Supportive Oncology

Supportive and Palliative Oncology—
A New Paradigm for Comprehensive Cancer Care

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Abstract

Patients with advanced cancer often experience symptoms related to increasing tumor burden, cancer treatments, and psychosocial stressors. They also have significant social, informational, and decision-making needs. Palliative care practitioners have developed expertise to address many of these supportive care concerns through interprofessional teamwork, validated assessments, multidimensional interventions, and frequent communication. In this article, we aim to provide an evidence-based update on several important palliative care topics, including management of pain, fatigue, anorexia–cachexia, depression, and anxiety, as well as patient–clinician communication and decision-making. Multiple randomized controlled trials have demonstrated that palliative care can improve symptom burden, quality of life, quality of care, satisfaction, and possibly survival and cost of care. To enhance the level of care for patients with advanced cancer, oncologists need to have a good working knowledge of the major palliative care principles, and to refer patients to palliative care programs often and early in the disease trajectory.

Keywords

Anorexia, cachexia, communication, decision-making, fatigue, healthcare systems, neoplasms, pain, palliative care, supportive care

Cancer is associated with significant morbidity and mortality. Patients with advanced cancer often experience multiple symptoms related to increasing tumor burden, cancer treatments, and psychosocial stressors (see Figure 1). Direct infiltration, compression, obstruction, inflammation, and various cancer-related complications, such as thrombosis and infections, may all contribute to symptom distress. Cancer treatments such as surgery, radiation, and systemic therapies are associated with multiple adverse effects. Cancer patients also frequently experience emotional distress as a result of changes to their health and functional status, social and financial stressors, existential concerns, comorbid psychiatric diagnoses, and decompensated coping mechanisms. Taken together, progressive cancer, cancer treatments, and psychosocial stressors can lead to multiple physical and emotional symptoms, ultimately decreasing patients’ quality of life and increasing caregiver burden. In several cross-sectional studies, cancer patients experience an average of eight to 12 symptoms.1 In addition to symptom burden, patients often have significant social, informational, and decision-making needs, requiring significant expertise and time to provide optimal care.

Over the past few decades, palliative care has evolved as a discipline to address the physical, psychologic, and spiritual needs for patients living with advanced illnesses and their families. Figure 2 shows a conceptual framework for the overlapping, yet distinct, roles of supportive care, palliative care, and hospice care.2 In addition to symptom management, palliative care focuses on patient–clinician communication, complex decision-making, caregiver care, and care for patients at the end-of-life.3 Multiple studies have demonstrated that palliative care is associated with improved symptom control, quality of life, quality of care, and satisfaction, while at the same time reducing the cost of care.4

Palliative care programs are typically situated in acute care facilities, and may include four types of services: inpatient consultation teams, acute palliative care units, outpatient clinics, and palliative home care.5 Inpatient consultation services are most commonly available, which provide symptom management and transition of care for patients under the supervision of oncologists. Acute palliative care units are intensive symptom control units for patients with severe distress, facilitating discharge planning, and end-of-life care.6 Outpatient clinics serve patients earlier in the disease trajectory, and are ideal settings for advance care planning and early symptom interventions.7 Home care teams deliver healthcare services to the patients’ home for those who are not already enrolled onto hospice programs. Palliative care is, by nature, interdisciplinary and consists of nurses, physicians, social workers, counselors, chaplains, physical and occupational therapists, volunteers, and other professionals to address the multidimensional aspects of care for cancer patients and their families.

Recognizing the importance of palliative care, multiple organizations including the American Society of Clinical Oncology (ASCO),5,6 the National

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Comprehensive Cancer Network (NCCN), the Institute of Medicine (IOM), and the American College of Surgeons Commission on Cancer (CoC) have promoted an increase in the availability and integration of palliative care programs in cancer centers. We shall provide an evidence-based review on some of the main palliative care skills, summarize the clinical outcomes related to palliative care programs, and discuss contemporary models to integrate palliative care with oncology.

**Palliative Care Skills**

**Physical Symptoms**

Common symptoms in patients with advanced cancer include fatigue, pain, dyspnea, nausea and vomiting, anorexia, weight loss, and delirium. Figure 3 illustrates the complex interaction among various symptoms, and how symptom expression can be modulated by multiple factors. For instance, pain expression may be exacerbated by psychologic distress. Understanding of this symptom expression cascade has multiple implications. First, symptoms occur commonly and often together, making it essential to assess them with symptom batteries. Second, symptoms are usually multifactorial in nature, necessitating multidimensional interventions. Third, symptoms can often be anticipated and should thus be screened routinely and managed expectantly. The remainder of this section focuses on several common symptoms, namely fatigue, pain, and anorexia–cachexia.

Cancer-related fatigue occurs in 30–90% of cancer patients. The pathophysiology of this symptom is poorly understood, but has been postulated to be related to the production of cytokines, serotonin neurotransmitter deregulation, hypothalamic pituitary axis disruption, circadian rhythm disturbance, vagal afferent activation, and alterations in muscle metabolism. Moreover, secondary factors such as anemia, sleep disturbance, inactivity, poor nutrition, pain, electrolyte abnormalities, and neuroendocrine changes may also contribute to fatigue. Given its high prevalence, fatigue should be routinely screened. A detailed assessment for associated symptoms, functional impairment, and possible causes is essential. Management of cancer-related fatigue consists of treatment of any reversible causes, such as pain and hypothyroidism. A recent Cochrane meta-analysis suggests that aerobic exercise is effective in reducing fatigue in both patients on treatment and afterwards. However, the optimal duration has yet to be defined. Guidelines suggest moderate intensity exercises for 30 minutes per day most days of the week. Psychostimulants such as methylphenidate and modafenil have mixed evidence for improving cancer-related fatigue, and may be useful in selected patients. More recently, randomized controlled trials involving dexamethasone and American ginseng also demonstrated some potential benefit.

Pain is another common symptom in patients with advanced cancer. It can affect patients’ sleep, appetite, mood, function, and quality of life. Assessment of cancer pain includes characterization of the nature, intensity, location, duration, and any previous treatments. For patients with mild pain, non-opioids such as acetaminophen may be appropriate. For patients with moderate to severe pain, opioids would be warranted. The following are some important principles when prescribing opioids:

1. All strong opioids have similar efficacy when administered at equianalgesic doses.
2. Long-acting opioids given every 12 hours are equally efficacious as short-acting opioids given every 4 hours.
3. The rescue dose of opioids should be 10–20% of the total daily dose given every 1–2 hours.
4. Patients should be educated in terms of the side effects of opioids. Nausea and drowsiness may occur in opioid-naïve patients, and usually resolve within the first few days. This is in contrast to constipation, which persists throughout opioid treatment, and needs to be treated with laxatives preemptively.
5. Opioid rotation and use of adjuvant therapies may help to limit to the dose of opioids, minimize opioid-induced neurotoxicities (e.g. delirium, myoclonus, hallucinations, vivid dreams), and improve pain control. Table 1 shows an equianalgesic table for opioid rotation.
6. Opioid dependence and addiction may occur in cancer patients, requiring careful monitoring.
7. Management of patients with total pain requires interprofessional input. Palliative care and pain services referral may be necessary.

Anorexia and cachexia are common concerns among cancer patients, especially those with advanced disease. Primary anorexia is mediated by inflammatory cytokines such as tumor necrosis factor-α, interleukins 1 and 6, and various anorexigenic factors such as leptin, cholecystokinin, and peptide YY. Other co-existing concerns such as taste changes, dental problems, mucositis, pain, dysphagia, early satiety, constipation, and depression may contribute to secondary anorexia. Proper assessment and treatment of these factors may help to improve appetite. Cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully
These three terms have overlapping yet distinct meanings. Hospice care is limited to providing services for patients with less than 6 months of life expectancy, predominantly in the community setting. Palliative care includes both programs in acute care facilities for advanced cancer patients and hospice care. Supportive Care is the most encompassing term, and includes survivorship, palliative care and hospice care programs.

The dotted boxes represent the expanding roles of these programs.

reversed by conventional nutritional support and leads to progressive functional impairment." Corticosteroids may stimulate appetite and improve wellbeing, but should only be used for short periods (i.e. 2 weeks or less) because of potential complications such as insomnia, infections, hyperglycemia, hypertension, edema, and adrenal suppression, particularly with long-term use. Megestrol acetate can improve oral intake and fat weight; however, it is associated with thromboembolism, edema, and adrenal suppression without improving lean body mass. A randomized controlled trial demonstrated that dronabinol was inferior to megestrol acetate for both appetite and weight gain in cancer patients after 4 weeks. Other agents being investigated for cancer anorexia–cachexia include anabolic agents (oxandrolone, testosterone, selective androgen-receptor modulators), appetite stimulants (ghrelin analogs), metabolic modulators (e.g. β-blockers), cytokine inhibitors (e.g. thalidomide, anti-cytokine antibodies), nutrients (e.g. eicosapentaenoic acid), and anti-inflammatory agents (nonsteroidal anti-inflammatory drugs [NSAIDs]).

**Psychologic Symptoms**

Cancer patients experience significant psychologic distress throughout the trajectory of illness, starting from the time of diagnosis. A recent study demonstrated an increase in both suicide and death from cardiovascular events during the first week of cancer diagnosis. Emotional distress may be a result of fears and worries related to the uncertainty of disease trajectory, changes in body image and sexuality, functional decline, loss of job, income, self-esteem and identity, altered family dynamics, decreased ability to participate in hobbies, as well as various spiritual and existential concerns. Indeed, approximately half of cancer patients have a psychiatric diagnosis, including adjustment disorders, major depression, anxiety, and delirium. These conditions may increase overall symptom expression and decrease quality of life. Similar to physical symptoms, psychologic disorders should be screened routinely. For instance, the question “Are you depressed?” has been found to be useful for depression screening. Nonpharmacologic management is vital to addressing psychologic concerns. Short-term psychotherapy, expressive supportive counseling, and cognitive behavioral therapy are useful for depressive and anxiety states in patients with advanced cancer. Exercise has also been shown to improve depressive symptoms, particularly with supervised programs at least 30 minutes in duration. For patients with severe depressive symptoms, selective serotonin reuptake inhibitors, tricyclic antidepressants, and psychostimulants may be helpful. Patients should also be referred to a psychiatrist for further assessment. A recent Cochrane review found no studies meeting the inclusion criteria on pharmacologic intervention for anxiety in the palliative care setting. Benzodiazepines are often used for anxiety. However, their use should be balanced against side effects such as drowsiness, fatigue, falls, delirium, and the potential for addiction. Neuroleptics and antidepressants may be reasonable alternatives for selected patients.

Spiritual distress is another important concern for patients, and may also exacerbate the expression of physical and emotional symptoms. FICA and SPIRIT are two common tools for spiritual assessment (Faith, Importance, Community, Address; Spiritual belief system, Personal belief system, Integration with a spiritual community, Ritualized practices and restrictions if any, Implications for medical care, Terminal events planning, respectively). Hospital chaplains, community spiritual leaders, and healthcare professionals all play an important role in the provision of spiritual care. Provision of spiritual care is, in turn, associated with improved quality of life, greater hospice utilization, and less-aggressive care at the end of life.
Table 1: Equianalgesic Ratio for Opioid Conversion

<table>
<thead>
<tr>
<th>Conversion Ratio for Parenteral Formulation</th>
<th>Conversion Ratio for Oral Formulation</th>
<th>Continuous-release Oral-dosage Forms (mg)</th>
<th>Immediate-release Oral-dosage Forms (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine (mg)</td>
<td>–</td>
<td>0.15</td>
<td>15 mg, 30 mg, 60 mg, 30 mg/5ml</td>
</tr>
<tr>
<td>Fentanyl (mg)</td>
<td>200</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>–</td>
<td>1</td>
<td>5 mg, 7.5 mg, 10 mg in combination with acetaminophen</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>10</td>
<td>5</td>
<td>2 mg, 4 mg, 8 mg, 1 mg/ml</td>
</tr>
<tr>
<td>Morphine</td>
<td>2</td>
<td>1</td>
<td>15 mg, 30 mg, 10 mg/5 ml, 20 mg/5 ml, 100 mg/5 ml</td>
</tr>
<tr>
<td>Methadone (mg/d)</td>
<td>–</td>
<td>5</td>
<td>5 mg, 10 mg, 5 mg/5 ml, 10 mg/5 ml, 10 mg/ml</td>
</tr>
<tr>
<td>MEDD &lt;30</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MEDD 30–99</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>MEDD 100–299</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>MEDD 300–499</td>
<td>24</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>MEDD 500–999</td>
<td>30</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>MEDD ≥1000</td>
<td>≥40</td>
<td>≥20</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>–</td>
<td>1.5</td>
<td>5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 5 mg/5 ml, 20 mg/ml</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>–</td>
<td>3</td>
<td>5 mg, 10 mg, 1 mg/ml</td>
</tr>
</tbody>
</table>

*Oral morphine is the standard unit for opioid conversion. To convert from another opioid to oral morphine, multiply the opioid total daily dose by the conversion ratio in the table above. Conversely, divide the oral morphine total daily dose by the conversion ratio to convert from morphine to another opioid. When rotating from one opioid to another, reduce the dose by 30–50% to account for cross-tolerance. For example, a patient on 12 mg/day of intravenous hydromorphone is taking an equivalent of 120 mg (12 mg x 10) of oral morphine. Thus, the dose of morphine the patient should be started on would be 60 mg/d (120 mg x 0.5). The prescriptions for this patient would be morphine sulfate (MS) contin: 15, 30, 60, 100, 200; Kadian: 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200; 15 mg, 30 mg, 10 mg/5 ml, 20 mg/5 ml, 100 mg/5 ml. 10 mcg of intravenous fentanyl is equivalent to 1 mg of intravenous morphine. Methadone can be used for both short- and long-acting purposes because of its long half-life and rapid onset. The conversion ratios are based on the National Cancer Institute website, available at http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/Table2 (last accessed 1/22/2013). MEDD = morphine equivalent daily dose.

Communication and Decision-making

A vast majority of cancer patients want to know about their disease status, treatment options, and outlook. Patients need this information to make important decisions about various healthcare (e.g. chemotherapy, hospice enrollment) and personal (e.g. financial, relationships) choices. Cancer patients are less likely to consider chemotherapy at the end of life if they believed that they have a poor prognosis.50 This is particularly true when palliative care is involved to facilitate the transition of care.51 Unfortunately, a recent study revealed that approximately 70% of metastatic cancer patients receiving chemotherapy did not know that their disease is incurable, suggesting a significant gap in communication.52 In addition to playing a central role in decision-making, communication is one of the major determinants of patient satisfaction.53,54 However, studies have found that oncologists consistently missed opportunities to provide empathic responses,55,56 and that a large proportion of them did not routinely discuss prognosis with their patients.57 One explanation is the concern that disclosing a poor prognosis could destroy hope, despite recent evidence to the contrary.58,59 Another potential reason is the lack of formal communication training among oncologists.8 Patients who reported to have had end-of-life discussions with their physicians were less likely to receive aggressive measures such as admission to an intensive care unit, mechanical ventilation, and resuscitation in the last week of life.56 They were also more likely to receive care consistent with their preference, to be enrolled onto hospice, and to have a higher quality of life.51 End-of-life discussions may cover prognosis, trajectory of illness, expected functional decline and symptom burden, goals of care, place of care, and advance care planning that includes an advance directive, surrogate decision-maker(s), and an out-of-hospital do-not-resuscitate order. Importantly, end-of-life discussions should occur longitudinally, particularly with sentinel events such as cancer diagnosis, disease progression, hospital admission, initiation of aggressive life-sustaining therapies (e.g. dialysis), and when death is expected.62 Communication techniques such as listening, making empathy statements, providing nonverbal cues, and prompting are important to facilitate these discussions.63 It is also important to clarify the decision-making preference with patients. Some prefer a passive role with their physicians making the final decision; others take an active role deciding their own care; and the
Figure 3: Symptom Transduction Cascade in Advanced Cancer

This highly simplified example illustrates the complexity of symptom expression in a cancer patient. Physical pain from a growing tumor may lead to decreased function, which could contribute to fatigue and depression. Depression in turn may increase pain expression and the level of fatigue. When opioids are used to treat pain, constipation and early satiety may occur, leading to weight loss. Weight loss may be further worsened by inflammatory cytokines. Changes in body image as a result of weight loss may lead to depression. Because symptoms are often inter-related and multifactorial in nature, multidimensional assessments and interventions are needed.

Figure 4: The Cancer Care Package

(A) The solo practice model involves the oncologist being responsible for both cancer treatments and supportive care. Because of limited time, skills, assessments, and resources, the supportive care aspect may not be addressed comprehensively. (B) The congress model involves multiple specialists providing consultation on each unique supportive care issue, with the oncologist focusing on the management of cancer. This model is prohibitively expensive and inefficient. (C) The integrated care model involves the oncologist collaborating closely with the palliative care team to provide comprehensive cancer care in a timely and efficient manner. GI = gastrointestinal

72

Supportive Oncology

remainsder choose a collaborative approach making decisions together with their healthcare professionals.64 Under a shared decision-making model, clinicians provide specific recommendations based on a good understanding of the patient’s preference and goals of care.65 Other communication and decision aids such as pamphlets, audiotapes of the interview, and information videos may also be helpful.66,67 Finally, palliative care teams can work with oncologists to facilitate complex decision-making and advance care planning.68

Palliative Care Outcomes

One major challenge in assessing the outcomes related to palliative care programs in the literature is the tremendous heterogeneity in terms of study design, inception cohort, palliative care interventions, and outcome measures. Nevertheless, multiple studies have demonstrated benefits associated with palliative care referral under the domains of symptom control, quality of life, quality of care, satisfaction, and healthcare costs.19

Improved Symptom Control and Quality of Life

A meta-analysis consisting of 26 studies showed that palliative care was associated with improved pain and other nonpain symptoms.70 Multiple randomized control trials comparing palliative care to routine oncologic care also demonstrated significant improvement in depressive symptoms and health-related quality of life in patients with advanced cancer.4,71

Improved Quality of Care

Palliative care involvement has a positive effect on multiple quality of end-of-life care outcomes. These include an increase in hospice referral and a reduction in intensive care unit admissions and deaths, emergency room visits, resuscitation, aggressive investigations, and chemotherapy use at the end of life.72,73 This is likely a result of proactive advance care planning and documentation of care goals.60

Improved Satisfaction with Care

Satisfaction is related to multiple aspects of care, such as patient–clinician communication, quality of life, and wait times.24 Increased satisfaction may improve patient adherence. A meta-analysis reported a significant increase in patient satisfaction with palliative care involvement.25 A more recent systematic review showed significant improvement in caregiver satisfaction and a trend towards improved patient satisfaction.26 There is also emerging evidence that palliative care involvement can improve bereavement outcomes.60

Reduced Healthcare Costs

The end of life in cancer patients is marked by a sharp functional decline, acute complications, and increased symptom burden, often necessitating emergency room visits, hospitalizations, and intensive care unit stays. This increase in resource utilization is associated with a sharp rise in healthcare expenses in the last month of life, which constitutes 40 % of the total expense in the last year of life.27 Through the avoidance of aggressive measures at the end of life, palliative care may not only improve quality of care but also reduce healthcare costs. This is supported by several randomized controlled trials and case series.72–79 However, it should be noted that comprehensive palliative care service with an interprofessional team can also be resource intensive, and other studies have reported cost neutrality with palliative care involvement.60 Taken together, palliative care is financially sound and improves healthcare value.8

Oncology and Palliative Care Integration

The Gap in Care

An increasing number of patients are diagnosed with cancer, and patients with advanced cancer are living longer because of novel developments in
cancer therapeutics. Patients expect not only to receive the best cancer treatments, but also the best supportive care. Recent studies have shown that there are significant gaps in care related to symptom management, psychosocial and spiritual care, patient–clinician communication, decision-making, and care planning. Thus, we urgently need to increase the level of palliative care at the primary, secondary, and tertiary levels to optimize delivery of comprehensive cancer care.

Primary palliative care is delivered by oncologists who see patients in the front line. A survey that included over 3,000 oncologists reported that 81% felt they received inadequate education about symptom control, 81% reported inadequate training in discussing prognosis, and only 10% had completed a rotation in palliative care or hospice. To address this knowledge gap, we need to increase the level of palliative care training among oncologists and oncology fellows, which would allow them to provide a high basal level of supportive care. However, it should be recognized that even with improved training, oncologists have limited time in a busy office to provide full assessment and treatment of all the supportive care concerns. They also do not often have access to an interdisciplinary team needed to address the multidimensional aspects of care. Moreover, there is a growing body of literature in cancer therapeutics and supportive care, making it difficult to keep up with both fields.

In addition to primary palliative care, many patients would benefit from secondary palliative care that involves referral to specialist palliative care teams. Palliative care programs were shown to be growing in a recent survey of US cancer centers, although there remains significant room for improvement in terms of infrastructure and the degree of integration. Even when a comprehensive palliative care program is available, we found that less than half of the patients who died of advanced cancer received palliative care at our cancer center. Moreover, patients were typically referred late in the disease trajectory (median 1.4 months from death), which significantly limits the effectiveness of palliative care programs.

Tertiary palliative care consists of academic palliative care specialists conducting research to advance our level of knowledge in supportive care. However, there are few palliative care research programs in US cancer centers. Furthermore, palliative cancer care research is growing at a slower pace compared with the rest of the oncology field. Increased research funding is needed to address this gap.

Models for Integration

Figure 4 illustrates three models in care delivery: the solo practice model, congress model, and integrated care model. The cancer practice package can be conceptually divided into cancer management and supportive care matters. In the solo practice model (Figure 4A), the oncologist is responsible for both cancer treatments as well as supportive care. Depending on the level of palliative care training, time availability, attitude, and resources of the oncologist, patients may receive a variable degree of palliative care. The congress model (Figure 4B) involves specialists from various disciplines addressing each supportive care factor, with the oncologist primarily focusing on cancer diagnosis and treatment. This model may result in fragmented care and can be prohibitively expensive to patients and the healthcare system. The integrated care model (Figure 4C) involves palliative care working side by side with oncologists to address the patients’ supportive care needs. Under this model, all patients automatically receive comprehensive needs assessments and interprofessional management. Symptom concerns, prognosis, and advance care planning are routinely discussed and re-visited with changes in health status. Patients under this model would routinely receive comprehensive care as a result of close collaboration between oncology and palliative care.

Studies that involved more comprehensive palliative care programs and patients earlier in the disease trajectory were more likely to have a positive impact. Importantly, these clinical trials included routine referral of patients with advanced disease rather than selected individuals, suggesting that many more patients than currently referred can potentially benefit from palliative care. At the same time, it should be noted that few existing palliative care programs can accommodate universal referral because of the limited infrastructure. Thus, a number of organizations have proposed criteria for referral. For instance, the NCCN suggested that patients with uncontrolled symptoms, moderate to severe distress, serious comorbidities, life expectancy less than or equal to 12 months, patient/family concerns about the course of disease and decision-making, or self-expressed interest should be referred to interdisciplinary palliative care teams for further management. A recent study showed that for every patient referred to palliative care, the oncologist saves a cumulative of 170 minutes of clinic visit time. Further research is needed to identify individuals most likely to benefit from a palliative care referral and to determine the optimal integration model.

Summary

Cancer patients have significant supportive care needs. Palliative care specializes in symptom management, communication and complex decision-making, and is associated with improved outcomes such as symptom burden, quality of life, quality of care, satisfaction, and possibly survival and cost of care. To ensure comprehensive care for patients with advanced cancer, we urgently need to increase the level of palliative care at the primary, secondary, and tertiary levels.

15. Champ F, Byron-Daniel J, Exercise for the management of