REVIEW ARTICLE

Spinal Metastatic Disease: A Review of the Role of the Multidisciplinary Team

Mark Curtin, MRCS, MCh, Robert P Piggott, MRCS, MCh, Evelyn P Murphy, MRCS, MCh,
Sudarshan Munigangaiah, MSc, MCh, FRCSI (Orth),
Joseph F Baker, BA, MB, MCh, PGDip Sports Med. MFSEM, FRCS (Tr&Orth),
John P McCabe, MSc, MCh, FRCS, FRCSI (Orth), Aiden Devitt, MCh, FRCS, FRCSI (Orth)

Department of Trauma and Orthopaedic Surgery, University College Hospital Galway, Saolta Hospital Group, Galway, Ireland

Historically, a simple approach centered on palliation was applicable to the majority of patients with metastatic spinal disease. With advances in diagnosis and treatment, a more complicated algorithm has devolved requiring a multidisciplinary approach with institutional commitment and support. We performed a database review including pertinent articles exploring the multidisciplinary management of spinal metastatic disease. The wide variation in clinical presentation and tumor response to treatment necessitates a multidisciplinary approach that integrates the diagnosis and treatment of the cancer, symptom management, and rehabilitation for optimal care of patients with spinal metastases. Advances in the field of radiology have led to earlier and more focused diagnosis of spinal metastasis and acts to guide therapy. Advances in surgical techniques, neurophysiologic monitoring, and anesthetic expertise have allowed surgeons to perform more extensive procedures leading to improved outcomes and reduced morbidity. Radiation oncology input that is essential as external beam radiation therapy can provide significant pain relief. Non-operative measures may include bisphosphonate infusions, management of complications (e.g. hypercalcemia of malignancy), monoclonal antibody infusions, and chemotherapy if indicated in the treatment of the primary malignancy. Input from psychology services is necessary to address the biopsychosocial ramifications of spinal metastasis. Allied health professionals in the form of physiotherapists, social workers, and dieticians also contribute in maximizing patients' quality of life and well-being.

Key words: Diagnosis; Metastasis; Multidisciplinary; Oncology; Spine

Introduction

Bone is the most frequent site of metastatic cancer and is responsible for a significant clinical burden and demand on health-care resources[1]. Advances in cancer care have prolonged the survival of patients with metastatic disease to the spine. Metastases limited to the skeleton have a more favorable outcome than visceral metastases, reflected by a median survival of 20 months after first bone relapse in comparison with 3 months after first liver recurrence[2,3]. The morbidity associated with metastatic spinal disease is significant: more than half of these patients will require radiotherapy or surgical intervention for spinal cord or nerve root compression[4]. The wide variation in clinical presentation and tumor response necessitates a multidisciplinary approach that integrates oncology, surgery, radiotherapy, rehabilitation, and palliative services for optimal care of patients with spinal metastasis. Furthermore, early identification of patients with a high likelihood of developing spinal metastases enables teams to be proactive in their diagnosis and treatment. With this in mind, the use of a multidisciplinary approach integrating the diagnosis and treatment of the disease with appropriate symptom management, palliation, and rehabilitation ensures optimal care. The purpose of our paper was to perform a database review of current treatment strategies for spinal metastatic disease, and to describe the importance of a multidisciplinary approach in its treatment.

Methods

A database review was undertaken. PubMed, OVID Medline, and the Cochrane database were searched. The search algorithm ([spine OR spinal OR vertebral] AND [tumor OR tumour OR neoplasm OR cancer OR

Address for correspondence Mark Curtin, MB, BCh, BAO, MRCS, MCh, Department of Trauma and Orthopaedic Surgery, University College Hospital Galway, Saolta Hospital Group, Galway, Ireland SW4 671 Tel: +353862031053; Fax: (091) 526588; Email: markcurtin10@gmail.com
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metastases]) was used in the "Topic" field to identify articles of interest. The following search parameters were used: (i) articles published in the years 1990–2016; and (ii) English languages. Pertinent but not all articles were used to review the multidisciplinary management of spinal metastatic disease (Fig. 1). This article does not contain any studies with human participants or animals performed by any of the authors.

Radiology

Radiology

Radiological investigations play a central role in the diagnosis and treatment planning of spinal metastases. Spinal metastases may be recognized based on imaging findings in patients without a known diagnosis of malignancy. If metastases are present, further imaging or imaging-guided biopsy techniques may be necessary to confirm the diagnosis or stage of the tumor. Plain radiographs are a quick and inexpensive first-line investigation; however, CT offers improved sensitivity and staging benefits. CT scanning is vastly superior to plain radiographs in the detection of trabecular and cortical bone destruction, soft-tissue extension, and involvement of neurovascular structures, thereby allowing more accurate decision-making[5]. Snyder *et al.* demonstrated that CT analysis was more sensitive and specific than radiographic criteria (59% *vs* 24% accurate) in predicting fractures in breast cancer patients with spinal metastases[5].

Bone scintigraphy is an effective means of assessing the metabolic activity of the spine, while plain radiographs can only demonstrate lesions with a loss of 30%–50% of bone mineral content[6,7]. Technetium-99m (^{99m} Tc) planar bone scintiscans detect metastatic bone deposits through increased osteoblastic activity, considered to be an indirect marker of an oncological process. For this reason, it is considered to be the most efficient modality for screening the whole body for metastasis[8,9]. 18F-fluoro-deoxy-D-glucose positron emission tomography (18FDG PET) offers superior spatial resolution and improved sensitivity, which is superior to bone scintigraphy in the detection of osteolytic metastases, while osteoblastic metastases show lower metabolic activity and are frequently undetectable by PET[9,10].

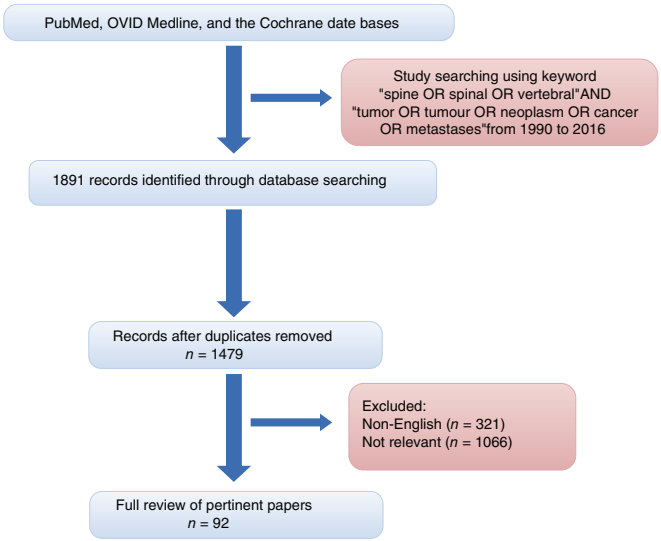

Fig. 1 Flow chart of literature searching.

It is worth noting that scintigraphy is non-specific in determining the origin of lesions identified, and is best used in conjunction with other modalities, such as CT or MRI[11,12]. Positron emission tomography (PET) identifies early marrow infiltration through aberrancies in glucose metabolism in neoplastic cells[13,14]. Daldrup-Link *et al.* report sensitivities for 18FDG-PET scanning, whole-body MRI, and ^{99m}Tc bone scintiscanning as 90%, 82%, and 71% respectively, in a comparative study of the three modalities[13].

MRI is useful in delineating soft tissue involvement in spinal metastases and is particularly useful in diagnosing spinal cord compression, which can be a devastating consequence of spinal metastatic disease. MRI depicts early hematogenous dissemination of the tumor to the bone marrow before metabolic bone reactions are detectable on scintigraphy[15]. Eustace *et al.* report respective sensitivities of 96.5% and 72%, specificities of 100% and 98%, and positive predictive values of 100% and 95% for MRI and scintigraphy [15,16].

Surgery

Developments in surgical techniques, neurophysiologic monitoring, and anesthetic expertise have allowed surgeons to perform safer and more extensive procedures with improved outcomes and reduced morbidity[4,17]. Surgery in patients with spinal metastases may be required to provide a tissue diagnosis but is more often required to provide spinal stability or neural element decompression[4]. The most common and significant outcome of surgical intervention is pain relief. This is generally attributed to removal of the metastatic deposit and prevention or correction of deformity with stabilization[18]. The Spinal Oncology Study Group (SOSG) developed the Spinal Instability Neoplastic Score (SINS), a standardized framework to help physicians assess and categorize spinal instability. This score has a sensitivity and specificity for potentially unstable or unstable lesions of 95.7% and 79.5%, respectively, with near-perfect inter-observer and intra-observer reliability for differentiating three clinical categories of stability (stable, potentially unstable, and unstable)[19,20].

Surgery remains the standard treatment for patients with rapidly progressive spinal cord compression or the presence of a significant osteolytic lesion, implying a high risk of fracture[21]. In such cases, the goal of treatment is palliative rather than curative. Historically, surgery was only considered in patients with a large tumor burden that progressed despite optimal oncological treatment with radiotherapy, as well as in patients with radiotherapy-resistant lesions. Now, many surgeons advocate vertebral-body resection and stabilization more as a preventive measure for spinal instability and as a supplementation for external beam radiation

therapy. A meta-analysis by Klimo and Schmidt concluded that surgery should be the primary treatment in patients with spinal epidural disease, with radiotherapy used as an adjunct[17].

Prior to the introduction and evolution of instrumentation, the mainstay of surgery for spinal metastatic disease with neural compromise was decompressive laminectomy[22]. Laminectomy alone may compromise the stability of the spine in an individual who already has reduced functional capacity from a systemic disease[23]. Subsequent radiotherapy can further compromise the soft tissues, including muscle, leading to myopathy[24] and late kyphosis at the site of decompression[25]. Pedicle screw constructs placed across the decompression site allow stabilization and can prevent late deformity. They also allow more aggressive tumor debulking or even resection in selected cases[26].

While posterior approaches to the spine allow decompression with removal of the posterior elements, it is more difficult to address disease of the middle and anterior columns. A variety of approaches can be utilized, such as a transpedicular, to access the middle and anterior column from a posterior incision[27]. Alternatively, anterior approaches may also be used in addressing lumbar and thoracic lesions in selected cases where there is a desire to achieve complete resection or in addressing a lesion that is both radio-resistant and chemo-resistant[28]. The anterior approach is more commonly utilized in the cervical spine where there is a need to use a construct that resists the compressive forces present in the anterior column[29].

Kyphoplasty or vertebroplasty are minimally invasive modalities used primarily for pain relief. Multiple studies have demonstrated the potential for significant pain relief in patients with osteolytic lesions[30–32]. New "minimally invasive" techniques have also been developed, such as percutaneous fixation and posterior element resection to achieve immediate stabilization and decompression while reducing the morbidity of the approach to the spine[33].

It must be acknowledged that performing spinal surgery upon this cohort of patients with metastatic disease carries a significant risk[34]. These patients are at high risk of a plethora of medical problems, including dehydration, hypercalcemia, coagulopathies, and anemia. In all cases, the aims of the surgical intervention need to be considered and the invasiveness of surgery needs to be weighed against the patients' physiologic condition and prognosis.

Radiation Oncology

All patients with symptomatic bone metastases and lesions in long bones should be evaluated by Radiation Oncologists prior to surgery. Radiation therapy (RT) provides successful palliation of painful bone metastasis that is time efficient and associated with few morbidities[35]. External beam radiation therapy (EBRT) provides significant palliation of painful bone metastases in 50%–80% of patients, with up to 30% achieving near total pain relief at the treated site[36]. Modern technological advances in radiotherapy delivery (e.g. stereotactic body radiotherapy [SBRT]) may augment the results of the primary treatment of metastatic spine lesions[37]. SBRT delivers a high dose of radiation to metastatic lesions with a steep dose gradient that may spare adjacent neural structures, notably the cord and conus[38,39]. MRI-guided robotic linear accelerator (LINAC) radiotherapy is under development, and capable of focusing beams to within 1 mm of spatial accuracy[40,41]. Similarly, advances in the realm of CT and MRI-based planning has vastly improved the precision of information pertaining to the location of the metastatic deposit and its relationship to surrounding tissues[42]. The traditional treatment plan is to irradiate two vertebral bodies above and two below the lesion with single-fraction image-guided intensity-modulated RT, in light of the fact that recurrence is seen most commonly in vertebral bodies neighboring the site of involvement[43].

The Radiation Therapy Oncology Group reported that 6-month treatment regimes with variable RT doses, such as 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions, provide complete analgesic relief in 57% of patients[44]. It has also been demonstrated that a total RT dose of 30 Gy given in 10 fractions provides pain relief for 77%–82% of patients with multiple bone metastases after a year of treatment[45,46]. The selection of fractionated or single fraction treatment seems to be patient and physician dependent. Fractionated treatment courses are associated with an 8% re-treatment to the same anatomic site owing to recurrence of pain, as opposed to a 20% rate following a single fraction[47]. However, the single fraction treatment approach optimizes convenience for both the patient and the radiation oncologist: an important consideration in the palliation of patients with spinal metastases.

A prospective randomized study by Teshima *et al.* compared the addition of methylprednisolone with external beam radiation therapy to radiation therapy alone for bony metastases[47]. The combination group was found to experience more rapid and longer duration of pain relief. The evidence pertaining to the use of moderate-dose dexamethasone (16 mg/day) plus radiation therapy for malignant cord compression is inconclusive[48,49].

The American Society for Radiation Oncology (ASTRO) stated that surgical decompression and postoperative radiotherapy is appropriate for spinal cord compression or spinal instability in highly selected patients with adequate performance status and sufficient life expectancy[34]. Bisphosphonate use, radionuclide use, vertebroplasty, and kyphoplasty for the prevention or treatment of cancer-related symptoms does not obviate the need for EBRT in appropriate patients[35,36].

Non-operative Measures

Oral analgesia as titrated by the World Health Organization Analgesic Ladder is considered first line in the treatment of bony pain[50]. Morphine is the most commonly used opioid for moderate to severe pain and may be combined with adjuvant medications such as tricyclic antidepressants and

corticosteroids. Side effects of medications can limit opioid dosage and cause significant morbidity. These include delirium, constipation, pruritus, nausea, vomiting, sedation, myoclonus, and respiratory depression[51–53]. Other non-invasive methods of pain relief include cutaneous stimulation, continuous repositioning, spine cryoablation, and regional nerve blocks[54–56].

Monthly infusions of bisphosphonates like zoledronic acid to patients with bone metastases reduces the frequency and delays the onset of skeletal-related events[57]. Their administration also provides significant improvements in bone pain and quality of life[58]. Bisphosphonate use in patients with spinal metastases has increased in the past decade. Their use has decreased bone pain scores and reduced skeletal-related events such as the need for local radiotherapy, hypocalcemia, pathologic fracture, and spinal cord compression[59,60]. Once injected, bisphosphonates are internalized by osteoclasts. This leads to a decrease in osteoclast activity and viability[61]. Complications of bisphosphonate therapy include renal impairment and mandibular osteonecrosis[62,63]. Bisphosphonate demonstrates maximal effectiveness and safety when combined with either single or multiple fraction radiotherapy[64,65]. This synergism is due to the fact that radiotherapy is believed to reduce numbers of tumor-produced osteoclast activating factors[66]. The American Society of Clinical Oncology guidelines and the International Expert Panel guidelines recommend starting bisphosphonates when the first radiographic indication of metastatic deposits in the spine is noted[67,68].

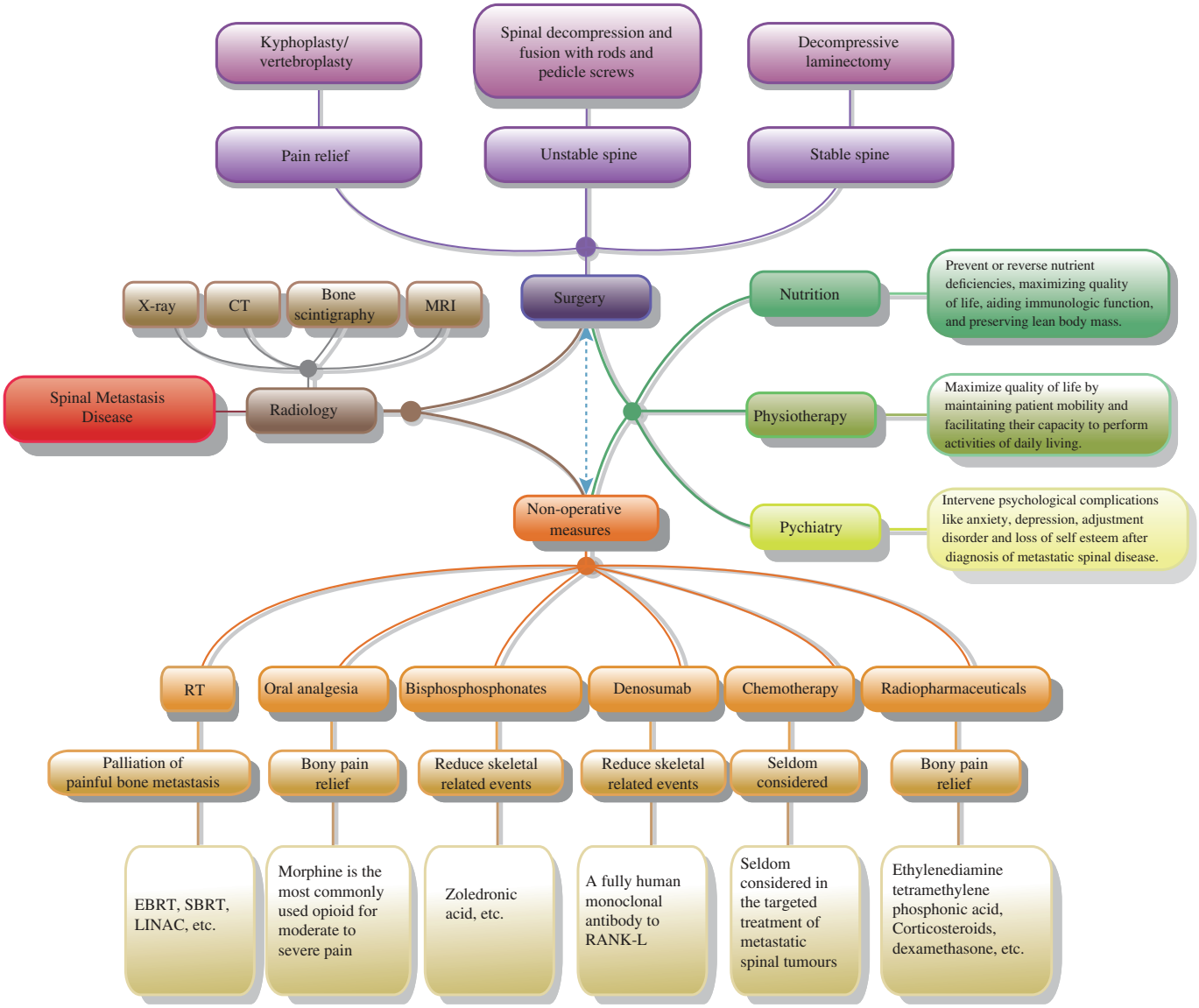

Fig. 2 Flow chart showing multidisciplinary treatment of spinal metastatic disease.

Denosumab, a fully human monoclonal antibody to RANK-L, has demonstrated in clinical trials inhibition of osteoclast-mediated bone destruction in breast, prostate, and myeloma tumors, and is considered non-inferior to zoledronic acid[69,70]. A meta-analysis performed by Lipton *et al.* compared the efficacy of denosumab to zoledronic acid in preventing skeletal-related events in people with prostate cancer, breast cancer, solid tumors, or multiple myeloma. Denosumab increased the time to first on-study skeletal-related event by 8.21 months, and reduced the risk of a first skeletal-related event by 17%[69].

Chemotherapy is very seldom considered in the targeted treatment of metastatic spinal tumors due to its systemic nature and also owing to the fact that it requires an extended course of administration prior to pain relief[71]. Complications are the source of morbidity and fear for the patient and include pain, gastrointestinal abnormalities, hematological disturbances, immunosupression, and biopsychosocial sequelae (alopecia and infertility)[72].

Pain caused by bone metastases has multiple causes, including periosteal elevation and inflammation[73]. Radiopharmaceuticals may be used in the palliation of bony pain. Ethylenediamine tetramethylene phosphonic acid is an IV radioisotope that preferentially binds to osteoplastic metastases and osteosarcomas, and a significant analgesic effect may be achieved in 83%–93% of patients[74]. Strontium-89 chloride infusions have also been trialed as a similar treatment. Response rates vary in the published literature from minimal to up to 77%[75]. Corticosteroids produce effects that include mood elevation, an anti-inflammatory effect, and reduction of spinal cord edema in bony metastases[76]. There is good evidence supporting the use of high dose dexamethasone (64 mg/day) in the treatment of pain from spinal metastases, particularly if epidural compression is present. It is associated with significant pain relief and the ability to remain ambulatory in up to 81% of patients[22].

Psychiatry

Involvement of the psychiatric services may be necessary in patients with a diagnosis of metastatic spinal disease. Psychological complications in this instance usually manifest as anxiety, depression, adjustment disorder, and loss of self-esteem[77,78]. Studies have shown that up to 50% of such patients may experience psychological issues following such a diagnosis[79,80]. Early involvement and assessment of this cohort of patients by psychiatric services is essential in the multidisciplinary management and treatment of spinal metastases.

Nutrition

Nutritional support is another consideration in the approach to metastatic spinal disease[81]. The goals of nutrition support include preventing or reversing nutrient deficiencies, maximizing quality of life, aiding immunologic function, and preserving lean body mass.

This cohort are at risk of anorexia and cachexia[82]. Important considerations include dysphagia after radiation, oesophagitis, and reduced motility owing to pain medications[83]. Anorexia has been noted to be an almost universal side effect in individuals with widely metastatic disease[84]. The multidisciplinary team must also consider decreased caloric intake as a result of diminished appetite and malaise and tumor competition for nutrients. Constipation may be secondary to opiate analgesia or spinal cord involvement by tumors causing an upper motor neuron lesion. Malnutrition may also exacerbate this. The addition of dietary calcium and vitamin D for bone health in the patients at risk of therapy-associated fractures is warranted.

Screening and nutrition assessment should be interdisciplinary. Physicians, nurses, dietitians, and social workers (as members of the health-care team) should all participate in nutritional management throughout the continuum of the management of metastatic spinal disease. Such screening tests include the prognostic nutrition index[85].

Suggestions for appetite improvement include keeping a daily menu, snacking between meals, eating small and frequent meals, and adding extra protein to meals[86,87]. Progestational agents such as megestrol acetate and medroxyprogesterone can lead to appetite stimulation and subsequent weight gain[88]. The preferred method of nutritional support is via the oral route. If the GI tract is rendered dysfunctional, TPN may be indicated[89].

Physiotherapy

Physiotherapists play a central role in the multidisciplinary approach to spinal metastasis. Their role is to maximize quality of life by maintaining patient mobility and facilitating their capacity to perform activities of daily living[90,91]. Pain reduction therapies may also be employed, such as hot/cold packs, massage, and electrical stimulation. Assistive devices or orthotics, such as frames, canes, and thoracolumbosacral orthosis (TLSO), are provided by the physiotherapy department to patients with spinal metastasis when required[91].

Discussion

To optimize the outcomes of patients with spinal metastatic disease, a multidisciplinary approach is necessary (Fig. 2). Advances in diagnosis and treatment of oncology patients have prolonged life expectancy and, in doing so, have altered the multifaceted treatment algorithm required. Yet, despite improved clinical approaches in all the elements of the multidisciplinary team, the complexity of the clinical problem and the need for a symbiotic input from a variety of health-care providers can pose a logistical and clinical challenge.

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