrastim), which requires less frequent administration, is more effective in preventing febrile neutropenia than the unpegylated form (filgrastim).[6] NICE guidelines advocate against the routine use of G-CSF, unless it is an integral part of a specific chemotherapy regimen. International guidelines recommend the use of G-CSF in selected patients with a risk of febrile neutropenia exceeding 20%.[7,8]

How do you evaluate febrile neutropenia?

Patients who present with a fever following anticancer treatment should be promptly assessed with a thorough history and examination, having particular regard to any potential focus of infection. The possibility of cellulitis, abscesses and infections of the oral cavity should not be overlooked. Investigations should include full blood count (FBC), renal function, liver function, C-reactive protein, lactate and blood cultures. Where a central venous catheter is in use, peripheral blood cultures should be obtained in addition. Urinalysis, chest X-ray, stool, sputum and cerebrospinal fluid culture should only be undertaken when clinically indicated. The differential diagnoses to be considered include malignancy-related fever, pulmonary embolism, and chemotherapy-induced fever (most commonly seen with bleomycin). Because of the potential risks of missing the diagnosis of febrile neutropenia, any fever in a patient undergoing chemotherapy should be treated as septic in origin until proved otherwise. All hospitals with an emergency department (ED) should ensure that links are established with local acute oncology

services (AOS) to facilitate the development of a febrile neutropenia management pathway, which should incorporate early review by a member of the oncology team.[9]

Only a minority of patients will develop life-threatening infections or suffer other serious complications, and there is increasingly a shift towards the stratification of patients with febrile neutropenia between those at high and low risk of septic complications. Risk stratification reduces the length of hospitalization and prevents overtreating those at low risk. Stratification is based on presenting signs and symptoms, the nature of the underlying malignancy, and existing comorbidities, and should be undertaken using a validated risk scoring tool, such as the Multinational Association of Supportive Care in Cancer (MASCC) risk index.[10,11]

Table 12.1 Multinational Association of Supportive Care in Cancer (MASCC) Index

Characteristic burden of illness:	Score
Either no or mild symptoms*	5
Or moderate symptoms*	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma or no previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age <60 years	2

* Points attributable to burden of illness are not cumulative. The maximal theoretical score is therefore 26.
A threshold ≥21 points defines 'low risk'.

The burden of illness (the first characteristic in the risk index) represents a measure of how unwell the patient is at presentation, but lacks objective definition. Clinical experience is needed to inform this judgement and it is recommended that risk stratification be undertaken by a healthcare professional with experience in managing the complications of anticancer treatment.[1]

Low-risk patients should be considered for treatment with oral antibiotics, followed by early discharge after taking into account their social circumstances. The minimum safe period of observation prior to discharge has yet to be determined, but most studies to date have observed patients for at least 24 hours prior to discharge.[3] Intravenous antibiotics are warranted if coexisting complications of chemotherapy, such as vomiting or severe mucositis, prevent the administration of oral medication. High-risk patients should receive empirical intravenous antibiotics as soon as possible. A national target time of one hour has been set from the point at which a likely diagnosis of febrile neutropenia is made (based on clinical assessment rather than laboratory results) to administration of antibiotic therapy.[12]

When choosing empirical antibiotics, the epidemiological spectrum of bloodstream isolates and regional patterns of antibiotic resistance should be considered. Treatment should follow local guidelines. In the absence of patient-specific or local microbiological contraindications, NICE guidance recommends β-lactam monotherapy using

piperacillin/tazobactam combination antibiotic as initial empirical treatment, and advises against the use of aminoglycosides in this context, as there is no evidence that combined therapy reduces mortality. Monotherapy is also associated with fewer adverse effects, e.g. nephrotoxicity, and avoids the need to monitor aminoglycoside levels.[1] Antibiotics should be discontinued in patients whose febrile neutropenia has responded to treatment, as evidenced by lysis of fever and subjective and objective improvement, irrespective of neutrophil count.[1] Where an organism has been isolated, treatment should be continued for a minimum of five days.

Persistent fever, in the absence of clinical deterioration or new focal signs, is not an indication for switching antibiotic therapy unless guided by culture results.[1,3] In the absence of a source of bacterial infection, patients with a persistent fever after 4–7 days who are expected to be neutropenic for longer than seven days should be considered for empirical antifungal therapy and investigated for invasive fungal infections.[3] Choice of empirical antifungal agent, if indicated, will depend on whether or not the patient has already received prophylactic antifungal treatment.[3]

How would you assess and manage each of these patients?

Patient 1:

This man is febrile on day 13 following chemotherapy. Assessment using the MASCC index (Table 12.1) stratifies him as being at low risk of septic complications, with a score of 26 (mild symptoms = 5; no hypotension = 5; no COPD = 4; solid tumour = 4; no dehydration = 3; outpatient = 3; age <60 years = 2). Peripheral blood cultures should be taken. Urinalysis, stool and sputum cultures, and chest X-ray are only necessary if clinically indicated by the history or physical examination. It would be appropriate to treat this patient with empirical oral antibiotics, as per local guidelines, but would not be unreasonable to wait for the results of initial investigations rather than initiating treatment immediately. In units lacking familiarity with risk stratification, commencing intravenous antibiotics – with subsequent stepdown to oral antibiotics after review by the acute oncology team – would also be an option. If this patient has a good understanding of the risks of febrile neutropenia, is compliant with treatment, lives with a responsible adult and can easily return to hospital in the event of complications, he could be considered for early discharge after 24 hours of clinical observation. It should be emphasized that this patient should have a low threshold for contacting the unit if he has further symptoms.

Patient 2:

This patient is at high risk of septic complications, with a MASCC index score of 10 (moderate symptoms = 3; hypotensive = 0; COPD = 0; solid tumour = 4; dehydrated = 0; outpatient = 3; age >60 years = 0). He should be treated with empirical intravenous antibiotics, as per local guidelines, without delay. Peripheral blood cultures, chest X-ray and other investigations indicated clinically should be undertaken, but these should not delay the first dose of antibiotics. In addition, he requires intravenous fluids and optimization of his COPD. Any other side effects of chemotherapy or the underlying cancer should also be addressed.

The patient should be reviewed daily. Empirical antibiotic treatment should be altered in light of any positive culture results. Persistent fever alone, in the absence of clinical deterioration, is not an indication for changing antibiotics. Intravenous antibiotics may

be switched to oral after 48 hours if the risk of developing septic complications is re-assessed, using the MASCC score, as low.[1] Antibiotic treatment can be stopped once the neutropenic sepsis has responded to treatment, irrespective of neutrophil count.[1] It is not uncommon for cultures to yield negative results, and in 70%–80% of cases the infective organism is never confirmed.[3]

Following recovery, the risks and benefits of continuing palliative chemotherapy should be reviewed by the patient's oncologist and discussed with the patient. If chemotherapy is continued, a dose reduction may be considered to reduce the risk of further episodes of febrile neutropenia. In the palliative context, chemotherapy dose reduction would be more appropriate than secondary prophylaxis with G-CSF, because the latter is unlikely to effect clinically important outcomes in this setting.

Patient 3:

This woman is not pyrexial at the time of presentation, but is severely shocked. Classic signs of infection can be diminished in immunosuppressed patients. With the history of recent chemotherapy and rigors she should be assumed to be suffering with neutropenic sepsis until proved otherwise. Rigors may be associated with flushing of the PICC line and enquiry into this should form part of the history taking. In addition, the PICC line should be examined for any signs of inflammation. This patient's MASCC index score is 16 (moderate symptoms = 3; hypotensive = 0; no COPD = 4; solid tumour = 4; dehydrated = 0; outpatient = 3; age <60 years = 2), putting her at high risk of septic complications. Blood cultures should be obtained from the indwelling venous catheter, and also peripherally if possible, but should not delay treatment.

The patient's clinical condition and history warrant fluid resuscitation and treatment with empirical intravenous antibiotics, as per local guidelines, without waiting for confirmation of the neutrophil count. In the absence of obvious infection associated with the indwelling venous catheter, or specific local microbiological indications, empirical glycopeptide antibiotics should not be included in this patient's initial treatment. There is little evidence of increased effectiveness of treatment or any reduction in short-term mortality with the addition of empirical glycopeptide antibiotics in this context, but greater hepatic and nephrotoxicity are recognized consequences.[1] If there is no strong clinical suspicion of central line infection there is no need for its removal in the initial phase of management, but this should be reviewed if there is no resolution of fever or there is evidence of post-flushing fever.[1] Early review by a member of the acute oncology team (AOT) at the DGH should be arranged. This can be facilitated by the development of an electronic system that automatically alerts the AOT of the admission of any patient who has recently received chemotherapy, and by the joint development of integrated care pathways by oncology, haematology and emergency medicine teams. There should be a low threshold for assessment by the intensive care team if there is no response to treatment.

For this patient, who is receiving adjuvant treatment, the balance of risks and benefits of continuing treatment are different than for 'Patient 2' (see above). As she has suffered febrile neutropenia despite the use of primary prophylaxis with G-CSF as an integral part of her chemotherapy regimen, additional secondary prophylaxis with a quinolone may be considered to maintain dose intensity, especially if she has suffered more than one episode of febrile neutropenia.

Recent developments

The NCEPOD report revealed that the management of febrile neutropenia did not meet a consistently high standard across the UK.[2] In addition, it highlighted that a proportion of patients delayed seeking medical advice for at least 24 hours. This has resulted in the evolution of acute oncology services nationally, and the development of a clinical guideline for the prevention and management of neutropenic sepsis by NICE (see Figures 12.1 and 12.2).[1] It has been recommended that all NHS Trusts have policies on the management of febrile neutropenia,[12] and that patients are provided with written information about febrile neutropenia, with advice on when and how to contact 24-hour specialist oncology services.[1] The 'bundle' framework established by the Surviving Sepsis Campaign should be incorporated into care pathways for febrile neutropenia.[13]

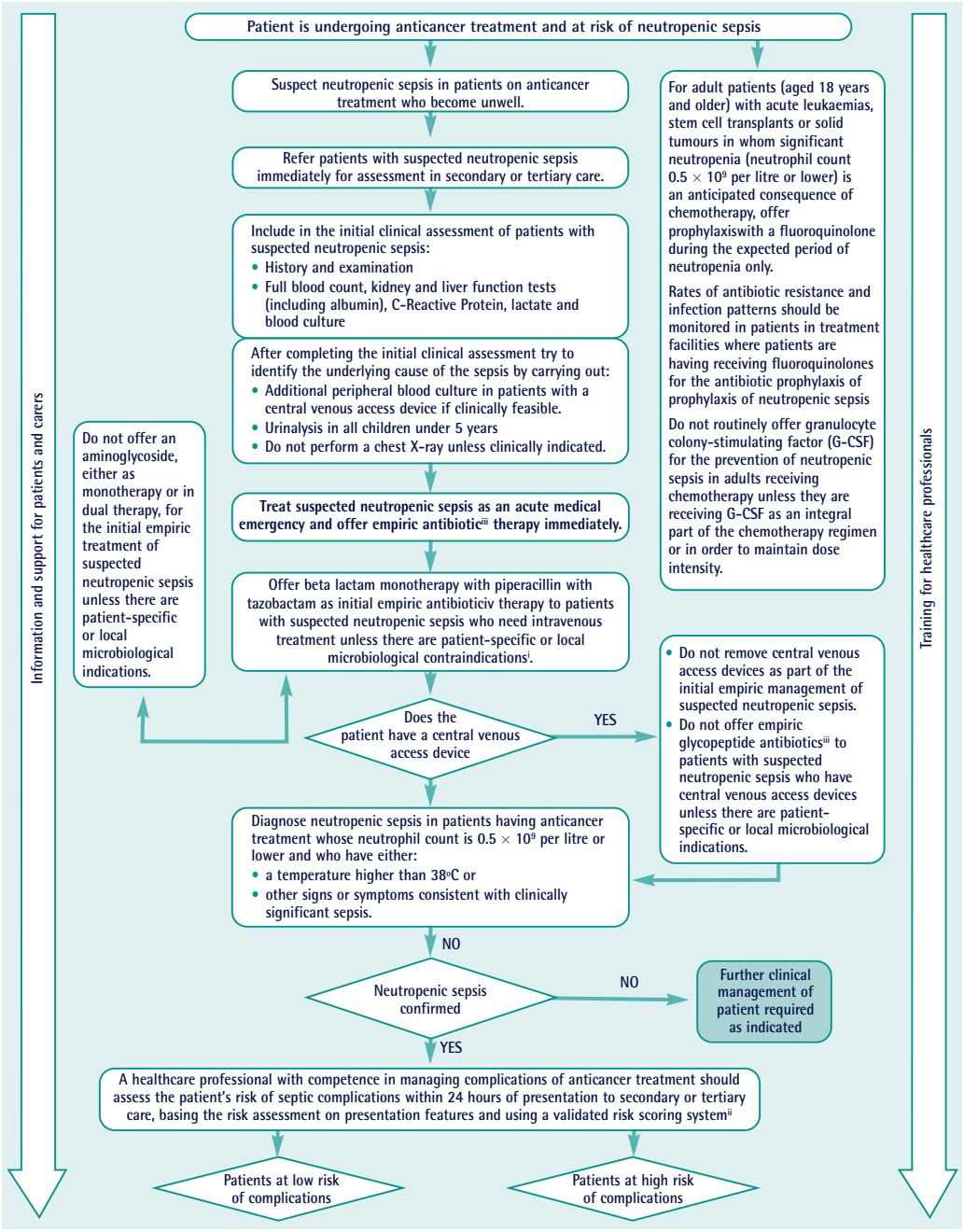
Although developed outside of the UK context, the Infectious Diseases Society of America (IDSA) has produced a clinical guideline for the use of antimicrobial agents in neutropenic patients with cancer.[3] Although local patterns of antibiotic resistance and microbiological epidemiology should always be considered in the treatment of febrile neutropenia, much of the evidence and guidance contained within the IDSA guideline is relevant to international practice.

Conclusion

Febrile neutropenia requires prompt diagnosis and treatment with empirical antibiotic treatment, irrespective of where patients present. All hospitals need policies in place for the management of febrile neutropenia to ensure every patient receives the highest standard of care. Risk stratification tools such as the MASCC index are central to avoid overtreating low-risk patients and for freeing up hospital beds by facilitating the early discharge of carefully selected patients, as well as ensuring the early and appropriate treatment of high-risk patients. Clinical experience in the management of febrile neutropenia and risk stratification is vital in ensuring this is done safely, and AOTs therefore have an important role in optimizing the management of febrile neutropenia outside of specialist oncology centres.

Patients need to be provided with print or multimedia information, to ensure they are aware of the signs, symptoms and risks of febrile neutropenia and the need to seek medical advice early. The importance of having access to a thermometer at home should be stressed.

Figure 12.1 Summary of recommendations for prevention and management of neutropenic sepsis in cancer patients. (Adapted from ref.(1) with permission.)

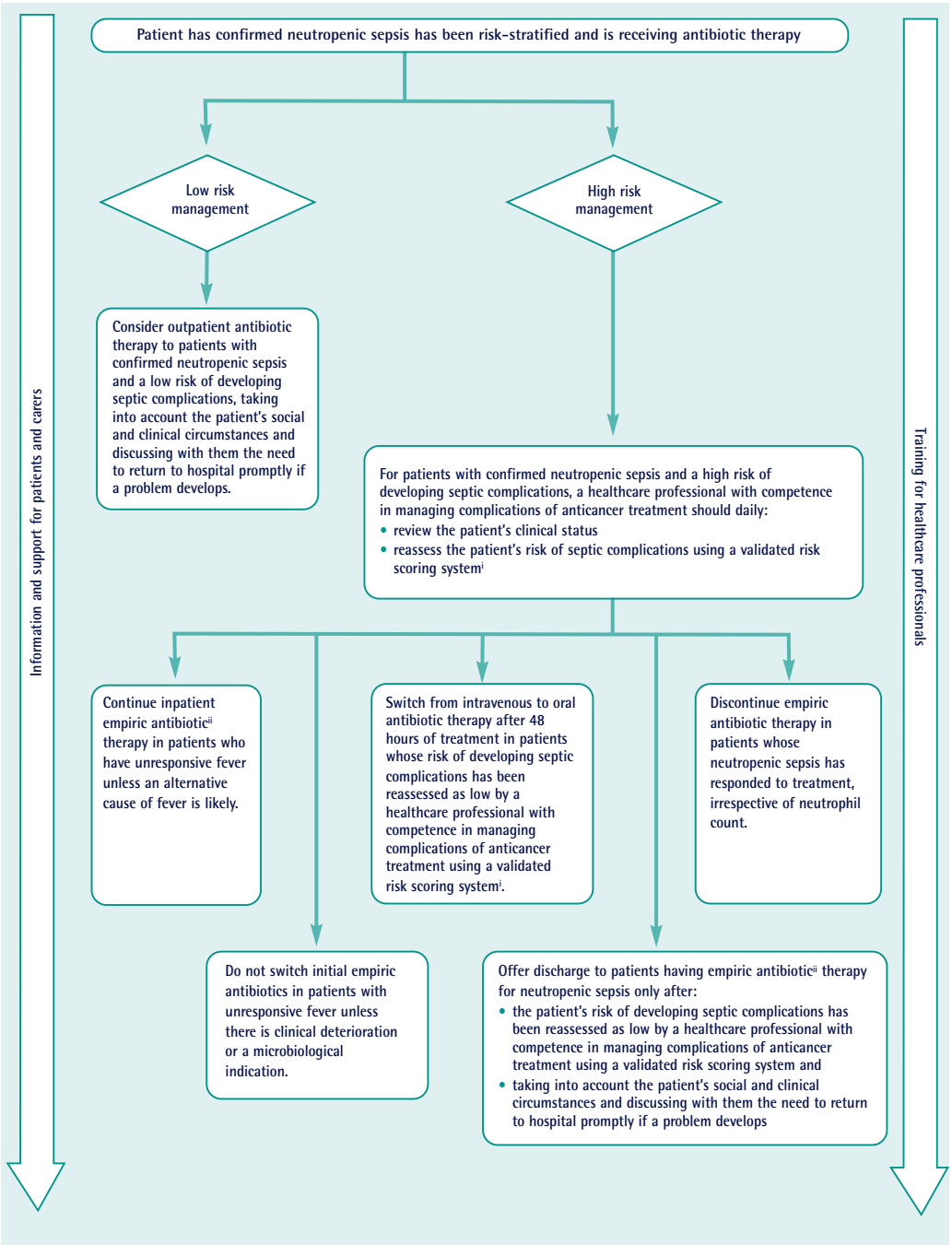


[i] Be sure to note local marketing authorization regarding piperacillin with tazobactam use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. If required, the child's parent or carer should provide informed consent, which should be documented.

[ii] For example, the Multinational Association of Supportive Care in Cancer (MASCC) risk index. See also Table 12.1.

[iii] An empiric antibiotic is given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

Figure 12.2 Overview of low- and high-risk management for cancer patients with confirmed neutropenic sepsis following risk stratification. Adapted from ref.(1) with permission.



[i] For example, the Multinational Association of Supportive Care in Cancer (MASCC) risk index. See also Table 12.1.

[ii] An empiric antibiotic is given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

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Complications of Cancer

PROBLEM

31 Spinal Cord Compression

Peter Robson, Martin Wilby

Case History

A 65-year-old man presents with thoracic back pain, tiredness and a 24-hour history of leg weakness (Medical Research Council Scale muscle power 4). His back pain has been present for three months. An urgent whole-spine MRI reveals a single-level lesion at T5 causing cord compression (Figure 31.1). There is no significant past medical history and examination reveals no other abnormality.

What underlying malignancies would you consider in your differential diagnosis?

What is the immediate management?

What are the options for treatment and how do you assess which is the most appropriate?

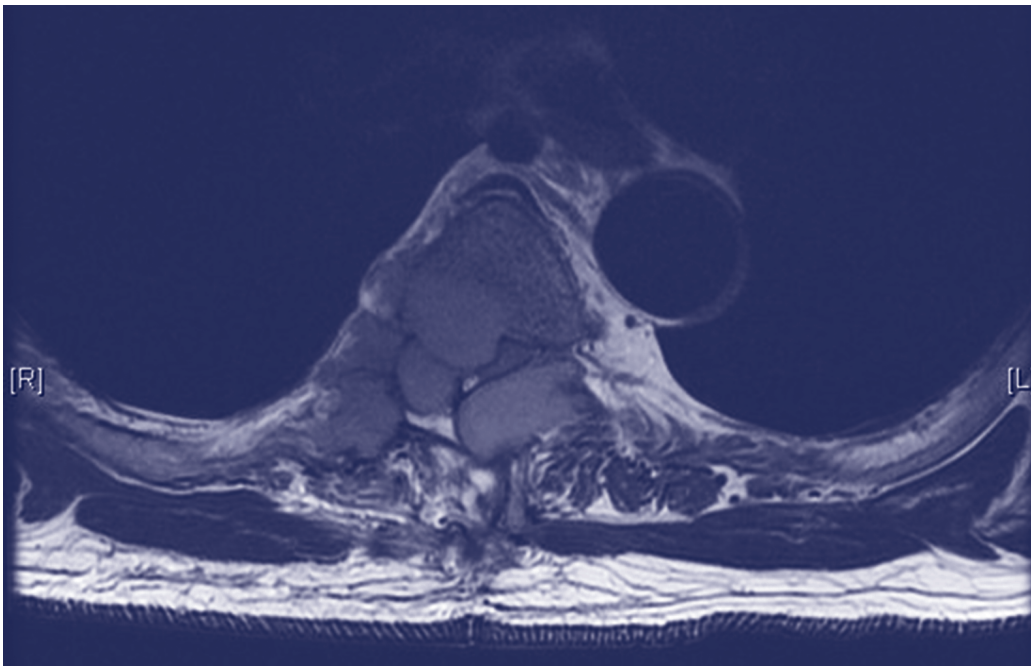

Figure 31.1 Axial T2-weighted (fluid white) magnetic resonance image showing soft tissue metastasis causing cord compression at the mid-thoracic level.

Background

What underlying malignancies would you consider in your differential diagnosis?

Prostate cancer is the most likely diagnosis in men of this age group. It frequently presents at diagnosis with signs and symptoms of metastatic disease, and may present with metastatic spinal cord compression (MSCC). The diagnosis of prostate cancer would usually be confirmed by clinical examination of the prostate and elevated PSA level. Other common primary sites would include lung cancer and myeloma, with renal and thyroid cancer being less common. In women, the breast would be the most common site of origin.

Although it would be uncommon for lymphoma to present in this way it must always be considered in the differential diagnosis. If lymphoma is suspected then a biopsy must be undertaken prior to commencement of any steroids. Treatment with corticosteroids prior to biopsy may prevent a diagnosis being made.

What is the immediate management?

Any patient presenting with signs or symptoms suggesting MSCC should be treated as outlined in the National Institute for Health and Care Excellence (NICE) guidance CG75 (see also Figure 31.2).[1] They should be laid flat to avoid further damage from a potentially unstable spine and to improve perfusion of the spinal cord. High-dose steroids are recommended (16 mg dexamethasone daily with proton pump inhibitor cover) to reduce oedema and inhibit prostaglandin synthesis. These should be used unless contraindicated,

or if there is a high clinical suspicion of lymphoma. Clinical trials have shown no statistical benefit and increased side effects with very high-dose steroids (100 mg) and their use is therefore not recommended.[2] Appropriate analgesia should be given to the patient.

MSCC is an oncological emergency and should be diagnosed from an MRI scan of the whole spine done within 24 hours of neurological signs/symptoms developing.[1,3] Following diagnosis, rapid treatment is required as extrinsic compression of the spinal cord may lead to irreversible damage and permanent neurological deficit. Initial signs are due to vasogenic oedema of the cord, which may be reversible with steroids and laying the patient supine. If the oedema progresses to ischaemic death of neurons (either indirectly via vascular damage, or directly by compression) then any deficit will become permanent. Once a patient has lost all motor power for >48 hours there is unlikely to be any recovery of useful function.

Contact should be made with your regional MSCC coordinator immediately following diagnosis to allow rapid management decisions to be made and appropriate transfer for specialist treatment.[1]

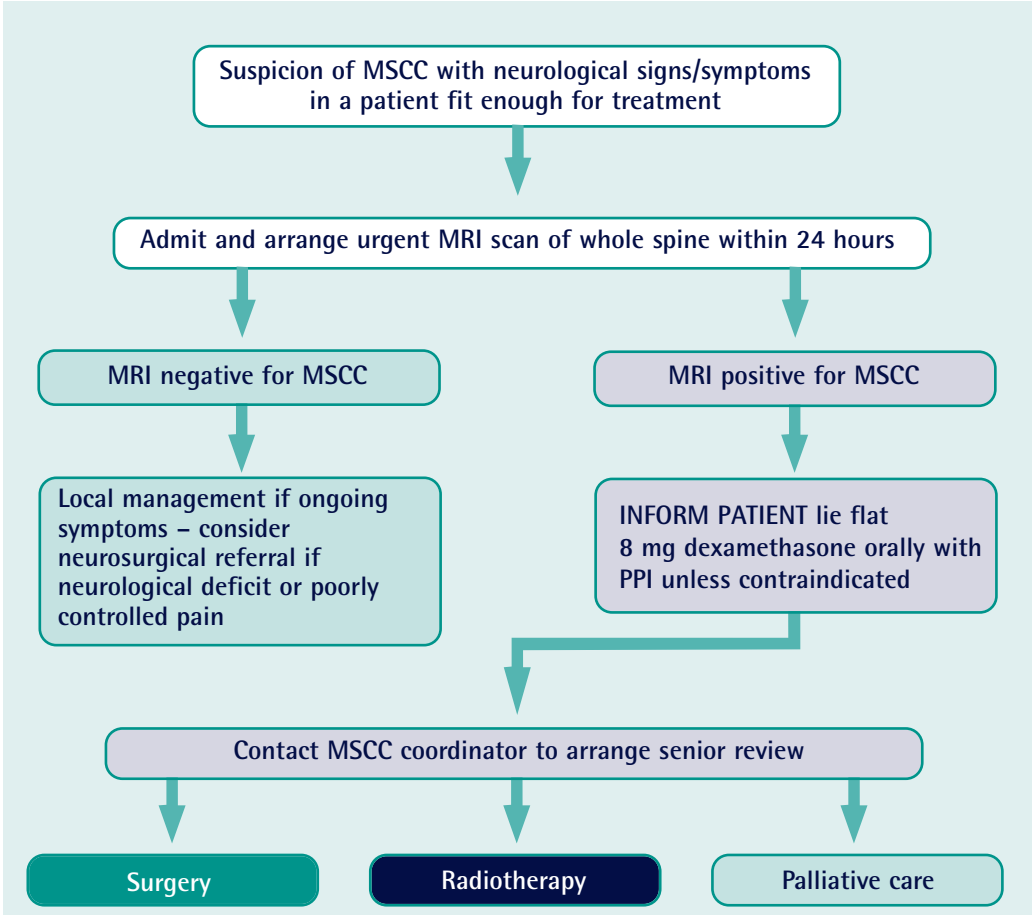

Figure 31.2 Flow chart for diagnosis and treatment of MSCC. PPI, proton pump inhibitor.

What are the treatment options and how do you assess which is the most appropriate?

The definitive treatment options for a patient presenting with MSCC are surgery or radiotherapy. However, careful consideration must first be given to whether the patient is deemed fit enough for transfer and treatment. Those patients who have had no motor function for over 48 hours are unlikely to recover any useful function following treatment. If the patient has significant pain then treatment with a single fraction of 8 Gy radiotherapy should be considered for pain relief. Patients whose pain is already controlled, and who are of very poor performance status, have widespread metastases and limited life expectancy, should be discussed with their primary tumour-site clinician before considering investigation and treatment.[1]

Table 31.1 Prognostic indicators suggesting surgery is more likely to be beneficial. (See also ref.4.)

Histology (breast, prostate, multiple myeloma, lymphoma or renal cancer)
Good motor function at presentation
Good performance status
Limited comorbidity
Single-level spinal disease
Absence of visceral metastasis
Long interval from primary diagnosis

Surgery may also be considered to aid diagnosis with a biopsy, or to stabilize the unstable spine in a patient with significant instability pain. It may also be the only effective option when there is compression of the cord by bony fragments following vertebral collapse. A CT scan may sometimes assist in this decision-making process. Staging CT scans are required to gain an impression of the extent of the patient's disease, but in the context of a patient with rapid neurological deterioration clinical judgement must be used. Age is not a contraindication, but patients require careful selection as overall there is relatively less benefit to surgery and radiotherapy in the elderly. Major surgery should only be considered in those expected to live more than three months.[1] Prior radiotherapy has been considered a contraindication to surgery, with wound breakdown and infection being three times more likely than if radiotherapy is performed following surgery.[5]

The role of surgery has been addressed in a randomized controlled trial.[6] Patchell *et al.* looked at patients with single-level disease proven on MRI, good performance status and an onset of symptoms within 24 hours. They were randomized between circumferential decompressive surgery followed by radiotherapy (30 Gy in 10 fractions) and radiotherapy alone. Analysis showed a clear difference in favour of the surgical group, who were able to walk for significantly longer (median 122 days vs 13 days, p=0.003), had higher rates of continence, muscle strength and functional ability, and required fewer opioid analgesics and corticosteroids.

There is clear evidence that, for a select group of patients, surgery followed by radiotherapy is a beneficial treatment. However, the majority of patients presenting with MSCC have a poor prognosis, often with more extensive spinal disease and poor

physiological reserve. The evidence for surgery in this group is less clear, with studies showing only modest benefit for the addition of surgery.[7] Newer surgical techniques involving percutaneous pedicle screws, cement-augmented balloon kyphoplasty, or a combination of the two, may be beneficial for this group of patients.[8] Careful patient selection is paramount. Following surgery all patients should be offered post-operative radiotherapy.

The majority of patients presenting with MSCC will be unsuitable for surgery. These patients should receive immediate radiotherapy (within 24 hours of MRI diagnosis of MSCC) as their definitive treatment. The aim of radiotherapy is to relieve compression of the spine and nerve roots by causing cell death in the rapidly dividing tumour tissue. This treatment is very effective at providing pain relief and is aimed at improving or stabilizing the neurological deficit.[1] The long-term survival of the patient is dependent upon the factors discussed previously; those patients with poor performance status, rapid deterioration, poor motor function and significant visceral disease have the poorest survival. Most patients have a limited life expectancy of only a few months, with a number of favourable patients surviving for much longer.[9] Radiotherapy schedules need to be individualized to take into account this variability in life expectancy. Studies have shown no difference in functional outcome or overall survival between schedules, but improved local control with longer treatments.[10] It is recommended that patients with a favourable prognosis should be considered for long-course treatment and those with a poor prognosis be given a single 8 Gy fraction.

If there is disease recurrence within the radiotherapy field then the options are surgery (taking into account the higher rate of wound breakdown and infection), further radiotherapy, chemotherapy, or best supportive care. Relapse immediately following radiotherapy treatment may be treated with surgery in patients who are fit enough, particularly employing newer minimally invasive surgical techniques to restrict wound size. In those who relapse locally a number of months after radiotherapy, and who remain well with good motor function, re-irradiation is a useful treatment option.[11]

Conclusion

This patient is fit and well, he retains good motor function, and urgent staging showed he has single site disease. His case demonstrates numerous factors suggestive of a good prognosis and in view of the evidence he should be considered for surgery. Surgery will relieve the spinal cord compression, stabilize the spine thus reducing pain, and allow a histological diagnosis to be made. This should be followed by palliative radiotherapy after the wound has healed. If the patient was not suitable for surgery then a biopsy should still be undertaken before treatment with palliative radiotherapy. Further systemic management will depend upon the histological diagnosis.

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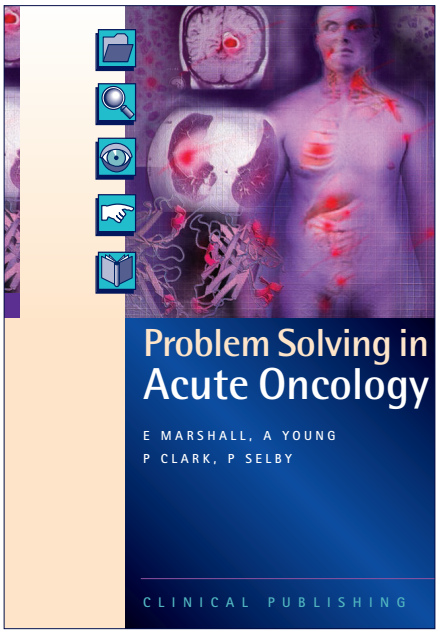

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