Supportive care in the management of Neuroendocrine Neoplasms

Introduction

Improvements in the treatment of neuroendocrine tumours have led to corresponding increases in the number of patients living longer.

Unfortunately, there remain reports of significant delays in diagnosis, with the disease still frequently having progressed to metastatic stages before the diagnosis is made. This has resulted in increasing numbers of patients, many living with metastatic disease and ongoing symptoms which impacts the quality of life, financial stability and psychosocial wellbeing of patients and their families.

This section is in three chapters, focusing specifically on three key areas of supportive care:

Chapter 12: Diet and nutrition

Chapter 13: Psychosocial care

Chapter 14: Exercise and NENs

Chapter 14: Exercise and Neuroendocrine Neoplasms (NENs)

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Practice Points:

- Exercise, including aerobic and resistance training, is now part of standard clinical guidelines for the management or adjuvant care of many other more common cancers, including breast, prostate and colorectal cancers.
- *Physical activity levels* and *lean body mass* are modifiable risk factors for cancer occurrence and recurrence. Clinicians are encouraged to explore these risk factors with all patients.
- Persistent symptoms, or treatments and medications, may make it difficult to exercise. Patients who wish to become or remain physically active throughout treatment for NENs can be supported with referral to an exercise physiologist, physiotherapist or other allied health practitioner.
- Body composition can be beneficially influenced by exercise, however, dietary change may also be necessary to achieve increases in lean body mass. Referral to a dietitian may provide additional support.
- Concerns regarding carcinoid syndrome and carcinoid crisis may hamper some patients' attempts to exercise. Monitoring of symptoms during exercise and measurement of blood pressure (where practical), may provide some reassurance to patients and clinicians that safe exercise is possible for people with NENs.

Introduction

Exercise has emerged over the last decade as a complementary therapy alongside standard care throughout the cancer continuum (Hart et al., 2017). Published evidence regarding exercise interventions for individuals with NENs is limited, however recent guidelines from Exercise and Sports Science Australia (Hayes et al., 2019), the American College of Sports Medicine (Campbell et al., 2019; Schmitz et al., 2019) and Cancer Care Ontario (Segal et al., 2017) all support the prescription of individualised exercise to improve health outcomes in cancer populations. The Clinical Oncology Society of Australia has also developed an Exercise Position Statement which calls for exercise to be embedded as part of standard practice in cancer care (COSA, 2018).

Given the chronic nature of neuroendocrine tumours, it is important to highlight both short and long-term benefits of exercise for patients once diagnosed. Moderate intensity exercise can reduce cancer-related fatigue, anxiety, depressive symptoms, and maintain or improve health-related quality of life, muscle mass, bone density, and physical function (Campbell et al., 2019). Long term, there are associations with reduced risks of cancer recurrence in many types of cancers, as well as reductions in cancer-specific and all-cause mortality (Hart et al., 2017; Hayes et al., 2019). The purported mechanisms behind these benefits include

improved immune function, modulation of circulating factors (such as insulin and growth factors) and reduction of inflammation and deconditioning (Hart et al., 2017). While it is recognised that most studies relating to exercise in cancer care show modest effect sizes, these small improvements are made in areas of life that matter greatly to individuals.

Exercise in itself is not curative of cancer, however exercise can offer surprising benefits. In their meta-synthesis of qualitative studies, Midtgaard and colleagues (2015) highlighted that individualised exercise can provide an opportunity for people with cancer to feel a sense of control, provide routine, independence and confidence with their bodies (Midtgaard et al., 2015). In addition, exercise is a well-established method for reducing the risk of other chronic diseases such as heart disease, type II diabetes and osteoporosis. Given individuals with NENs are not exempt from the effects of inactivity, and Leyden et al. reported that 54% of people with a NENs diagnosis stopped or cut back their activity levels, exercise is a valuable addition for the prevention and care of co-morbidities (Leyden et al., 2018).

When and how to exercise?

"Exercise" is a broad construct, an umbrella term for movement or activity that generates a physiologically adaptive response. Exercise does not need to look like sport, athletic pursuit, or a gym or aerobics class to give benefit; it just needs to be strenuous enough to stress body systems positively. Importantly, there is no one-size-fits-all approach to exercise prescription; what may be vigorous for one individual, may be light and relaxing for another (Campbell et al., 2019; Hayes et al., 2019). Many clinicians, as well as patients and their families, may be cautious or uncertain about encouraging people with NENs to exercise, so these notes have been provided as guidance on types of exercise that may be suitable and achievable.

[See Appendix, Table 1: Exercise Prescription Recommendations]

[See Appendix, Table 2: Exercise Considerations and Cautions]

Exercise cautions and caveats

Despite historical recommendations that people with cancer avoid exercise or avoid exercise at certain times (e.g. during chemotherapy or radiotherapy), there appear to be very few drawbacks for people with cancer exercising almost any time they feel capable of doing so. Generally, it is important to avoid complete rest to prevent deconditioning and loss of habitual exercise behaviour and associated self-efficacy. Rather than risking a patient becoming inactive, exercise prescription can be modified to reduce the risk of harm while still maintaining the short and long-term benefits.

Note: The recommendations and considerations in Tables 1 and 2 are not a substitute for individual clinical advice and care. These tables provide general guidance only and should not be used in place of individual exercise prescription. People with NENs may need a safety assessment or medical review prior to commencing exercise.

Carcinoid Crisis: Of particular concern to patients with NENs is carcinoid syndrome and the possible sequelae of carcinoid crisis. Carcinoid syndrome is the constellation of symptoms purported to be mediated by hormones secreted by some NENs or a result of distributive shock (i.e: shunting blood from one region of the body to another) (Condron et al., 2019). Two of the most common symptoms are flushing and diarrhoea, which may occur in isolation or as part of carcinoid syndrome. Carcinoid crisis is a life-threatening extreme of carcinoid syndrome, resulting from overwhelming levels of biologically active compounds being

released from a secretory tumour. Carcinoid crisis is typified by flushing, precipitously low blood pressure (giving light-headedness, confusion, and fatigue) and difficulty breathing. Carcinoid crisis may be triggered by tumour manipulation such as biopsy, surgery or anaesthesia (Condron et al., 2019). Although it is unclear whether exercise *per se* manipulates tumours or promotes hormone secretion from NENs, exercise is a short-term physiological stressor that may produce vasodilation and blood volume redistribution - common wisdom that exercise could trigger carcinoid crisis is a concern for many patients. For a patient, the heightened skin colour and gasping for breath that occurs with a bout of high or maximal intensity exercise might look and feel like a carcinoid crisis. For these reasons, it is recommended that patients commence with moderate intensity exercise (***see Appendix, Table 1***), gradually progress exercise intensity, and monitor symptoms throughout exercise sessions. Where possible, it is recommended that blood pressure be monitored before, during and following exercise sessions, however recognising this advice is not always practical for patients self-monitoring blood pressure (***see Appendix, Table 2***). Modest elevation in systolic blood pressure is a normal response during aerobic exercise (Kim & Ha, 2016) and may be used to distinguish physiological responses to exertion such as facial redness and increased respiratory rate from an evolving carcinoid crisis.

The importance of behaviour change support

Traditionally, behaviour-change guidance has not been incorporated into exercise guidelines. This has changed with the most recent ESSA position statement, which recognises that behaviour change strategies are an important component of an exercise prescription in order to encourage the adoption and maintenance of exercise (Hayes et al., 2019).

Providing tailored behaviour change support

There are many useful frameworks that can help guide the development and implementation of personalised behaviour change initiatives (Bartholomew et al., 2011; Michie et al., 2011). At the core of these frameworks, and in guidance provided in the ESSA statement (Hayes et al., 2019) is that it is important to: 1) understand the broader context (e.g. physical, psychosocial and financial issues); 2) clarify patient goals; 3) identify key behavioural influences and select and apply behaviour change strategies that address them; and 4) monitor progress and refine support as needed.

Clarify patient goals

Understanding patient goals is essential not only for prescribing appropriate exercise, but also for understanding the strength and source of motivation for exercise. Research conducted in other tumour groups for example shows that goals can range from exercising to reduce side-effects, to being fit enough to travel, or even alleviating guilt ("I know I *should*") (Short et al., 2017). Motivation for ongoing exercise is likely to differ as a function of these goals, and patients may need help to develop goals that are meaningful and achievable.

Tailor behaviour change strategies

Behaviour change strategies should target the key modifiable factors that influence a person's behaviour. In general, these can be grouped into factors that influence capability (e.g. skills, health status), opportunity (e.g. access to equipment, appointment times) and motivation (e.g. confidence, knowledge, support, associations with exercise) (Michie et al., 2011). ***Table 3***, adapted from Michie et al (2011) shows how behavioural influences can be described and mapped to specific strategies. Creating a strategy in this way for each patient or patient sub-group (including NEN patients) can facilitate strategic, well-targeted behaviour change support.

[See Appendix, Table 3: Example of Behavioural Influences mapped against Behavioural Strategies]

Monitor progress and refine support

The factors that influence behaviour can and often do change over time. As well as monitoring progress of functional outcomes, participants' progress towards their personal goals, and any changes in capability, opportunity or motivation should be tracked. Contingency plans that focus on building new routines, developing other support structures and addressing ways to overcome barriers should be put in place, especially at the end of a structured program.

Finding additional exercise support for people with NENs

At present, hospital-based exercise programs are not widely available but this is steadily improving. Exercise professionals with oncology expertise working in other settings can be located using the Exercise Sports Science Australia website [https://www.essa.org.au/find-aep] and filtering by 'cancer' or on the Australian Physiotherapy website [https://choose.physio/]. Telehealth options are also available if there are no appropriately qualified exercise professionals in the patient's area or if there are other access barriers/ preferences. Community-based programs are also an option, however consultation with an exercise professional experienced with NENs beforehand is recommended. Medicare rebates may be obtained with referral from a GP under a Chronic Disease Management plan. Some private health funds also offer rebates for exercise programs.

Conclusion

To enable exercise to be embedded within standard clinical practice, COSA calls for all health professionals involved in the care of people with cancer to "Discuss, Recommend and Refer".

Discuss: Clinicians are encouraged to question patients about their current activity levels during each visit and encourage patients to begin or continue to be active. Provide positive and educational messages regarding the short- and long-term benefits of exercise, as well as some basic exercise prescription advice (Newton et al., 2018; Schmitz et al., 2019).

Recommend: If participation in a standard exercise program (such as a community gym or independent exercise) is safe and viable, then this can be encouraged. Clinicians are urged to encourage patients to adhere to exercise guidelines.

Refer: If patients require additional behavioural change support, guidance, exercise testing or supervision, referral to an exercise professional with cancer-specific education (accredited exercise physiologist or physiotherapist) is advised.

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APPENDIX

Table 1. Exercise Prescription Recommendations

	Aerobic Exercise	Resistance Exercise
Mode	Aerobic exercise is any rhythmical exercise involving repetitive use of large muscle groups such as walking, cycling, dancing or using exercise machines (e.g. elliptical trainer, rower, stair climber, stationary cycle, arm ergometer). The aim of this type of exercise is to stimulate the heart rate and breathing rate. The choice of exercise mode is influenced by patients' goals, injuries and preferences.	Resistance exercises use resistance to muscle contraction (both concentric and eccentric phases) in dynamic or static (isometric) form. Resistance exercises can target major muscle groups in the lower- and upper-body or specific exercises to target particular muscle groups. Resistance exercise may be undertaken using machine-weights, free-weights, body weight, resistance bands, or any other form of resistance or mechanical load (e.g. water).
Intensity	Moderate intensity (progressing to vigorous) aerobic exercise is recommended unless symptoms preclude moderate or higher intensity exercise or the patient prefers to exercise at low intensity. Moderate intensity during aerobic exercise is determined by attaining 65% to 85% of age-adjusted estimated maximum heart rate (calculated as either 220 – age [Fox equation], or 208 – (0.7 x age) [Tanaka equation], and/or perceived exertion rated as *somewhat hard*, equivalent to 12-13 out of 20 (using the 6-20 Borg scale) or 4-6 out of 10 (using the 0-10 rating of perceived exertion scale). The Fox and Tanaka equations give slightly differing estimates of age-adjusted maximum heart rate, and the standard error on these estimates may be up to 14.4 beats per minute (Sarzynski et al., 2013). Standard error of estimate differs with sex, race, body mass index, and aerobic fitness. The Borg scale is based on an assumed resting heart rate of 60bpm and each exertion level on the Borg scale aligns to an estimated heart rate, thus the Borg scale and heart rate estimations of exercise intensity may be of limited usefulness among clinical populations. Qualitative descriptors of intensity (e.g. *somewhat hard, hard, very hard*) are therefore recommended.	Moderate (progressing to vigorous) resistance exercise is advised unless patient preference is to exercise at low intensity, or presence of symptoms prevents higher intensity activity. Progressively increasing load volume (sets x repetitions x mass) is necessary to increase muscle mass and strength. Resistance training intensity can be measured using qualitative descriptors of intensity: Low intensity ranges from very light to light. Moderate intensity ranges from moderately challenging, somewhat hard to hard. Lastly, vigorous intensity ranges from very hard to very, very hard.
Frequency and duration	The gold standard is a minimum bout of 20 minutes of continuous aerobic exercise per day. It is recommended that patients avoid two or more consecutive days of no exercise. Deconditioned patients and individuals who are not able or confident to complete bouts of at least 20 minutes, are advised to complete multiple smaller blocks (5-10 minutes) of exercise over the course of a day, on as many days a week as possible.	Two sessions per week are recommended to stimulate physiological changes within the patient. There should be at least 48 hours of recovery between sessions loading the same muscle groups. If patients wish to complete three or more resistance exercise sessions per week, split body programming is advocated to allow sufficient muscle recovery between sessions.
	Patients and clinicians need to understand there is a dose-response relationship between exercise duration, intensity and physiological outcomes. For example, if lower intensity exercise is preferred, the total duration of each exercise bout needs to be extended to obtain physiological changes comparable to that attained from higher intensity activity in shorter bouts.	

Progression and regression	As function and fitness improve, variations in mode, frequency (per day and/or across the week), duration and intensity of aerobic exercise may be introduced.	As function and strength increase, variations in number and type of exercises prescribed, as well as load (sets, repetitions, mass) may be introduced.
	To continue making improvements progression is required, however increases in parameters should be gradual to reduce the risk of exacerbating treatment-related concerns, injury or disengaging the patient. Conversely, regression of exercise is useful to allow recovery from injury or symptom flare, without disengaging the patient from exercise altogether. We recommend that exercise prescription be flexible enough to allow patients to autoregulate prescription parameters based on cancer-specific considerations during any given exercise session (e.g. provide options for patients to modify timing, type, and duration of activity).	

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Table 2. Exercise Considerations and Cautions

Cancer-related concerns	Exercise considerations and cautions
Systemic	
Fatigue	– Lower exercise intensities may be as useful as high intensities. Alternately, shorter stints of higher intensity exercise may be better tolerated. Program exercise depending on patient preference. – Consider daily/weekly schedule to determine the best time to exercise. – Avoid full rest.
Fever	– Oral temperature >38°C/100·4 °F; cease exercise until the fever has waned.
Infection	– Cease exercise until the infection has been treated.
Carcinoid crisis	– Flushing and shortness of breath may occur during bouts of high intensity exercise but should subside promptly with rest. If not resolving, refer for immediate investigation. – Monitor blood pressure if symptomatic. Blood pressure monitoring may be undertaken by practitioner or patient. Practitioners are encouraged to monitor patients' blood pressure before, during and after exercise. Patients can self-monitor blood pressure at home using low cost, portable, electronic sphygmomanometers. If hypotensive (resting systolic blood pressure ≤90 mmHg or diastolic blood pressure ≤60 mmHg), do not commence or continue exercise session but refer for immediate investigation. Carcinoid crisis may be life-threatening if untreated.
Gastrointestinal	
Nausea/Vomiting Diarrhoea	– Decrease intensity and/or duration of exercise. It may be useful to split sessions up over the course of a day to maintain the habit of exercise. – Modify or stop exercise modes that exacerbate side effects. – Maintain good hydration and nutrition practices.
Flushing	– Provide home-based exercise if the patient is concerned about flushing. – If acute flushing develops during exercise session and does not promptly resolve with rest, refer for immediate investigation (see carcinoid crisis).
Haematological	
Anaemia	– It is important to lower exercise intensity according to symptoms. Break aerobic exercise into shorter bouts or provide rest periods during the session. – Supervised exercise is recommended. – Exercise intensity should be measured using perceived exertion scales rather than heart rate. – Haemoglobin concentrations <80 g/L: relative contraindication to exercise, low to moderate intensity only; concentrations 80–100 g/L: monitor signs and symptoms of fatigue and exertion, adjust exercise intensity or duration to accommodate fatigue or weakness.
Thrombocytopenia	– Supervised exercise recommended and monitor signs of bleeding. – Avoid exercises that are associated with increased falls risk or blunt force trauma.
Neutropenia	– Provision of home-based exercise may reduce the risk of infection. Otherwise, ensure exercise equipment is cleaned before use, avoid crowded areas and ensure appropriate hygiene practices among patients and clinicians. – Avoid high intensity exercise. – Neutrophil concentrations <1·5 × 109/L (neutropenia) is a relative contraindication to exercise; avoid group and public exercise.

Musculoskeletal	
Sarcopenia	– Emphasis should be on resistance training (all major muscle groups) to prevent further muscle loss and aim to build mass if possible. – Referral to a dietician is advisable.
Post-surgical wound healing	– Wound healing post-surgery varies between location, surgery invasiveness and patient response. – Medical clearance is generally required to return to exercise. Follow medical advice regarding patient limitations. – To reduce deconditioning, exercising non-affected body parts may be possible as long as it does not increase risk of infection, pain or reduce wound healing.
Pain	– Choose exercises that avoid irritating the painful site/s. – Slowly progress to include a small amount of exercise that involves painful area as long as there is no connection between exercise and increased pain levels.
Bone density loss	– Include impact loading exercises to prevent further bone density loss. If inexperienced or deconditioned, provide a period of moderate to high intensity resistance training before beginning impact loading exercises. – Include balance exercises to reduce falls risk if necessary.
Bone metastasis	– Avoid exercises that load bone metastasis lesion sites. – Impact exercises are contraindicated.
Cardiovascular and respiratory	
Dyspnoea, wheezing	– Encourage exercise daily to reduce deconditioning. – Perceived exertion or breathlessness scales likely more useful than heart rate in monitoring intensity. – If acute dyspnoea or bronchospasm develops during exercise session, and does not promptly resolve with rest, refer for immediate investigation (see carcinoid crisis).
Rapid heart rate	– Heart rate monitoring is encouraged. Intensity should be reduced if necessary.
Chest pain	– Exercise is contraindicated if there is a sudden onset of chest pain or if exercise increases chest pain. Seek referral for immediate investigation.
Hormonal	
Blood glucose levels	– For patients with known history of poor blood glucose control or type II diabetes mellitus, monitor blood glucose levels at an appropriate time before, during and after exercise. It can be helpful to schedule exercise at a similar time of day and time post-meal (e.g. 1-2 hours post-meal) to standardise response and reduce the risk of a hypoglycaemic event. Blood glucose monitoring may be undertaken by practitioner or patient. Patients can self-monitor blood glucose at home using low cost, portable, electronic glucometers.
Neurological	
Peripheral neuropathy, dizziness	– Low impact exercises may produce less discomfort. – If patient unstable, modify exercises to provide a level of support (seated training rather than standing). – Include supervised or supported balance/proprioception exercises.

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Table 3. Example of Behavioural Influences mapped against Behavioural Strategies

Influencer	Description	Strategies for achieving patient-driven goals
Capability (Physical and Psychological)	Has fatigue. Ran cross country as a child, no experience strength training. Has not used any self-regulatory strategies re exercise.	– Set graded tasks and ensure prescription allows for good days and bad days. – Provide clear instructions and feedback for strength training exercises to help build strength training skills and confidence. – Encourage and provide tools for self-monitoring progress towards goals, plus exercise symptoms.
Opportunity (Physical and Social)	Financial strain	– Discuss options for accessing rebated sessions through Medicare. – Consider how frequently patients may be able to attend paid sessions and discuss plans for maintaining exercise in between sessions if large gaps.
Motivation (Reflective and Automatic)	Feels guilty when they don't exercise. Doesn't like exercise. Wants to beat cancer.	– Provide education about what benefits can be expected from exercise. – Focus on exercise types and intensities that are enjoyable for the patient. – Create a supportive and friendly environment. – Encourage planning and a consistent routine that will aid goal attainment and habit formation.

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