South Australian Gastroenteropancreatic Neuroendocrine Tumours Pathway

Optimising outcomes for all South Australians diagnosed with Gastroenteropancreatic Neuroendocrine Tumours

September 2013

Government of South Australia

SA Health

Development

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The Statewide Cancer Clinical Network recommends readers also refer to the Clinical Oncology Society of Australia Wiki Platform for up to date information and education on clinical practice guidelines.

Statement of intent

This pathway is not intended to be used as a standard of care. Adherence to pathway recommendations will not ensure a successful outcome in every case, nor should they be considered as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement for management must be made by the appropriate health professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This decision should be made only after discussion of the diagnosis and available treatment options with the patient. It is advised, however, that significant departures from the *South Australian Gastroenteropancreatic Neuroendocrine Tumours Pathway* should be documented in the patient's case notes at the time the relevant decision is made.

Navigating the document

This document contains a number of **hyperlinks** that you can click to navigate between relevant sections of the pathway and other important resources. Hyperlinks appear as blue and underlined copy. You can also **search for keywords** throughout the document by selecting **CTRL+F** and typing in the keyword.

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This clinical pathway was developed by the Neuroendocrine Tumour Working Party of the Statewide Cancer Clinical Network.

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EXECUTIVE SUMMARY

BACKGROUND

Neuroendocrine tumours were originally thought to be rare, but are the second most common gastrointestinal malignancy after colorectal cancer, and the incidence is increasing. There is an identified need to improve awareness of symptoms of NETs within the health profession, which is critical for timely diagnosis and access to multidisciplinary clinicians within centres of subspecialty expertise.

SOUTH AUSTRALIAN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS PATHWAY

Purpose

The *South Australian* (SA) *Gastroenteropancreatic Neuroendocrine* (GEP NET) *Tumours Pathway* provides recommendations based on current evidence for best practice, and consistent care in the management of persons diagnosed with Neuroendocrine Tumours (NETs) across South Australia. The SA GEP NET Pathway has been developed through a collaborative effort involving a wide range of health professionals, including NET specialist practitioners, generalist staff and consumers.

The Pathway adopts a multidisciplinary approach to the care of people affected by NETs with involvement of all relevant health professionals. The pathway sets out key requirements for the provision of optimal care which needs to be considered in the NET patient journey. However, it should be noted that not all patients will progress through each step of the pathway. This is a consequence of many factors, including disease outcomes, management decisions, and patient decisions.

The pathway is a statement of consensus based on current best practice, evidence and accepted approaches to cancer treatment and management. Recommendations should be followed subject to the health professional's independent medical judgment and the patient's preference in each individual case.

Scope

The scope of these guidelines is to focus on well- to poorly-differentiated gastroenteropancreatic neuroendocrine tumours (GEP NETs).

Given the limited availability of high-level randomised trials evidence in the clinical management of GEP NETs, the pathway and recommendations have been developed based on currently available national and international guidelines, while ensuring relevance and appropriateness to local practice. The Clinical Oncological Society of Australia (COSA) consensus guidelines for the diagnosis and management of GEP NETs (2010) and the European Neuroendocrine Tumour Society (ENETs) Tumour guidelines for the diagnosis and treatment of Neuroendocrine Gastrointestinal Tumours (2012) are key guidelines to guide management of neuroendocrine tumours in South Australia.

Navigating the pathway

The following icons are used in this pathway.

The **'red-flag'** indicates signs and symptoms for earlier detection to expedite referral, treatment and access to supportive care, and maximise quality of life of persons diagnosed with a GEP NET.

The 'GP icon' indicates parts of the pathway of particular relevance to general practitioners.

SOUTH AUSTRALIA CANCER PATHWAY KEY PERFORMACE INDICATORS

The SA Cancer Pathway Key Performance Indicators (KPIs) are drawn from the state-wide Performance Indicator Framework for SA Cancer Services (2010).[1] These overarching KPIs provide a standardised framework for annual reporting by Local Health Networks to the SA Cancer Service.

- **100% of patients with an urgent new cancer referral from their general practitioner (GP) see the specialist within 2 weeks.**
- **100% of patients diagnosed with cancer have documented clinical staging.**
- **100% of patients are offered enrolment in clinical trials where available.**
- **100% of patients commence treatment within 42 days of confirmed tissue diagnosis.**
- **100% of patients who are admitted to hospital have an advance care directive.**
- **100% of patients have a treatment summary (or discharge summary) sent to their nominated GP within 2 days of completion of the treatment episode.**
- **100% of relapsed/progressive disease patients have a documented multidisciplinary care plan resulting from a multidisciplinary team meeting.**
- **100% of patients have a documented survivorship plan on completion of treatment.**

KEY RECOMMENDATIONS

This document contains recommendations relating to the diagnosis, treatment and supportive care of people with GEP NETs in South Australia. Key recommendations are highlighted below.

A complete list of recommendations relating to the diagnosis, treatment and supportive care of patients with a GEP NET in South Australia are included at the end of each section, and in **Appendix A.**

Pathway Recommendation	Service/System recommendation
All patients with a Neuroendocrine tumour diagnosis are prospectively discussed at a GEP-NET MDM within 4 weeks of diagnosis	> Currently the service should provide funding for: o 2 Pathologists o 2 Radiologists o 2 Nuclear Med Specialists in order to handle the volume of patients referred to GEP NET MDM's and requiring follow up > MDM should meet every 4 weeks, with Chair rotating every 2 years > MDM should combine twice yearly with Hepatobiliary MDM at RAH and FMC to facilitate discussion for surgical approaches and liver directed therapies > Funding for administrative support for preparation, monitoring and follow up functions required by the multidisciplinary team is sought > An urgent improvement to information and communications (ICT) technology is required to enable multidisciplinary team participation across sites with high resolution support for radiology and pathology imaging reviews > Participation in the GEP NET MDM becomes an expectation of cancer health professionals as core business
Every person diagnosed with a neuroendocrine tumour should have an identified cancer care coordinator along the continuum of care to ensure that care aligns with pathway recommendations	> Implement and evaluate the state wide GEP NET cancer pathway and recommendations. > Patients with neuroendocrine tumours should have their cancer journey streamlined by appropriate triage of referrals according to urgency of need. Recognition of the role of a NET Nurse Coordinator to provide and coordinate supportive care from diagnosis throughout the treatment course including follow up, education, management of symptoms, surveillance, referral for palliative care > Patients will have access to consistent and high quality information on which to base treatment decisions, to support both patient and family members. > Contact details of identified care coordinator should be provided to all patients at the earliest opportunity

Pathway Recommendation	Service/System recommendation
Currently the service should seek reimbursement for appropriate radiopeptide scans and therapeutic interventions	> All South Australians should have timely access to radionuclide peptide imaging agents, including Ga-68 labelled SSAs, which are considered to be the most sensitive radio-nuclide agents for the diagnosis, staging/restaging and assessment of response to therapy. > It is recommended that there be funding for a state based service for the provision of radiopeptide therapy for those patients deemed suitable for this therapy by the GEP-NET MDM > There is support for research to evaluate new therapeutic agents or combination regimes > SA GEP NET Cancer Pathway Working Party to approach the Australasian Association of Nuclear Medicine Specialists (AANMS) and Medical Services Advisory Committee (MSAC) to lobby nationally for Medicare reimbursement > SA Nuclear Medicine Imaging Services to be contacted regarding recommendations for imaging requirements for persons with NETs
Ensure quality and safety of Neuroendocrine Tumour cancer care is monitored at a state level	> SA NET Database at the Queen Elizabeth Hospital is a state-wide systematic centralised data base that captures minimum data of all persons with a diagnosis of NET. The database requires investment in administrative and clinical support to ensure that all cases are reported; providing accurate incidence and prevalence > There is support for research to evaluate new therapeutic agents or combination regimes > Initiate a process for centralised review and reporting of key performance indicators (KPI's) and benchmarks for clinical service outcomes linked to SA NET minimum agreed database
Endorse a national synoptic pathological reporting for GEPNETs	> Histopathological diagnosis should follow UK Royal college of pathologist guidelines which are European Neuroendocrine Tumour Society (ENETS) > Consensus discussion with Royal College of Pathologists of Australasia for classification and staging

1. INTRODUCTION

Comprehensive cancer pathways provide evidence-based recommendations to guide best practice and consistent care in the management of patients diagnosed with cancer in South Australia.

1.1 ABOUT CANCER PATHWAYS

Comprehensive cancer pathways improve and standardise cancer care for all South Australians regardless of their location, origin, age or financial status. The pathways encourage the integration of clinical and supportive care with the associated considerations and key requirements for providing cancer services in SA.

Each cancer pathway is developed to guide delivery of optimal and consistent care and support of cancer patients and their families across SA. Each pathway is underpinned by the key principles of cancer care:

- patient-centred care
- safe and high-quality care
- multidisciplinary care
- supportive care
- care coordination.

Further information on the key principles of cancer care is provided in **Appendix B.**

Cancer pathways and their recommendations have been developed for the guidance of:

- **health professionals involved in the management of patients with cancer**; including public and private health professionals, general practitioners and dental practitioners
- **SA Health**, the Cancer Clinical Network Steering Committee (CCNSC) and associated committees and working groups
- **local health networks** in South Australia including: Country Health SA Local Health Network; Central Adelaide Local Health Network; Northern Adelaide Local Health Network; Southern Adelaide Local Health Network; and Women's and Children's' Health Network
- **Aboriginal community-controlled health services**
- cancer care projects
- stakeholders at **non-government organisations** (NGOs).

Aboriginal and Torres Strait Islander Companion Document to the Statewide Cancer Control Plan

There is a significant difference in the burden of cancer for Aboriginal and Torres Strait Islander people in Australia due to poorer identification of cancer, higher incidence of preventable cancers, and higher comorbidities that can limit treatment options.

The Aboriginal and Torres Strait Islander Committee of the SA Cancer Clinical Network has developed an *Aboriginal and Torres Strait Islander Companion Document to the Statewide Cancer Control Plan (2011–2015) and Cancer Care Pathway*, to provide **clear direction on approaches to improve outcomes for Aboriginal and Torres Strait Islanders** in South Australian with a cancer diagnosis.

The Aboriginal and Torres Strait Islander Companion Document to the Statewide Cancer Control Plan (2011–2015) provides further information and context to the issue of cancer. For full details, visit www.sahealth.sa.gov.au.

1.2 INTRODUCTION TO THE SOUTH AUSTRALIAN GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOUR PATHWAY

The *SA GEP NET Pathway* is a guide to the optimal management and care of patients diagnosed with GEP NETs. This pathway is a statement of consensus based on current best practice, evidence and accepted approaches to the treatment and management of GEP NETs. It has been developed through a collaborative effort involving a wide range of health professionals, including NET specialist practitioners, generalist staff and consumers.

Aims of the SA GEP NET Pathway

- To improve care and outcomes for patients with NETs in South Australia
- To provide guidance and consistency of practice in patient management and to reduce the variation in current practice observed throughout South Australia
- To encourage early diagnosis and early appropriate referral in the general population and in high risk groups
- To reduce misdiagnosis at all levels, and to reduce the timescale to a correct diagnosis
- Increase patient referrals to a Multidisciplinary Team
- Consistent information provision and decision making tailored to patient's needs
- Provision of psychosocial care including assessing and responding to emotional, psychological, spiritual, social and familial requirements
- To optimise coordinated care delivery for patients with NETs at all stages of their disease.
- To ensure that all patients with NETs are offered the best chance of cure or palliation irrespective of where they present or are treated
- Particular attention needs to be paid to education about NETs within both the hospital and community setting and across disciplines, and the role of health professionals in raising awareness of the condition

The pathway provides a guide for the patient journey to ensure patients with GEP NETs and their families receive optimal care and support. It promotes a consistent and **standardised approach to managing care**, to ensure that people affected by GEP NETs experience coordinated care**.**

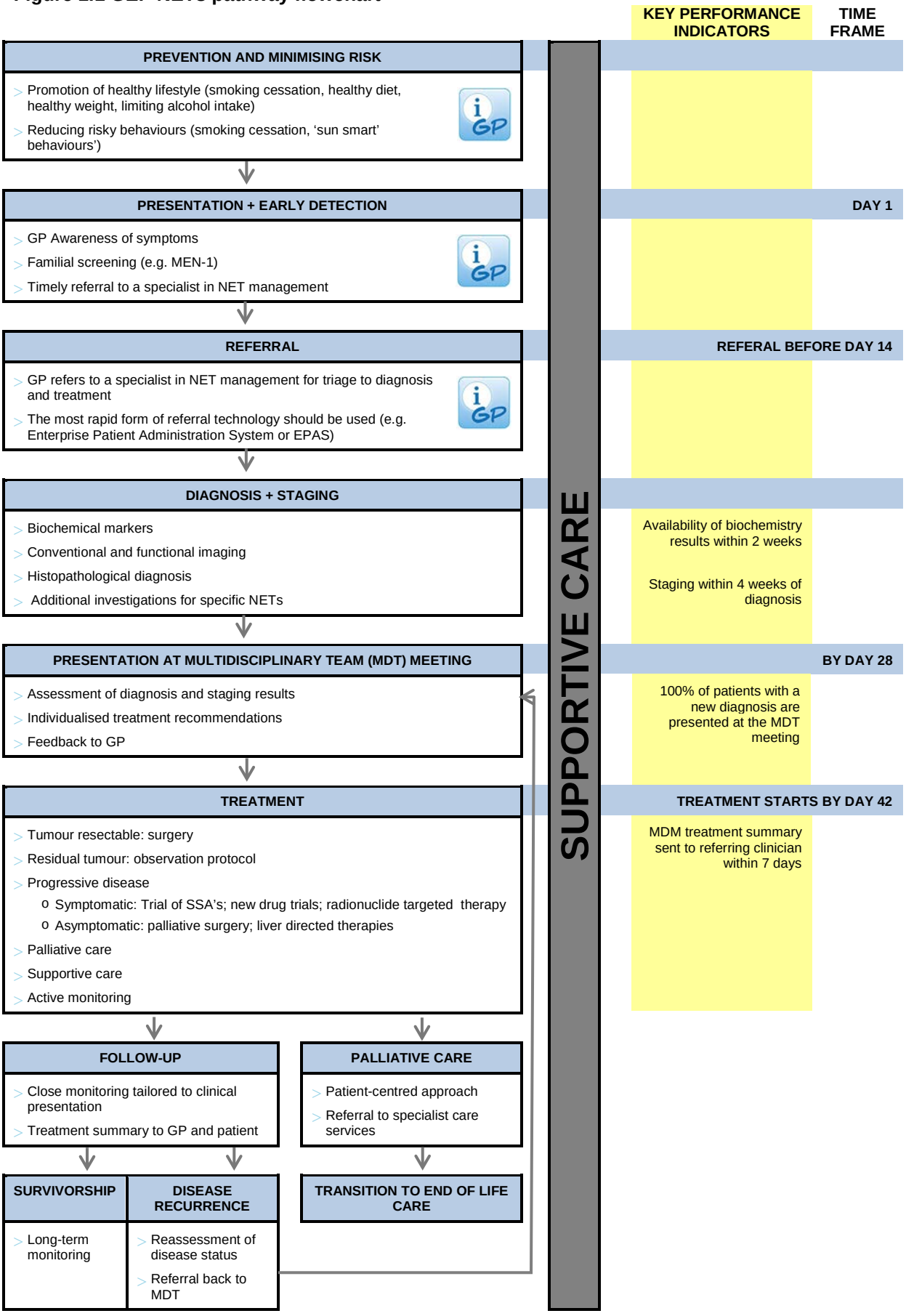
As treatment modality for patients with GEP NETs become increasingly complex, a coordinated service provision between private and public hospitals, general practitioners, community and palliative care services is essential.

People affected by Neuroendocrine Tumours have diverse and complex clinical and supportive care needs. The South Australian NET Pathway provides a structured pathway of the patient journey. **Figure 1.1 identifies the critical steps and optimal care requirements for the person with a GEP NET.** It is acknowledged that many people affected by NETs may not follow every step of the pathway, due to variations in clinical presentation that will influence individual decisions about care.

1.3 FURTHER INFORMATION

- **Appendix C:** Recommended Patient Information Links
- **Appendix D:** Recommended Key Performance Indicators (KPI's). This represents the priority performance measures required to close the gaps in current GEP NET care.

Figure 1.1 GEP NETs pathway flowchart



2. GEP NETs IN SOUTH AUSTRALIA

The incidence of NETs, in South Australia has risen and survival has improved in the past two decades, consistent with trends seen elsewhere. Given the relatively long survival of patients with NETs, the prevalence is higher than generally expected with prevalence likely to be higher than other gastrointestinal cancers such as oesophageal and pancreas.

These patients should have access to the same services and resources as other cancer patients which requires investment, improved access to specialised treatments, and state-wide nurse/cancer coordinators to improve utilisation and coordination of available resources.

2.1 INCIDENCE AND TRENDS

In South Australia between 1980 and 2006, NETs comprised 0.6% of all recorded cancers. Over half the recorded NETs (52.5%) occurred in females. The most common primary site a NET was the lung (25.9%) followed by large bowel (23.3%). Other common sites included the small intestine (20.6%), unknown primary site (15.0%), pancreas (6.5%) and stomach (3.7%).[2]

The incidence of NETs has increased over the past two decades for males and females of all ages. The age-standardised incidence increased from 1.74 per 100,000 in 1980–89 to 3.25 per 100,000 in 2000–06.[3]

The prevalence of NETs in South Australia is unknown. While considered to be rare, the relatively long survival of patients with NETs means they are more prevalent than expected. In the United States the prevalence is estimated to be greater than the prevalence of oesophageal, gastric, or pancreatic cancers.

2.2 MORTALITY AND SURVIVAL

In 2006 in South Australia, relative 5-year survival from NETs was 69%. Five-year relative survival was higher for NETs arising in the appendix (94%), rectum (86%), lung (80%), and small intestine (75%), and relatively low for tumours arising from unknown primary site (28%), pancreas (42%), colon (excluding appendix) (65%), and stomach (66%).[4]

Survival has improved in more recent years, increasing from a relative 5-year survival of 61% between 1980 and 1989, to 73% between 2000 and 2006 (Table 1.1).[5]

The reason for the increased survival of neuroendocrine cancers seen is unknown. NETs frequently develop slowly, and many years can elapse between symptom onset and diagnosis. Increased survival may reflect advances in treatment; however it could also reflect earlier diagnosis and the effect of lead-time bias.[6]

Further registry data collecting stage, tumour grade, proliferative index, and treatments received are required to investigate this in greater depth. The SA NET registry will address this.

Table 2.1 Relative risk (95% confidence limits) of death from neuroendocrine tumours: SA Cancer Registry, 1980-2006*

Predictors	Relative risk
Age at diagnosis (yrs.):	
Under 50 (ref) [n=220]	1.00
50-59 [n=179]	1.74 [1.13, 2.66]
60-69 [n=233]	2.03 [1.37, 3.01]
70-79 [n=219]	2.66 [1.77, 3.99]
80+ [n=92]	4.74 [2.99, 7.51]
Organ site:	
Other (ref) [n=593]	1.00
Appendix [n=90]	0.22 [0.09, 0.53]
Colon [n=58] *(excl. appendix)*	1.60 [1.02, 2.53]
Pancreas [n=61]	3.16 [2.14, 4.66]
Unknown [n=141]	4.09 [3.13, 5.36]
Period of diagnosis:	
1980-89 (ref) [n=221]	1.00
1990-94 [n=169]	0.64 [0.46, 0.88]
1995-99 [n=170]	0.59 [0.42, 0.81]
2000-06 [n=383]	0.41 [0.30, 0.56]

*** Multivariable Cox proportional hazards regression**
Table adapted from Luke et al (2010)

2.3 ETHNIC AND SOCIOECONOMIC DIFFERENCES

The incidence of NETs in South Australia does not appear to vary by sex, socio-economic status, place of residence or Indigenous status. However, lung and appendix tumours occur more commonly in younger patients and small intestine and unknown primary site in older patients.[7]

In North America, the most common primary site varied by race with the most common primary site in white patients the lung and the most common site in Asian, Pacific Islander, American Indian and African American patients the rectum.[8] The data from South Australia is less certain, with primary tumours arising from the appendix appearing more common in overseas-born cases, and primary tumours arising from the small intestine appearing less common in those from Europe. The significance of this is uncertain.[9]

2.4 FURTHER INFORMATION

- **South Australia Cancer Registry of the Department of Health**, South Australian Government http://www.health.sa.gov.au/pehs/branches/branch-cancer-registry.htm
- Cancer Council SA, **Centre for cancer research** http://www.cancersa.org.au/aspx/search.aspx
- Cancer Council SA, **Graphical presentation of cancer trends** http://www.cancersa.org.au/research/cancer-statistics

RECOMMENDATIONS

- The SA NET database requires investment in administrative and clinical support in order to allow all treatment outcomes to be reported , reviewed and measured
- The development of neuroendocrine tumour treatments requires cell lines for ongoing genetic and molecular studies. Funding is needed to be sought to support ongoing research in this area.

3. MULTIDISCIPLINARY AND COORDINATED TEAM CARE

Multidisciplinary care is a team approach to health care that it is required for effective treatment planning and ongoing management of cancer.

3.1 OVERVIEW OF MULTIDISCIPLINARY CARE

A central component of multidisciplinary care is the multidisciplinary team (MDT) treatment planning meeting. MDT meetings, held face-to-face or via tele- or video-conference, bring together health professionals from diagnostic, treatment and support disciplines with relevant expertise to plan care or treatment for all patients. Membership of the MDT for NET is discussed in Chapter 9.

Multidisciplinary care is essential for all patients, regardless of location (rural/metropolitan) or insurance status (public/private). A team approach facilitates **enhanced interaction and coordination** between health professionals involved in the care of patients with cancer, as well as **increased patient satisfaction**.

The approach to multidisciplinary care is underpinned by **five core principles**:[10,11,12]

- a team approach
- communication among team members
- access to the full range of therapeutic modalities for all patients, regardless of geographical remoteness or size of institution
- provision of care in accordance with agreed standards/pathway
- involvement of patients in decisions about their care.

Further information on benefits and principles of MDC is provided in **Appendix E.**

3.2 ROLE OF THE GENERAL PRACTITIONER IN THE MANAGEMENT OF PEOPLE WITH NETs

GPs play an important role in the early detection, treatment and follow-up care of patients with cancer and in communication of prevention messages.

Early detection of cancer through recognition of symptoms, appropriate and timely referral to specialist care and establishment of partnerships with cancer specialists can ensure GPs play a critical role in the quality care, treatment and survivorship for cancer patients.

The role of the GP is paramount in the clinical and supportive aspects of care outlined below.

A factsheet of relevant information for GPs is provided in Appendix F.

Clinical care[13,14]

Early detection, investigation and referral

- Recognition of signs/symptoms
- Documentation of history and clinical findings
- Responsibility for initiating and review of results of initial investigations
- Use GP diagnostic flow chart
- Prompt referral to appropriate specialist using GP referral form
- GPs may wish to attend and participate in MDT meetings

Throughout treatment and post-treatment surveillance

- Liaison with specialist, possible roles include:
  - patient assessment
  - pre-chemotherapy assessment,
  - haematological and biochemical status (particularly in rural areas)
  - monitoring of toxicities

Post-treatment surveillance

- Use of protocols that require regular tests/investigations
- Monitoring of symptoms, including prompt referral back to specialist
- Monitoring of long-term complications that arise from chemotherapy, radiotherapy and surgery, reviewing and referring to supportive cancer services as required

Supportive care[12]

Throughout treatment and post-treatment

- Patients should be informed and educated of suspected diagnosis and possible treatment options
- Ensure rural/remote patients receive additional information regarding services
- All individuals, particularly those at high risk, i.e. economically disadvantaged, intellectually challenged, mental health issues, limited or no family support, culturally diverse populations, Indigenous populations, adolescent and young adult (AYA) or geriatric, and rural/remote locations should be provided on going psychosocial support and referral as required
- Ensure patients have access to supportive organisations
- Development of mental health plan and input from psychologist to assess for anxiety and other psychological symptoms

Support for caregivers

- Provide support to patient's caregiver/s

Palliative care and end-of-life

- GP has a particular role in palliative and end of life care given their awareness of the whole person, the needs of the family and the context of their life[12]

A factsheet of relevant information for GPs is provided in Appendix F.

3.3 OVERVIEW OF COORDINATED CARE

Patients with NETs should have their cancer journey streamlined by a recognised coordinator, who will facilitate referral for supportive care from diagnosis throughout the treatment course.

A range of models for cancer care coordination have been established in recent years, with a general consensus that coordinated care assists in ensuring safety and quality outcomes in health care.

Coordinated care can be provided by any health professional on the multidisciplinary team or other members of the hospital support staff. A coordinator provides a central contact point for patients with GEP NETs, their family members and the treating team. Coordination critically underpins the delivery of appropriate care.

The provision of coordinated care can involve clinical and/or supportive care components, and requires:

- highly developed communication and psychosocial skills to recognise a patient's non-clinical needs as well as problems directly associated with cancer treatment[15]
- a strong knowledge base in the management of GEP NETs
- knowledge of the system in order to streamline timely referrals, and focus on support and care for the patient throughout the GEP NETs journey.

Clinical care[16]

- Coordination with other health professionals to streamline the patient journey
- Triage and coordination of investigations
- Care consistent with evidence-based guidelines
- Prompt referral to specialist, allied health and support services

Supportive care[15]

- Providing timely and consistent information for patients and their families
- Point of contact for patients along their cancer journey
- Assessment and screening of patients for clinical and supportive needs and to identify people at risk of adverse clinical or psychosocial outcomes

3.4 FURTHER INFORMATION

- **Better Access to Mental Health Care MBS Items – Psychologists and Other Allied Mental Health Professionals,** Australian Government Department of Health and Aging: http://www.health.gov.au/internet/main/publishing.nsf/Content/mental-progs
- **Neuroendocrine tumours: A guide for nurses**: a tool for nurses caring for NET patients http://www.carcinoid.org/content/neuroendocrine-tumours-guide-fornurse
- **Online course** for nurses caring for people with NETs: http://www.cancernursing.org
- **UK NET Patient Foundation**: www.netpatientfoundation.org
- **Distress Management Guidelines** (free once registered), National Comprehensive Cancer Network: http://www.nccn.org/index.asp
- **Clinical practice guidelines for the psychosocial care of adults with cancer,** National Health and Medical Research Council: http://canceraustralia.nbocc.org.au/health-professionals/clinical-best-practice/psychological-guidelines
- Cancer Council SA, **Helpline for referral to counselling** (or call 13 11 20) http://www.cancersa.org.au/aspx/Patient_information_and_resources.aspx#Counselling
- Cancer Council SA, **A multidisciplinary team approach to cancer care** http://www.cancersa.org.au/cms_resources/documents/MDCT%20brochure%20dl%20booklet%20FINAL%20121010.pdf
- Cancer Council SA, **Cancer, What Now DVD** http://www.cancersa.org.au/aspx/Cancer_What_Now_DVD.aspx

RECOMMENDATIONS

- All patients with a NET diagnosis should have access to a NET specialist nurse coordinator throughout their cancer journey. Patients should be referred to a NET specialist nurse coordinator at the point of diagnosis/consultation with a specialist.
- The booklet "*Neuroendocrine Tumours: A Guide for Nurses*" is recommended as a valuable tool for general and specialist nurses caring for NET patients in SA. Treatment options will need to be amended for local context.
- Cancer Council resources should be used as standard practice, and include the brochure *'A multidisciplinary team approach to cancer care'*.

4. SUPPORTIVE CARE

Supportive care addresses the physical, emotional and practical needs of the cancer patient. Supportive care requires generalist and specialist health services to provide support to people with cancer and their families and/or caregiver/s.

Collaboration between all members of the multidisciplinary team is essential and all needs must be addressed in a culturally and linguistically appropriate manner.

Further details on the principles of supportive care are provided in Appendix G.

The provision of supportive care requires an initial assessment and identification of the patient's specific needs. This is achieved through regular discussion and systematic review of the patient and their caregivers. Regular reassessment is essential, as needs frequently change throughout the cancer journey.

A screening tool, such as the NCCN Distress Thermometer, can be used to identify any physical, emotional and practical factors that may be causing a patient to experience distress.[17] A detailed assessment of supportive care needs should be conducted on patients at high risk of distress to help identify those who require more specific one-to-one intervention and follow-up. [18]

Following assessment, patients should be referred to an appropriate supportive care professional, such as a specialist nurse, psychologist, allied health professional or social worker. When required, it is important to ensure patients and their caregiver/s have access to an interpreter, culturally appropriate resources and support.

This chapter of the pathway explores suggested management for common supportive care needs. Self-management strategies, such as relaxation techniques and meditation, may also be beneficial.[19]

4.1 PHYSICAL NEEDS

Cancer and cancer treatments can often cause a variety of physical side effects and changes to a patient's physical appearance. Patients with **physical supportive care needs** require referral to a **specialist nurse or to a community support group**.[20,21]

Fatigue

Fatigue is a common and debilitating side effect of cancer and its treatments. Many factors contribute to fatigue, including immobility, sleep disorders, poor nutrition and reduced performance status. It is often experienced along with treatable factors, such as pain, nausea, anxiety, anaemia, medication side effects and other health related co-morbidities.[20]

Fatigue affects physical, recreational and social activities, and can lead to delays in treatment, dose reductions or even discontinuation of therapy.[22] Some patients report that fatigue is extremely distressing and has a negative impact on quality of life – more so than other symptoms, such as pain, nausea and depression.[23]

All patients should be screened for presence and level of fatigue at regular intervals using a simple validated tool, such as a visual analogue scale (VAS) 0-10 (0 no fatigue, 10 worst fatigue imaginable).[20] Other tools can be used to measure the impact of fatigue.

Management of fatigue should target the contributing factors, with appropriate treatment and referral to appropriate specialists. Evidence has shown that exercise interventions can have the strongest therapeutic benefit.[24] Patients should be encouraged to maintain physical fitness and functional mobility by participating in a regular exercise regime during and after treatment.[25]

Pain

Pain is common in patients with cancer, and can be described in terms of soft-tissue pain, bone pain or neuropathic pain.

It is vital to determine the underlying cause of pain in order to direct treatment. Interventions may include opioids, relaxation therapy, massage, and educational programs aimed at enhancing pain control. Radiotherapy is often helpful for localised pain, such as that associated with bone metastases or neural impingement.[26]

Severe pain that is difficult to control generally requires specific pain management from acute and/or chronic pain specialists.

Important principles of pain management are outlined in the *Therapeutic Guidelines Palliative Care Version 3, 2010*.

Memory and cognitive disturbance

Patients treated with chemotherapy and radiation therapy may experience alterations in cognitive function.[22] A baseline assessment of cognitive function is important to rule out subtle manifestations of metastatic disease and to identify the need for strategies such as repetition of information.[22]

Fertility

Certain cancer treatments can affect a patient's fertility. The likelihood of infertility in males, and infertility and/or premature menopause in women should be addressed as a component of the education and informed consent prior to treatment commencing.

All patients of reproductive age or younger should have fertility preservation options discussed/offered. Sperm, ovarian tissue or egg banking may be suggested.

If pregnancy is an option for particular patients after treatment, it is important to ensure that counselling addresses the issue of a potential reduced timeframe of fertility.

Discussion and referral to social worker, gynaecologist, psychologist or psychiatrist may be appropriate.

Oral health

Chemotherapy for any cancer type, blood and marrow transplantation and radiation in the area of the GEP NET can cause oral complications ranging from dry mouth to infections that can interrupt treatment regimens.

Close monitoring of oral health is recommended before, during and after treatment for cancer to reduce the severity of complications, optimise treatment and enhance patient quality of life.

4.2 EMOTIONAL NEEDS

Being diagnosed and treated for cancer can affect a patient's emotional wellbeing. Patients experiencing high levels of **emotional distress** are at risk of developing symptoms including anxiety and depression. **Referral to a psychologist or psychiatrist** is likely to be appropriate

Depression

Patients undergoing treatment for cancer may experience physical and emotional stress and may continue to feel exhausted and depressed for long periods.[27]

Depression is linked to poor quality of life, increased length of hospital stay and poor coping skills. Each of these issues affects morbidity outcomes.

Regular screening and ongoing monitoring for depression by health professionals as part of long-term follow-up care is required. Referral to a psychologist or psychiatrist may be appropriate.

Body image

Body image is the way a person feels about their appearance. Some cancer treatments can cause physical changes to a patient's body, such as hair loss, scars from surgery, loss of a body part, changes to the skin, weight gain or weight loss. Physical changes can result in poor body image.

Patients should be provided with individualised and accurate information about any expected physical changes before treatment.

Support and counselling by a specialist psychologist, psychiatrist or social worker may assist patients to make appropriate treatment decisions that incorporate the potential effect on their appearance.

Sexuality

Sexuality encompasses not only the physical aspects of sexual function, but also refers to how people view themselves and express themselves sexually and how they believe others see them.[28]

Some effects may be temporary, while others are permanent. Physical problems may include low libido, dyspareunia and impotence. Other issues affecting sexuality include coping with changes in appearance, low self-esteem and changes in roles and relationships. Issues of sexuality should be raised with all patients, and identification and referral to a counsellor with expertise in the area may be required.[29]

4.3 PRACTICAL NEEDS

Patients experiencing **social, financial or practical issues**, or who have minimal social supports, require referral to a **social worker or welfare worker**.

Social, financial and practical needs

Patients may experience a range of social, financial and practical needs, for example:

- additional costs related to nutrition
- patients travelling from rural and remote areas may require assistance with travel and accommodation, including assistance with the Patient Assistance Transport Scheme (PATS).

Referral to a social worker for further assessment and identification of appropriate funding support may be required.

Rural patients

Clinicians referring patients from rural and remote communities for treatment and support services need to ensure that the patient and their family members are informed about assistance for travel and accommodation costs.

A cancer care coordinator can provide a link to the multidisciplinary team for rural patients and specialist rural nurses can provide access to programs or interventions requiring psychological support. Remote technology providing patients with access to counselling, and enhancement of skills of rural nursing staff have been demonstrated to improve psychological support.

Advanced Care Planning

Advanced care planning allows people make their preferences for important health care and personal decisions known in the event that they lose decision-making capacity.

Advanced care planning should be discussed with patients following a cancer diagnosis and early in the course of their disease.[30] Advanced care planning may involve:

- discussing prognosis and possible future scenarios
- appointing of a substitute decision maker, and involving this person in on-going discussions
- deciding on current and future goals of care
- discussing patient choice for place of care
- documenting all discussions in an easily retrievable format.[31]

Patients should be supported to discuss life goals, values and personal views and choices about their preferred outcome of care with a trained professional, family and/or close friend.

Communicating with patients and carers

Patients and their carers require both verbal and written information to assist them in understanding details about the disease, reasons for and likely effects of diagnostic procedures, treatment options (including known risks and potential adverse effects), preventative actions, and information about effective coping strategies.

This information should be culturally appropriate, and individualised where possible. People for whom English is not a first language may require access to a qualified interpreter during verbal communication.

It is recommended that health professionals ask patients whether they want additional information and discuss how much they wish to be involved in decisions about treatment. Family members, carers and/or others should be encouraged to attend consultations to provide support. Specific instructions for self-care may help patients and family members to maintain their desired level of independence throughout the cancer care journey.[32]

All health professionals involved in a patient's care should know what information has been given to the patient. A record of information provided, along with the patient's preferences for information and involvement in decision-making, should be included in the notes and given to the patient's GP, together with a comprehensive summary of the management plan. Communication needs to be effective, with fast and efficient links between hospitals and primary care teams.[33]

4.4 RESPECTING DIVERSITY

People from Aboriginal and Torres Strait Islander backgrounds

People from Aboriginal and Torres Strait Islander backgrounds represent approximately 2% of the South Australian population.[34,35,36] Just over half live in rural and remote areas, particularly areas to the north of Adelaide.[32] This number is approximately double the state average of 25% for all South Australians.[32]

Aboriginal and Torres Strait Islander people are **more likely to present with advanced illnesses and may have multiple co-morbid illnesses** in addition to cancer. Aboriginal and Torres Strait Islander people also have **unique supportive care considerations** associated with their cultural concept of health and wellbeing, needs for the delivery of health services, the involvement of family and community in health care and the cultural understanding of cancer.

The unique consideration for the care of Aboriginal and Torres Strait Islander populations are detailed in Box 4.1 overleaf.

Box 4.1 Considerations for the care of Aboriginal and Torres Strait Islander populations

Aboriginal and Torres Strait Islander people have an holistic view of health and wellbeing

- Health and wellbeing encompasses all aspects of physical, emotional, social, spiritual and cultural wellbeing and a specific kinship with family.[37,38]
- There is a belief that wellbeing is determined socially, rather than biologically or pathologically.[39,40]

Structured and busy specialist clinical services may not cater well for the cultural needs of Aboriginal and Torres Strait Islander people

- This can contribute to a broader sense of disillusionment, indifference and apathy.
- Adherence to unfamiliar treatments that have unpleasant side effects may be poor, especially when there are competing pressures to meet community responsibilities.
- Without cultural and allied support, patients can become lost in unfamiliar health service environments they do not understand and where their needs are poorly understood.

Many Aboriginal and Torres Strait Islander people experience discomfort with health professionals of the opposite gender

- There are divisions in the roles of 'men's and women's business', including differences from western values in relation to reproduction and sexuality.[41]
- For example, it is often not appropriate for Aboriginal and Torres Strait Islander men to discuss any part of their body in the presence of a woman.[42]

Family and community involvement in health decision making is of paramount importance in Aboriginal and Torres Strait Islander culture

- Aboriginal and Torres Strait Islander culture places a high importance on kin, with holistic, family-based care being valued over segregated care.[43]
- Aboriginal and Torres Strait Islander health is more a collective consideration about family and community.[44,45]

Many Aboriginal and Torres Strait Islander people have a strong sense of home, and value being at home or close to home, particularly when ill[40]

- Aboriginal and Torres Strait Islander people have strong links to the land and a sense of 'home'.[46] This connection can be strong regardless of whether they are living a culturally-traditional lifestyle in remote locations, or in urban areas.
- Some patients may be reluctant to leave their community for treatment, even though this care may only be available in a remote urban setting.[44]

The concept of cancer may be poorly understood by some Aboriginal and Torres Strait Islander people, leading to a number of misconceptions

- It is notable that there is no word meaning 'cancer' in most, if not all Aboriginal and Torres Strait Islander dialects. Unlike many other illnesses, the concept of cancer is not embedded in traditional Aboriginal and Torres Strait Islander story-telling.[42]
- While cancer 'spreading' is widely understood, there is commonly a difficulty in understanding biomedical cancer language and pathology terminologies.[42]
- Common misconceptions are that cancer is contagious, only effects non-Aboriginal people, is curable without treatment, and that western treatment is ineffective.[42,47] It is commonly believed that a diagnosis of cancer is a death sentence, and that cancer is not treatable.

When **managing the health care of Aboriginal and Torres Strait Islander people**, it is important to include the input of those who are familiar with the Aboriginal and Torres Strait Islander culture and language.[48]

Staff with specific expertise in the management and support of Aboriginal and Torres Strait Islander patients are located in the larger metropolitan public hospitals. Aboriginal health nurses and Aboriginal hospital liaison workers are available to provide assistance following patient referral by the multidisciplinary team.

Engaging cultural and allied support can:

- help Aboriginal and Torres Strait Islander people navigate unfamiliar health service environments
- provide advice on culturally safe and respectful care to MDTs
- assist in understanding of the needs of Aboriginal and Torres Strait Islander people residing in rural and remote areas.

Culturally and linguistically diverse communities

Australia has one of the most culturally diverse communities in the world. In 2011, one in four of Australia's population was born outside of Australia.[49] It is therefore essential to consider the culturally and linguistically diverse needs of all people in relation to diagnosis, treatment and management of cancer.[50]

All patients are individuals and require a person-centred approach to care. Health professionals should **engage in respectful enquiry about preferences that intersect with health care**, including religious or spiritual values, cultural values, gender preferences and dietary requirements.[51] These aspects are connected to a successful health care experience and outcomes.

Within the culturally and linguistically diverse community, language barriers and lack of knowledge of the South Australian health care system limit access to health information and health care services.

The **unique considerations for the care of culturally and linguistically diverse populations** are detailed in Box 4.2.

Box 4.2 Unique consideration for the care of culturally and linguistically diverse populations

People may have a variety of **cultural perspectives or preferences**, including:

- patient preference to see a medical professional of their own sex
- myths and misconceptions about cancer diagnosis
- cancer may be a taboo subject perceived to cause discrimination, contamination, shame or retribution
- religion may play a fundamental role in the person's attitude towards their disease and treatment
- patients may have perceptions attributed to pain and suffering
- family and extended family have a central role in many cultures. Family members often share rights and responsibilities for decision-making and this may influence the choice of treatment.

Attitudes to caring and support may vary between and within cultures. It is important for health professionals not to make assumptions or stereotype individual patients.

Patients should be encouraged to seek support from family and friends, and from community, ethnic and religious organisations, if appropriate. Regardless of cultural background, wherever possible, patients should be offered the opportunity to bring a family member or friend with them to consultations and treatment. People may not be accustomed to the concept of support from external agencies, so this requires a sensitive and respectful approach.

4.5 FURTHER INFORMATION

- **Appendix H** lists **cancer resources and support groups** in South Australia
- **Appendix I** outlines the process for referral of patients to psychosocial care
- Cancer Voices South Australia, a volunteer organisation that **serves as a consumer advocate for people living with cancer**: http://www.cancervoicessa.org.au/
- National Comprehensive Cancer Network (NCCN), **Clinical Practice Guidelines in Oncology Cancer-Related Fatigue**: www.nccn.org
- Bolimos M, 2009, **Coping with cancer related tiredness (fatigue)**, published by the Royal Adelaide Hospital (Occupational Therapy Department and Cancer Centre)
- Eastern Cooperative Oncology Group assessment tool: http://ecog.dfci.harvard.edu/general/perf_stat.html
- Chris O'Brien Lifehouse at RPA, **An everyday guide to living with cancer in Australia**, includes a detailed Support Directory: http://www.lifesupportmagazine.co.au
- Resources tailored to the needs of **country cancer patients**, their families, carers, supporters and health professionals: http://www.countrycancersupport.com.au
- Cancer Council SA, **Cancer Helpline**: 13 11 20

RECOMMENDATIONS

- All patients diagnosed with Neuroendocrine tumours have access to culturally appropriate care and effective communication throughout the cancer pathway
- Health professionals should be trained in supportive care screening to encourage inclusion of supportive care issues as part of multidisciplinary care.
- The NCCN Distress Thermometer in automated electronic (touch-screen) format which may be used to screen patients with results scored and transcribed so that information is readily available to guide the consultation. QUICATOUCH and or similar programs can be effective in monitoring patients and increasing the number of timely and appropriate referrals for psychological treatment.

5. SUPPORTIVE CARE NEEDS OF PEOPLE AFFECTED BY NEUROENDOCRINE TUMOURS

The supportive care needs of patients with cancer vary in complexity and severity along the disease trajectory. Some supportive care needs are common to many cancers (See Chapter 4), while others are specific to neuroendocrine tumours.

The disease progression for a GEP NET can stretch over many years, and require multiple treatment modalities to limit tumour burden and alleviate symptoms. Patients require multidisciplinary coordination from different medical specialists, each with expertise in a specific area of managing NETs.

A study examining quality of life in a group of patients with GEP NETs identified four domains of specific supportive care needs:

- physical functioning
- flushing
- gastrointestinal effects
- depression.[52]

The specific supportive care needs of patients with GEP NETs will vary in complexity and severity along the disease trajectory. A supportive care assessment includes assessment of the physical, psychosocial, spiritual and information needs of the patient and the carer/family members.

5.1 SPECIFIC SUPPORTIVE CARE NEEDS FOR PATIENTS WITH NEUROENDOCRINE TUMOURS

Carinoid syndrome is the term used to describe a number of symptoms related to carcinoid tumours. Symptoms can include flushing and diarrhoea, and heart failure in more rare circumstances.

Supportive care needs associated with carinoid syndrome are discussed below.

Gastrointestinal effects

Chronic diarrhoea can occur in up to 80% of patients with carcinoid syndrome.[53] The stools in diarrhoea associated with carcinoid syndrome are watery and result from intestinal hypermotility and hypersecretion.[54]

The increase in gut motility in patients with carcinoid syndrome is likely to be caused by serotonin, which is released by certain types of NETs,[55] and stimulates small bowel and colonic secretions and motility.[56]

Secretory diarrhoea can be treated with loperamide and ondansetron. Supplementation of vitamins and nicotinic acid is recommendation with severe diarrhoea, cholestyramine for bile salt malabsorption-related diarrhoea, and oral pancreatic supplements for steatorrhoea following treatment with SSAs.[57]

Flushing

Flushing occurs in patients with carcinoid syndrome due to excess hormone levels from the GEP NET.

For many patients, flushing may be reduced by avoiding stress and foods known to provoke symptoms (e.g. alcoholic beverages, spicy meals). Octreotide is particularly effective in abolishing flushing and has been reported to improve carcinoid syndrome in up to 88% of the patients.[58]

Further information regarding evaluation of flushing disorder is discussed in Chapter 7 (Early Detection).

Carcinoid heart disease

Carcinoid heart disease occurs in approximately 50% of patients with carcinoid syndrome. It is caused by the release of vasoactive hormones (such as serotonin, histamine, tachykinins and prostaglandins) by metastatic carcinoid tumours in the liver.[59]

Detailed information on the clinical presentation, diagnosis and treatment of carcinoid heart disease is provided in **Appendix J**.

Nutritional support

The clinical syndromes and various management strategies for GEP NETs may lead to altered gut and pancreatic function, and result in nutritional consequences.[60]

Weight loss ranging from 9 to 21 kg over several months has been reported in one third of patients with pancreatic tumours and one fifth of patients with intestinal tumours.[61] Weight loss may be due to malabsorption, diarrhoea, anorexia or abdominal pain.

Although less common, overproduction of hormones can lead to unintended increase of body weight. For example, high levels of insulin produced by an insulinoma will cause hypoglycaemia. Eating resolves some of the symptoms of hypoglycaemia and this increased food consumption results in weight gain.[62]

Currently, there are no national (or international) dietary guidelines developed specifically for GEP NETs. Nutritional and dietary management is essential for GEP NET patients. An overview of nutritional care is provided in Table 5.1 and specific nutritional strategies developed to cope with symptoms and effects of treatment are outlined in **Appendix J.**

Table 5.1 Overview of nutritional supportive care

Nutritional goals	> Nutrition therapy is an adjunct to medical therapy to help resolve symptoms with possible nutritional implications such as; diarrhoea, bloating and loss of appetite. > Development of a nutritional care plan must be individualised for each patient to: o ensure adequate intake of different essential nutrients, and to avoid unnecessary dietary restrictions o improve general health and quality of life o maintain stable weight and avoid unintentional weight loss or weight gain o monitor any changes in body composition (i.e. loss of lean body mass).

Nutritional Screen	> Malnutrition screening should be undertaken on all patients at diagnosis by nursing, medical or other staff to identify patients who are malnourished or are at high risk of malnutrition. > This should trigger an automatic referral to the dietitian for early intervention. > Validated malnutrition screening tools recommended include the Malnutrition Universal Screening Tool (MUST) or Malnutrition Screening Tool (MST). > Nutrition screening should occur at repeated intervals through each stage of cancer treatment: o Weight should be recorded at least weekly for all inpatients, and recorded at each outpatients visit o A weight loss of >2kg within a 2 week period requires prompt referral to the dietitian, who will assess the patient within 1 week of referral
Nutritional Assessment	> Nutrition assessment should be conducted by the dietitian on referral using a validated nutrition assessment tool (e.g. the Patient generated Subjective Global Assessment (PG-SGA) or Subjective Global Assessment (SGA).
Nutritional Implementation	> Nutritional implementation includes counselling of the patient and/or caregivers to maximise nutritional intake and facilitate optimal symptom control. > Nutritional counselling is effective during phases of treatment and supportive care. > The dietitian with an expertise in NET management is an integral part of the multidisciplinary team, and will monitor these patients and provide ongoing dietary changes to address the various side effects of therapy.
Nutritional Requirements	> It is advised that all patients with one or more symptoms of carcinoid syndrome (flushing, diarrhoea, weight loss) or poor intake of food take standard multi-vitamin and mineral supplements, in conjunction with physician and dietitian advice. > Each individual should be monitored regularly as protein and energy goals may require adjustment, during various therapeutic modalities (e.g. systemic chemotherapy and combination therapy with SSAs.) > Patients may be recommended to increase intake of protein foods by 50–100%. Even in the absence of clinical symptoms (i.e. carcinoid syndrome) > Niacin deficiency can occur as a result of increased tryptophan metabolism into serotonin. Criteria for niacin supplementation include; elevated serotonin levels, flushing, weight loss, poor appetite/poor intake of food. > Pancreatic enzymes, such as pancrease, Creon are recommended for patients with steatorrhoea, particularly related to SSA therapy. > Patients who have undergone surgery are likely to suffer from a variety of post-surgical syndromes, which can lead to nausea, reflux, abdominal discomfort and diarrhoea. The impact of these problems can often be reduced by appropriate dietary adjustments. Effective clinical outcomes have been reported in patients receiving weekly to fortnightly dietetic intervention after treatment.[63]

Using SSAs (SSAs)

SSAs (SSAs) are used to in control symptoms of excessive hormone secretion in well-differentiated NETs. SSAs (Octreotide, Lanreotide and others) have been developed that work as receptor agonists to block hormone release.

SSAs can also be used as an adjunct to surgery, and reduce the risk of carcinoid crises and other severe events. The treatment goal in patients with functioning or metastatic tumours is to improve quality of life, while monitoring or alleviating the tumour-associated symptoms and possibly prolonging survival.[64]

Patients may be commenced on a short-acting SSA to assess treatment tolerability before converting to a long-acting preparation. Dose adjustments may then be required depending on clinical response.

Monitoring of plasma octreotide levels may be helpful in treating patients with symptom exacerbation, but its role in routine clinical practice is yet to be incorporated into practice guidelines, and more studies are needed.[65]

The antitumor effects of SSAs in combination with other agents and targeted therapies (e.g. interferon-α, mTOR inhibitors) and the overview of the use of SSAs in the prevention of carcinoid crisis is further discussed in Chapter 10.

RECOMMENDATIONS

> At risk patients should receive early nutritional intervention by an experienced dietitian in the management of NETs

6. PREVENTION AND MINIMISING RISK

Cancer is one of the most common causes of morbidity and mortality in South Australia, accounting for more potential Years Life Lost (YLL) than any other condition.[66]

Based on current incidence rates by age, at least one in three South Australians is diagnosed with cancer before 75 years of age.[51]

6.1 CANCER RISK FACTORS AND PREVENTION

Cancer represents Australia's greatest disease burden, ahead of cardiovascular disease. Cancer is a disease associated with ageing. With the number of people aged over 65 years set to double by 2051, cancer incidence is projected to continue rising.[67]

Current evidence indicates that approximately one-third of cancer deaths in Australia can be attributed to known and avoidable risk factors. Appropriate prevention strategies have the potential to reduce cancer incidence

Risk factors

The key **modifiable risk factors** for cancer are defined as the SNAPSS risk factors. These are:

- **S**moking/exposure to tobacco smoke
- **N**utrition (concerns about poor diet/nutrition)
- **A**lcohol (risky alcohol consumption)
- **P**hysical activity (inadequate exercise or being overweight)
- **S**un exposure (exposure to harmful ultraviolet radiation)
- **S**tress.

Prevention strategies

Prevention and early detection strategies include:[68]

- promotion of healthy lifestyles (stopping smoking, healthy diet, healthy weight, limiting alcohol intake)
- reducing risky behaviours (stopping smoking, 'sun smart' behaviours).

6.2 MAJOR RISK FACTORS FOR GEP NETs

Hereditary predisposition

Certain hereditary conditions can increase an individual's risk of develop a GEP NET, including:

- Multiple endocrine neoplasia type 1 (MEN-1)
- Multiple endocrine neoplasia type 2 (MEN-2)
- Von Hippel Lindau disease (VHL gene)
- Phacomatoses (neurocutaneous syndromes).

Familial clusterings of GEP NETs are rare, except for a small proportion associated with MEN-1.

Individuals who have hereditary conditions that may predispose them to developing a GEP NET should be screened for diagnosis and monitoring on an annual basis. More information about familial screening is provided in Chapter 7.

6.3 FURTHER INFORMATION

- The **Cancer Council SA** provides information on risk minimisation and healthy lifestyle:
  - **healthy diet, maintaining a healthy weight, being physically active**: http://www.cancersa.org.au/aspx/nutrition physical activity.aspx
  - **limiting alcohol**: http://www.acncersa.org.au/aspx/alcohol.aspx
  - **early detection** of cancer: http://www.cancersa.org.au/aspx/early detection.aspx
  - strategies for **relaxation**: http://www.cancersa.org.au/aspx/Relaxation.aspx
  - be **Sun Smart**: http://www.cancersa.org.au/aspx/sunsmart.aspx
- **Drug and Alcohol Services South Australia**: http://www.dassa.sa.gov.au
- **QuitSA:** http://www.quitsa.org.au/aspx/index.aspx
- **Cancer Council Australia**: http://www.cancer.org.au/cancersmartlifestyle.htm
- Australian **Indigenous Health Infonet**: http://www.healthinfonet.ecu.edu.au/

RECOMMENDATIONS

- Health promotion strategies should promote the importance of a healthy lifestyle for all South Australians.

7. SCREENING AND EARLY DETECTION

Early detection and prompt, appropriate referral for NETs is associated with improved treatment outcomes and survival rates.[69]

Due to the variable and nonspecific symptoms of GEP NET, detection and diagnosis is often delayed until the disease has progressed to an advanced state. Studies indicated that the median time from first appearance of symptoms to diagnosis is 9.2 years.[70]

7.1 SCREENING

The term 'screening' refers to population-based testing of people who do not have symptoms of cancer and are not at high risk of cancer to identify signs of disease requiring investigation before symptoms are apparent. No formal screening programs currently exist for GEP NETs.

Familial screening

Some people have hereditary conditions that may predispose them to developing a GEP NET. These people should be screened for diagnosis and monitoring on an annual basis.

Predisposition	Screening details
High risk of developing **MEN-1 associated GEP NETs**	> Should be offered a program of combined clinical, biochemical and radiological screening. The optimal radiological screening will depend on clinical judgement and individual patient preferences. > Minimum screening is annual plasma biochemical evaluation of a fasting GI tract hormone profile that includes measurement of gastrin, glucagon, vasointestinal polypeptide, pancreatic polypeptide, chromogranin A, and insulin with an associated fasting glucose level.[71] > Suggested minimum imaging is annual pancreatic and duodenal visualisation with Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or endoscopic Ultrasound.
Sporadic enteropancreatic NETs (insulinoma, gastrinoma) or **foregut** (bronchial, thymic NETs)	> Biochemical screening (serum calcium, PTH) for primary hyperparathyroidism as a marker of MEN-1, rather than genetic testing is indicated. > Genetic testing should be considered if the patient is young (e.g. aged under 30) or if the tumour is the presenting feature of MEN-1 and primary hyperparathyroidism has not yet developed.

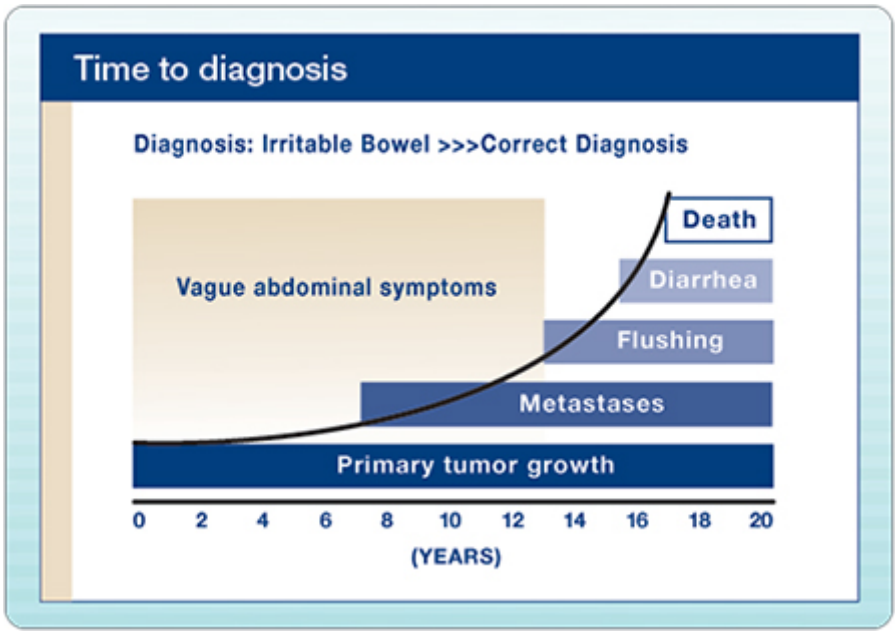
Familial Cancer Clinics are held at most major public hospitals in Adelaide and in some regional centres (Port Augusta and Mount Gambier). The Familial Cancer Unit at the Women's and Children's Hospital offers genetic counselling and genetic testing for South Australia. Endocrinologists and endocrine surgeons should be encouraged to liaise with the clinical geneticist. Informed consent is mandatory prior to genetic testing.[72,73]

7.2 SIGNS AND SYMPTOMS OF GEP NET

The database of the National Cancer Institute, Surveillance Epidemiology and End Results (SEER) analysis indicates that approximately 40% of patients with GEP NETs are diagnosed after the tumours metastasised, leading to delays in treatment.[74]

Many GEP NET patients often exhibit nonspecific symptoms, such as a **history of abdominal symptoms misdiagnosed as irritable bowel syndrome** (IBS). By the time of correct diagnosis, the tumour has metastasised, causing **symptoms such as flushing and diarrhoea**.

Figure 7.1 Common profile of time to diagnosis for GEP NETs



(Adapted with permission from: Vinik A, Moattari AR. History of Carcinoid Tumors. Use of somatostatin analog in management of carcinoid syndrome. *Am J Dig Dis Sci*. 34:14-27, 1989.)

Improving community awareness

Despite an increase in GEP NETs incidence, mainly due to improved diagnosis and treatment; awareness amongst health professionals and the general public remains low. In addition, the sporadic occurrence of NETs makes primary prevention difficult.

Survey results from a survey of 652 registered Australian Doctors revealed deficits in knowledge of the epidemiology, varied clinical presentation and behaviour of NETs, and a lack of awareness of Chromogranin A as a biomarker for diagnosis and monitoring.[75]

Targeting education to general practitioners based on awareness (and increased clinical suspicion) of the clinical presentation for patients with NETs is extremely important.

7.3 IDENTIFICATION AND REFERRAL OF PATIENTS WITH SYMPTOMS OF A GEP NET

Initial presentation

GPs should have a strong clinical suspicion of patients who present with **a combination of symptoms, or persistent symptoms, listed in the carcinoid syndrome profile guidelines,** including:

- repeated dry flushing on face
- frequent diarrhoea, even whilst not eating
- brochoconstriction (wheezing and asthma like symptoms)
- episodes of hypotension
- palpitations; new heart murmur or any valvular heart disease.
- abdominal pain
- unexplained weight loss

The collection of symptoms may be seen in 8–35% of patients with NETs.[76] Symptoms get worse with activity or with eating, drinking (e.g. chocolate or red wine).

Patients presenting with clinical symptoms suggestive of a GEP NET should receive **prompt referral to a specialist with expertise in the management of GEP NETs** for extensive diagnostic workup, with further referral to a NET multidisciplinary team.

Appendix F provides a guide to assist general practitioners gain awareness of the varied clinical presentation and behaviour of NETs.

Investigation and assessment

Investigations should be undertaken **after urgent specialist referral has occurred**, and may include:

- obtaining a careful history to identify symptoms related to excess hormone secretion by NETs
- review of relevant family history
- evaluation of a carcinoid tumour profile (e.g. detailed history of flushing, precipitating factors , duration, and associated symptoms such as diarrhoea and bronchospasm)
- undertaking a differential diagnosis of the classic symptoms of the ‘carcinoid syndrome’.

Investigations must not:

- replace urgent specialist referral for biochemical testing(5-HIAA and serum Chromogranin A level) to confirm diagnosis, and OctreoScan® for imaging and tumour staging
- delay urgent specialist referral.

Confirmation of diagnosis includes appropriate biochemical confirmation and tumour localisation studies following prompt referral to a specialist experienced in the management of NETs.

RECOMMENDATIONS

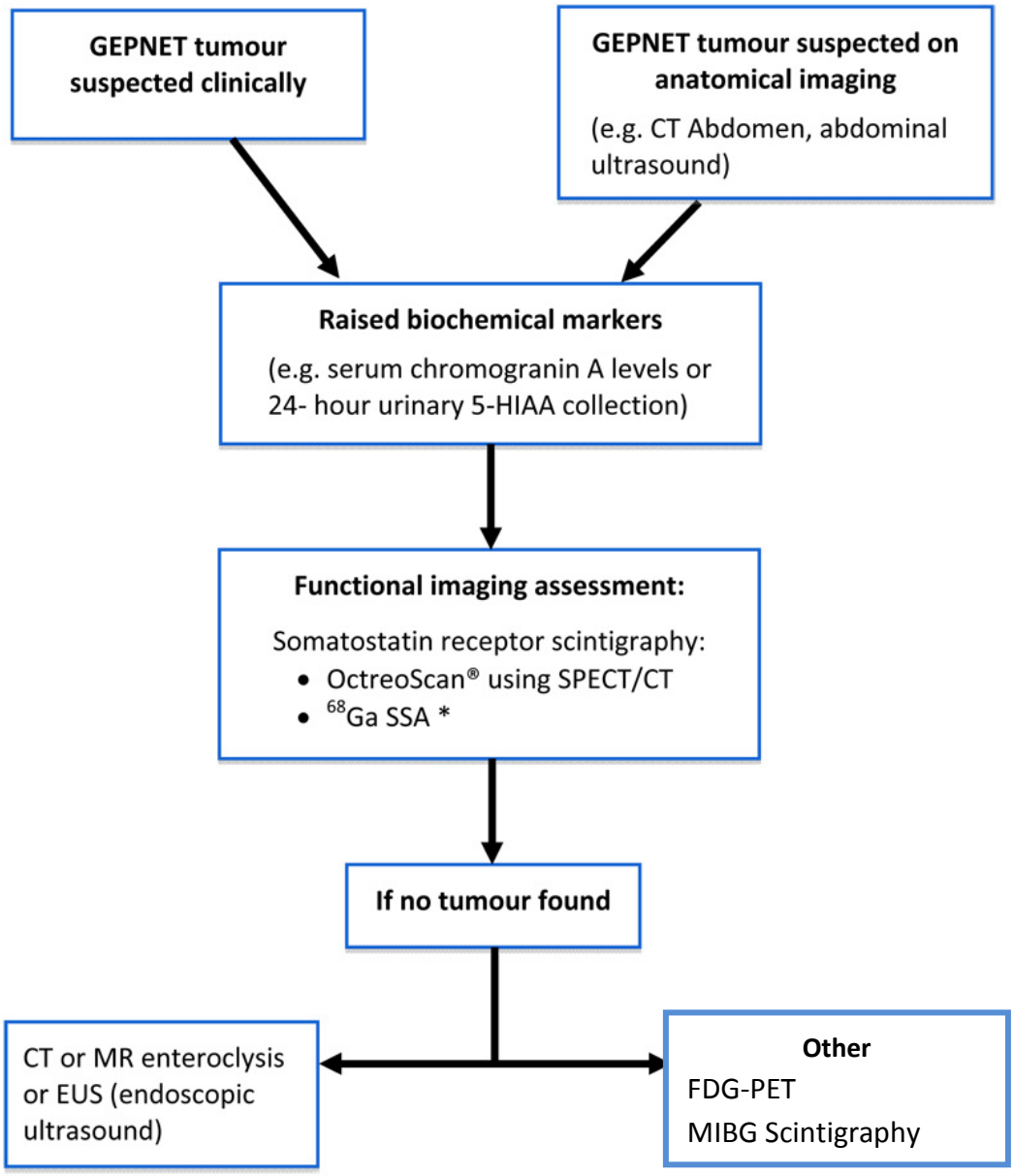
- The following patients should be referred for genetic testing; apparently sporadic enteropancreatic tumours, bronchial or thymic NETs (patients under 30), all Phaeochromocytomas or Paragangliomas.
- Improved education and awareness campaigns directed to the General Practitioner will hopefully improve timely referral to specialists with NET expertise. The utilisation of the UK NET Foundation Treatment Pathway Toolkit with localised SA content is recommended.
- Clear referral pathways for availability for specialists in NET management and membership to SA GEP-NET MDM (e.g. endocrinology services, medical oncologists, surgeons) should be web based. This will assist in providing information on available services and guidelines for GP's for the management of NETs.

8. DIAGNOSIS AND STAGING

In cases of a suspected GEP NET, it is essential to confirm the diagnosis and establish the histopathological sub-type of the tumour.

Diagnosis of GEP NETs is based on specific clinical symptoms, peptide and amine secretion, and specialised radiological and nuclear imaging. Detailed histology is then the next gold standard in diagnosis.[77]

Figure 8.1 Diagnostic pathway for a GEPNET



8.1 PATHOLOGICAL INVESTIGATIONS

Biochemical markers

Neuroendocrine tumours frequently demonstrate elevation of one or more biochemical markers (Table 8.1) which may be used to:

- assist with initial diagnosis
- monitor the course of disease
- measure tumour response to therapy.

Some markers may be associated with a syndrome due to hormone excess. Positive immunohistochemistry for a marker may not be associated with measurable hormonal overproduction and a syndrome. Hormone production may alter over the course of disease.[78]

Table 8.1 Biochemical markers of GEP NETs

Biomarker	Detail
Chromogranin A (CgA)	> Serum Chromogranin A (CgA) is the **most established NET marker** for monitoring progression or treatment response. > CgA stabilises intracellular vesicles and regulates post-translational protein processing. It is elevated in between 60% and 100% of patients with NETs. > It is proportional to tumour size, and may be useful to estimate prognosis, monitor response to therapy and possibly for monitoring for progression.[79] > CgA should be used in combination with imaging to measure tumour bulk and response. > CgA can be used for monitoring: o for relapse in patients with completely resected disease o patients who have had metastatic disease treated, for the evaluation of response or progression. [80] > Reference intervals and individual patient results differ significantly between different CgA assays and cannot be directly compared. [81] Serial measurements should be performed using the same assay. If assays are changed, patients should undergo a new baseline measurement.[82] > CgA may be elevated in several non-NET conditions, including renal impairment, chronic liver disease and heart failure.[83] > CgA is not a measure of tumour bulk for gastrinomas; therefore other hormonal markers need to be measured.[84]

Biomarker	Detail
5-HIAA (5-hydroxyindoleacetic acid)	> Midgut carcinoids are likely to produce carcinoid syndrome with 5-HIAA elevation. > Fore- and hindgut NETs produce less serotonin than midgut tumors. The sensitivity for 5-HIAA is lower in patients with midgut carcinoid tumors without the carcinoid syndrome.[85] > 24-hour urine 5-HIAA needs to be collected with strict dietary and medical restrictions.[86] Certain foods, medications and medical conditions can lead to false high or low levels (See Box 8.1) > Urine 5-HIAA has a high degree of biological variation (intra-individual CV = 20.3%)[87]. It may therefore be necessary to repeat the test especially if it is being used to make a diagnosis.

Box 8.1 Substances which interfere with urine 5-HIAA measurements

Falsely high levels

> Tryptophan-rich foods: tomato, avocado, pineapple, banana, kiwi fruit, plum, walnuts, pecans, eggplant

> Drugs: amphetamines, paracetamol, caffeine, nicotine, phenobarbital, ephedrine, reserpine, phentolamine, melphalan, fluorouracil, cisplatin, glyceryl guaiacolate (found in many cough syrups)

> Non-NET medical conditions: coeliac disease

Falsely low levels

> Drugs: ethanol, methyldopa, levodopa, phenothiazines, aspirin, heparin, methyldopa, monoamine oxidase inhibitors, isoniazid

> Non-NET medical conditions: end stage renal failure

Measuring biochemical markers

Both CgA and urinary 5-HIAA are **proportional to disease bulk and disease progression**. However CgA is the more sensitive of the two in all regards and also in detecting small recurrences after radical therapy.[98]

Urinary 5-HIAA levels are correlated with the risk and presence of carcinoid cardiac disease. There appears to be some correlation between urine 5-HIAA and carcinoid crisis, but literature is scant. Tumour bulk may also be a factor.[88]

Timing for biochemical marker testing are outlined in Table 8.2.

Table 8.2 Timing for measuring biochemical markers in GEP NETs

Timing	Detail
Pre-operative measurement	> CgA and urine 5-HIAA should be measured prior to surgery in asymptomatic patients. Measurement of other markers should be considered, depending on the tumour site. > If the patient is asymptomatic and CgA normal, there is no need to do additional tests as everything else is likely to be normal.[89]
Radically resected disease	> Tumour markers should be measured at 6 months and 12 months and then yearly, lifelong. > Where there are poor prognostic factors (e.g. high grade tumours) tumour markers should be measured every 6 months, lifelong.
Metastatic but asymptomatic disease	> Measure tumour markers every 3 months initially and then less frequently if stable > Urine 5-HIAA should always be measured at baseline: o if it is elevated, do annual Urine 5-HIAA estimations o if Urine 5-HIAA is negative at baseline there is no need to measure again.[90]

8.2 DIAGNOSTIC IMAGING

Once a detailed assessment of a patient's symptoms and laboratory results has been conducted, a multimodal approach using combinations of imaging studies will facilitate tumour localisation and extent of disease.

Indications for imaging

Imaging for detection and diagnosis of GEP NETs is indicated in the following situations:

- **Screening of at-risk populations.** Patients with a family history of MEN-1 syndromes can be considered for screening (ideally with MRI), according to established MEN syndrome guidelines.[91]
- **Primary lesion detection.** Investigations for localising and measuring the primary tumour are useful for surgical planning. A multimodality approach with CT, MRI and somatostatin receptor scintigraphy (SSRS) is recommended. Gallium-68 somatostatin receptor positron emission tomography (PET)/CT is recommended for the detection of an unknown primary.[92]
- **Staging/assessing extent of disease.** Evaluation of the extent and location of metastatic disease may revise staging, selection and planning of therapy.[93]
- **Biological characterisation.** Assessment of the nature of cellular biology, particularly when considering molecular targeted therapies for patients with inoperable or metastatic disease.[94]
- **Follow-up and assessing efficacy of treatment.** The imaging modality of choice should be the one that best demonstrated the tumour at diagnosis. The follow up interval depends on tumour grade and clinical circumstances.[95]

Structural and functional imaging is indicated at one or more points during the course of the disease. The combined use has proven to increase the accuracy of staging of the diagnosis of NETs.[96] However, the wide variation between patients in the course of disease and treatment precludes setting of prescriptive imaging schedules.[97]

Table 8.3 Structural imaging modalities for GEPNETs

Modality	Detail
CT and MRI	> Typically the initial imaging modality used in the evaluation of patients with suspected GEP NETs. > Used to determine anatomical location, extent of tumours, and for monitoring response to treatment. > The scanning protocol and imaging characteristics differs widely according to the anatomical location, histological grades and treatment status of the tumour. o **CT enteroclysis (CTE)** is the image modality of choice for the diagnosis and localisation of primary small bowel tumours, with reported sensitivity and specificity of 85% and 97% respectively.[98] o **Magnetic Resonance (MR)** enteroclysis may be considered as a radiation-free alternative (especially for those who are young) for small bowel assessment. o In the event that CT/MR enteroclysis is not available, **CT/MR enterography** with or without intravenous contrast should be considered as acceptable alternatives.[99,100] o **Multi-slice CT (MSCT)**[101] is the image modality of choice for evaluating liver lesions. o If liver lesions are in doubt, **DCE-MR** (MRI with imaging agent such as Primavist) may be useful. However, MRI for this purpose is neither funded under the MBS, and is not considered a pre-requisite for surgery.[102]
Upper GI endoscopy with ultrasound capability	> Endoscopy is the investigation of choice for the detection of small, primary gastric, duodenal and colorectal GEP NETs.[103] > Upper GI endoscopy when combined with endoscopic ultrasound (EUS), has been adapted for staging minimally invasive biopsies of structures close to the lumen of the upper GI tract; particularly lesions in the pancreas (those in the head and body), lesions in the duodenal wall, and adjacent regional lymph node metastases. > EUS-guided biopsy is operator dependent, with results of sensitivities as high as 79–100% (but low as 30–60% in submucosal lesions), and should be referred to centres with significant expertise in such studies.[104]

Table 8.4 Functional imaging modalities for GEP NETs

Modality	Detail
Single Photon Emitting Agents	There are three common forms of single positron emitting imaging ***Indium-111 Pentreotide (OctreoScan®)*** > The only radiolabeled SSA to be listed on the Australian Register of Therapeutic Goods (ARTG) > It is reimbursed under the Medicare Benefits Schedule for: o detection of suspected gastroenteropancreatic endocrine tumour, based on biochemical evidence, but negative or equivocal conventional imaging o exclusion of additional disease sites in patients with surgically amenable gastroenteropancreatic endocrine tumour based on conventional techniques. > Should be considered in select patients suitable for molecular targeted therapy using SSAs as either long-acting or radiolabeled agents within the broader context of current therapeutic options. > All patients on long-acting SSAs should have these ceased for a minimum of 4 weeks prior to OctreoScan® imaging. > Involves an intra-venous injection followed by imaging at several time points over 24 – 48 hours. > High-cost and limited availability. ***Iodine-123 MIBG or Iodine-131 MIBG*** > Meta-iodobenzylguanidine (MIBG) is concentrated to varying extent by up to 70% of carcinoid tumours. > When radiolabelled with iodine-123, MIBG is also used in the diagnostic workup of carcinoid tumours. [105] > Diagnostic use is generally confined to those tumours that do not express somatostatin receptor subtypes 2 and 5 (sst-2 or sst-5 receptors). > Some institutions use iodine-131 MIBG as a palliative therapeutic option. This agent is neither approved nor funded for such use." [106] ***Lutetium-177 Octreotate*** > Used as therapeutic beta-emitting radio-isotope but also emits gamma photons, which can be used for diagnostic imaging. > When used purely as a diagnostic imaging agent it has a similar radiation dose to the patient as Indium-111 OctreoScan. > There is no Medicare funding for this agent and it is only available in the few centres in Australia that provide Lutetium-177 Octreotate therapy.

Modality	Detail
Positron Emission Tomography (PET)/ Computed tomography (CT)	> PET/CT imaging (Positron emission tomography/Computed tomography) is not currently approved or funded for the evaluation of GEPNETs, but can be useful to both detect and biologically characterise lesions. > Physicians and patients should be aware that, based on preliminary data, PET/CT is probably the functional imaging technique of choice for diagnosis and staging of GEP NET at the present time. > Availability is limited, formulations are often non-standardised, and access is generally restricted to research institutions. > PET/CT can be performed using a number of different tracers including: o 18F-fluorodeoxyglucose (FDG) o 68Ga- pentetreotide o 18F-dihydrooxyphenylalanine (F-DOPA) o 11C-5-hydroxytryptophan o 64Cu-octreotide.
Nuclear Medicine MIBG imaging in Phaeochromocytoma	> MIBG enters NET cells by an active uptake mechanism via the epinephrine transporter and is stored in the neuro-secretory granules. > In imaging, MIBG is labelled to either iodine-131 or Iodine-123, and is used: o to detect extra-adrenal, metastatic or recurrent sites of disease o when negative or equivocal CT or MRI findings o to confirm the biochemical activity of Ct/MRI detected masses o when equivocal biochemical results. > Low-grade physiological uptake of MIBG can be seen in up to 30% of normal adrenal medullas. > A number of drugs such as labetolol, reserpine, calcium channel blockers and some tricyclic anti-depressants can interfere with the uptake of MIBG and need to be stopped prior to the study.

8.3 HISTOPATHOLOGY REPORTING

Synoptic reporting is recommended to standardise content and enhance consistency in pathologic diagnosis and patient management. Currently, the Royal College of Pathologists Australasia (RCPA) does not have any Structured Reporting Protocols for neuroendocrine tumours.

Pathologists are advised to refer to protocols developed by the Royal College of Pathologists, United Kingdom or the College of American Pathologists.

The **pathological report should include:**

- tumour site and size
- multifocality
- lymphovascular and perineural invasion
- extent of local invasion
- surgical margins
- nodal status
- presence of background disease.

Tumour grading

The tumours should be graded according to the World Health Organisation (WHO) ENETs grading system. This system stratifies according to mitotic count and Ki67 labelling index.

It should be noted that in some grading systems, there are differences according to the site of the tumour.

Tumour staging

Staging is site specific and should be in the form of the TNM system included in the 7th Edition of the Staging Manual of the American joint Committee on Cancer (AJCC) or the ENETs staging system, as long as the system used is explicitly stated.

8.4 FURTHER INFORMATION

- **Guidelines for the diagnosis and management of gastroenteropancreatic neuroendocrine tumours (GEPNETs):**
  - http://wiki.cancer.org.au/australia/COSA:NETs_guidelines/Biochemical Markers
  - http://wiki.cancer.org.au/australia/COSA:NETs_guidelines/Imaging
  - http://wiki.cancer.org.au/australia/COSA:NETs_guidelines/Histopathology
- Chapter 12: Follow up care for GEPNETs
- **E-NET guidelines:** http://www.neuroendocrine.net/.
- The Queen Elizabeth Hospital Nuclear Medicine Department, Information Sheet: **Receptor Targeted Imaging with Indium Octreotide (OctreoScan®) or Lutetium Octreotate**

RECOMMENDATIONS

- The cost of CgA is not covered by Medicare. For patients not treated in a public hospital, there will therefore be an out-of-pocket cost for this test, currently about $30. CgA is a key element of investigation, and testing should be available in South Australia , with Medicare reimbursement
- CgA results should be available in accessible electronic format within 14 days
- Patient samples of Serum CgA should be measured in the same lab consistently (and over time) to reduce potential for variability in results.
- That all South Australians have timely access to radionuclide peptide imaging agents, including Ga-68 labelled SSAs, which are considered to be the most sensitive radio-nuclide agents for the diagnosis, staging/restaging and assessment of response to therapy
- To increase access of patients with neuroendocrine tumours to appropriate imaging by:
  - the Medicare descriptor for OctreoScan Scintigraphy be modified to allow use of imaging to assess suitability for unlabelled and Radio-labelled SSAs therapy
  - the MBS be modified to allow re-imbursement for the use of other radio-nuclide imaging agents in neuroendocrine assessment, including Gallium-68 labelled SSAs and lutetium-177 octreotate.

9. PRESENTATION AT NEUROENDOCRINE TUMOUR MULTIDISCIPLINARY TEAM MEETING

Multidisciplinary team (MDT) members meet regularly to provide treatment recommendations, while taking into account the clinical and psychosocial aspects of patient care, individual patient preferences and circumstances.[107]

9.1 MULTIDISCIPLINARY TEAM MEETINGS

MDT meetings provide the opportunity for:

- discussion of all new patient presentations
- review of patients following surgery, neoadjuvant treatment and tumour recurrence
- discussion of clinical trial access and patient eligibility.

The benefits of multidisciplinary care for patients, families and clinicians are well documented. Further information on multidisciplinary care is provided in Chapter 3 Multidisciplinary and coordinated care, and in **Appendix B.**

Treatment and supportive care within the MDT should be coordinated, ensuring that the patient, GP and MDT members are clear about individual responsibilities for coordination of care.

Referral to an MDT meeting

The referring specialist to the MDT meeting is responsible for patient care until care is formally referred or passes to another practitioner. Any health professional can refer to the MDT meeting for additional treatment, discussion and management planning should complexities arise along the care continuum.[108] The referral process for presentation at an MDT meeting is outlined in Box 9.1.

Box 9.1 Referral for presentation of a patient with GEP NET cancer at an MDT meeting

- Patient consent must be obtained (written or verbal) before presentation at the GEP NET MDT meeting
- Referring clinician must liaise with MDT meeting Chair or delegate (usually MDT meeting coordinator)
- Referring clinician completes MDT meeting referral form (specific to each hospital) and ensures submission by the stated date and time. This is usually at least 48 hours prior to the meeting, as the list is finalised by the MDT meeting coordinator 1 day prior
- Referring clinician must ensure radiology is available for the meeting. The MDT meeting co-ordinator may be able to facilitate this when provided with relevant information to source radiology images/pathology (location, day of imaging for private films)
- Routine diagnosis and staging should be complete prior to the MDT meeting
- Access to technology includes; videos, clinical photographs, diagnostic endoscopy/video documentation

Reporting of an MDT meeting

The MDT meeting should be held weekly to allow for timely discussion of patients, avoid delay in management of patients and provide timely feedback to patients.

At the meeting, individual patient data from clinical, medical imaging and pathology sources are reviewed to provide a tissue diagnosis and TNM stage. MDT meeting discussion aims to develop a consensus treatment plan based on clinical characteristics, individual patient preferences and circumstances, tissue diagnosis and TNM stage.

The treatment consensus is recorded by the MDT meeting Chair and is communicated to the referring clinician for discussion with the patient (Box 9.2).

Box 9.2 Patient MDT meeting summary

- Referring documentation records should be:
  - kept by the MDT meeting Chair / MDT meeting coordinator / MDT meeting administrative support
  - filed in the patient's clinical record
- **MDT meeting recommendation proforma** (Oacis or EPAS clinical summary) should include:
  - treatment and management recommendations
  - clearly defined goal of treatment
- Summaries and letters need to be communicated in a timely manner with the patient's GP and private practitioners who do not have access to EPAS.
- The primary treating specialist (that is, the specialist with whom the patient primarily discusses decision making for their clinical management) should be documented
- The signature of the MDT meeting Chair is required on the MDT meeting recommendation proforma, and these record should be made available to the referring clinician and inserted into the patient clinical record
- The MDT meeting coordinator should retain the Chair's copy of the agenda in a secure manner for audit purposes

9.2 GEP NET MULTIDISCIPLINARY TEAM

The GEP NET MDT comprises both core members who attend all meetings and associate team members who may attend on referral for treatment for cancers that may need to be managed jointly (Table 9.3).

Table 9.3 Membership of the GEP NET MDT

Core members	Members via referral	
Medical oncologist	Psychologist	Consultant geneticist
Endocrinologist	Gastroenterologist	Radiation oncologist
Nuclear medicine specialist	Cardiologist	Palliative care consultant
Surgeon	Geneticist	Specialist nursing staff
Radiologist/ Interventional radiologist	GP	Geriatric cancer assessment team
Pathologist	Dietitian	Adolescent and young adult cancer assessment team
+/-Specialty registrar	Social Worker	CALD and ATSI services
GEPNET nurse coordinator	Pharmacist	Acute/chronic pain service
	Clinical trials coordinator	Rural/remote liaison nurse

9.3 COMMUNICATION OF MDT MEETING OUTCOMES

Following presentation at the MDT meeting, the referring clinician or delegate is responsible for discussing the meeting recommendations (including rationale, aims, likely beneficial and adverse side effects and other treatment options) with the patient / family / carer within 3 working days.[51]

The final treatment plan, taking into account the patient's preferences, should be documented and communicated to the patient, their family and treating clinicians. Details of changes due to patient preferences or further results should be documented in the patient record by the referring clinician and communicated to the GP and other relevant treating clinicians.[51]

9.4 FURTHER INFORMATION

- **Appendix K:** GEP NET MDT Terms of Reference
- Cancer Clinical Network **Multidisciplinary Team Meeting Terms of Reference**: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/health+reform/clinical+networks/cancer+clinical+network
- **Medicare items available** for cancer treatment: www.cancer.org.au/home.htm

RECOMMENDATIONS

- GEP NET MDM meetings should be appropriately resourced including a MDM coordinator and /or administrative support (administrative A03 level).
- Development of an action plan for long term support of research of GEP NETs at a national level is required. Adaptation in South Australia of "The Forgotten Cancers Project" from the Cancer Council of Victoria (the first epidemiological-based research project in the world focussing on less common cancers) is one project that aims to raise the profile and understanding of GEP NETs, and help to advocate for Federal funding.
- Web based information for the SA GEP NET MDM, and contact details should be linked to SA GEP NET Audit.
- All patients with a GEP NET diagnosis should be discussed prospectively at a multidisciplinary meeting within 4 weeks of a confirmed diagnosis.
- A copy of the treatment plan, including any revisions made following patient discussion, should be sent to the referring GP within 3 working days. A copy should also be placed in the patient's case file, and also sent to the referring clinician.
- Where possible, patients should be offered clinical trial enrolment.

10. TREATMENT

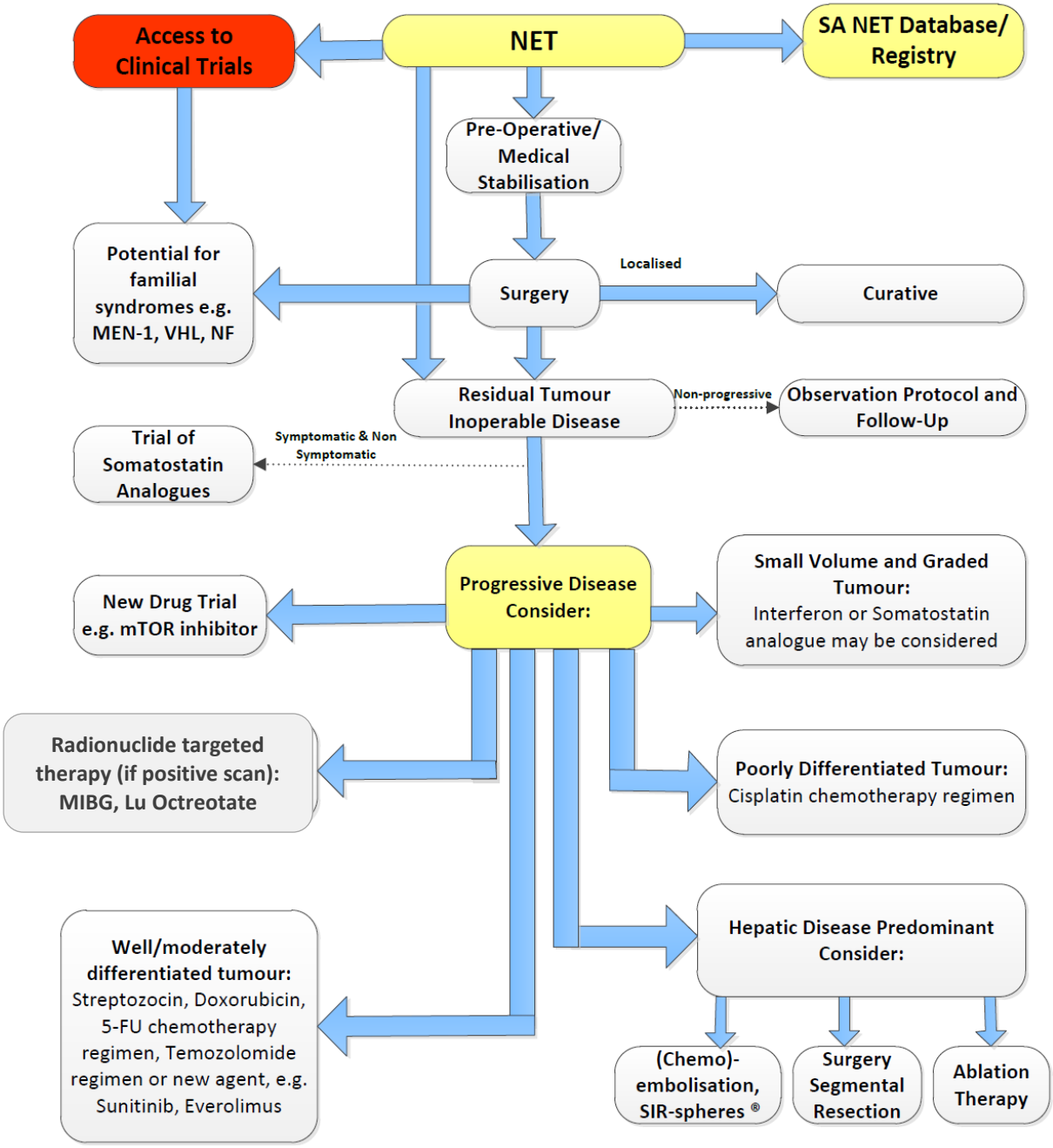
Following staging and recommendations from multidisciplinary discussion, patients with localised GEP NETs should be considered for surgical resection.

This chapter provides a high-level overview of the approach to treatment and management of GEP NETs.

Treatment for GEP NETs should be guided by a multidisciplinary treatment plan that meets immediate or long term objectives, within a multidisciplinary framework.[109]

Following pre-operative stabilisation, surgical resection is considered standard care for GEP NETs. The goal of surgical treatment is to obtain tissue for diagnosis, document the extent of disease, remove tumour for potential cure, palliate symptoms and to prolong survival.[110]

Figure 10.1 Overview of the GEPNETs treatment pathway



The role of clinical trials

The evidence base for GEP NETs is low, with few randomised controlled trials of treatments. It is still important to offer enrolment for clinical trials, where appropriate.

A number of websites provide information about clinical trials for consumers. The Consumers Health Forum of Australia have published a *Consumer Guide to Clinical Trials,* which can be accessed at: https://www.chf.org.au/pdfs/chf/CHF-Clinical-trials_COL__WEB.pdf

10.1 SURGICAL TREATMENT FOR GEPNETs

Primary surgical resection of the tumour and regional lymph nodes is the only curative treatment for gastrointestinal NETs. Surgical resection is possible in 20% of patients.[111] The surgical treatment plan and general approach for different types of GEPNETs is outlined in Table 10.1.

Other surgical approaches may also be employed to manage metastases, side effects or symptoms of GEPNETs. These are detailed in Table 10.2.

The conduct of surgery with intent to cure depends on:

- extent of local and distant tumours
- identification of synchronous non-NETs
- recognition of fluid and electrolyte depletion from diarrhoea.

All patients with a non-pancreatic NET with carcinoid syndrome or a raised CgA should have:

- consideration of pre-operative blockade with SSAs
- assessment for carcinoid heart disease with echocardiography

Clinicians considering surgical treatment for hypergastrinaemic patients should be aware that most patients are not given SSAs, but are given PPIs for treatment. [112]

Table 10.1 Surgical Treatment Plan[113]

Neuroendocrine tumour	Treatment

Gastric	- Normal gastrin levels (Type 3)
	  - radical gastric resection and lymphadenectomy
	- Hypergastrinaemia (Type 1)
	  - tumour or tumours ≤ 1 cm: endoscopic resection where feasible, or observation
	- tumour or tumours > 1 cm: surgical resection
	- Zollinger-Ellison syndrome (Type 2)
	  - Tumours ≤ 2 cm consider proton pump inhibitors +/- SSAs
	  - Tumours > 2 cm consider gastric resection

Duodenal (excluding gastrinoma)	- **Tumours ≤ 1 cm**: endoscopic or local resection - **Tumours > 1 cm**: resection of applicable duodenum plus draining lymph nodes (Possible options would include local resection, partial duodenectomy or pancreaticoduodenectomy)

Neuroendocrine tumour	Treatment
Pancreatic (functioning & non-functioning)	> Resection of tumour and peripancreatic nodes including pancreaticoduodenectomy where appropriate
Pancreatic (Insulinoma)	> Enucleation where possible: distal or central pancreatectomy if anatomically unsuitable > Blind resections not recommended
Gastrinoma	> Duodenal / Occult o Observation OR o Duodenectomy with enucleation and periduodenal lymphadenectomy > Pancreatic head o Tumours ≤ 5 cm and non-invasive; enucleation where possible with periduodenal nodal dissection o Tumours > 5 cm or invasive; pancreaticoduodenectomy with peripancreatic nodal dissection > Pancreatic body / tail o Enucleation / resection
Jejunal / ileal	> Segmental resection with wide lymphadenectomy where possible.
Appendiceal	> **Tumours ≤ 2cm :** simple appendicectomy > Tumours > 2cm, positive margins, positive nodes or deep meso-appendiceal invasion, goblet cell carcinoid (+ bilateral salpingo-oophorectomy for goblet cell carcinoid): Right hemicolectomy
Colon	> Local resection using standard oncological criteria
Rectal	> **Tumours ≤ 2cm:** endoscopic or trans-anal excision > **Tumours > 2 cm:** anterior resection or abdominoperineal resection (APR)
Hepatic metastatic disease	> Resection should be considered in the presence of resectable primary and hepatic metastatic disease

Table 10.2 Other surgical approaches to the management of GEP NETs

Surgery	Detail
Prophylactic cholecystectomy	> Prophylactic cholecystectomy should be considered at laparotomy to prevent complications from gallstone disease as a result of long term SSA use. > It may prevent local complications from liver directed therapy.[114]
Lung (Bronchopulmonary NETs)	> Surgical resection is the preferred treatment of bronchopulmonary NETs in those patients with adequate functional pulmonary reserve. > Bronchial ultrasound may assist in determining the resection margin. > The surgical approach chosen is dependent on the size, location and tissue type. > **Tumours <2cm:** Conservative resection via a wedge or segmental resection has been shown to result in low recurrence rates and excellent long term survival > **Tumours>2cm:** may require more extensive surgical resection with a Lobectomy.[115]
Resectable metastatic disease	> Resection of primary and metastatic disease should be considered if pre-operative assessment suggests that all the disease is completely resectable.[116]
Debulking surgery	> The aims of debulking resection include: o acceptable operative morbidity and mortality o palliation of symptoms o prevention of obstruction. > Assessment of resectability should be by a gastrointestinal/hepatobiliary surgeon experienced in the treatment of neuroendocrine disease: o history for each patient is very different and therefore consideration of the tumour grade, Ki67 proliferation index, molecular imaging characteristics, comorbidites and symptoms should be used in the decision making process. > Debulking resections can be justified in exceptional palliative situations; however removal of at least 90% of the tumour volume is necessary.[117] If the primary tumour is still present, it should be removed at this time as well.[118]
Orthotopic Liver Transplantation (OLT)	> Liver transplantation for metastatic disease isolated to the liver has been used for patients with disease that is unresponsive to medical therapy and not otherwise treatable. [119] > The results for transplantation of such patients in Australia have been poor. > Liver transplantation is generally not recommended, but may have a role in exceptional circumstances.

10.2 TREATMENT OF GEP NETs WITH LIVER METASTASES

One of the major prognostic factors that dramatically affects survival in patients with GEP NETs is the presence of liver metastases. Due to the portal venous drainage of the gastrointestinal tract and pancreas, haematogenous spread to the liver is quite common. Dissemination from a primary GEP NET to the liver parenchyma will occur in up to 75% of patients.[120]

Meeting the goals of GEP NET management in patients with liver metastases (symptom control, biochemical control, objective tumour control and quality of life improvement) relies on a multidisciplinary environment with access to diagnostic scintigraphy, interventional radiology, nuclear medicine, surgical and medical oncology expertise. Treatment options can include:

- surgery
- medical therapies
- targeted nuclear medicine (e.g. peptide receptor radionuclide therapy)
- interventional radiological treatment.

Liver directed therapies may be contraindicated by pre-existing hepatic insufficiency. Selection of patients must be based on a combination of morphologic and functional imaging to establish the presence and extent of extra-hepatic disease.

Table 10.3 Treatment approach to GEPNET liver metastases

Treatment	Details
Surgery	> Surgical resection remains the gold standard in the treatment of NET liver metastases, achieving a survival rate of 60 – 80% at 5 years with low mortality (0 – 5%) and acceptable morbidity (close to 30%). > The minimal requirements for resection with **curative intent** are: o resectable well-differentiated liver metastases with acceptable morbidity and < 5% mortality o absence of right heart insufficiency o absence of extra-abdominal metastases o absence of diffuse peritoneal carcinomatosis confirmed by PET/CT using 68 GA-SSA".[121]
Ablative techniques	***Percutaneous Microwave Ablation (MWA)*** > Purcutaneous microwave ablation has shown to be effective in controlling local tumour growth and relieving symptoms of NET liver metastases. > Complications from MWA are usually mild and may include pain and fever. Other potential complications include those caused by heat damage to normal tissue adjacent to the tumour, structural damage along the probe track, liver enzyme elevation and liver abscess. > The National Comprehensive Cancer Network (NCCN) 2009 guidelines, list MWA as one treatment option (along with RFA) for liver metastases as hepatic regional therapy in NETs, when there is unresectable disease and/or distant metastases. > Clinical experience with MWA in South Australia occurs at the Flinders Medical Centre and the Royal Adelaide Hospital.

Treatment	Details
	Percutaneous Radiofrequency Ablation > Percutaneous Radiofrequency Ablation has been shown to be effective in both relieving the symptoms of NET liver metastases and achieving reduction of tumour mass in functioning and non-functioning metastases. > Options include laparoscopic and percutaneous approaches (with the benefit of CT or MRI guidance), depending on the location and extent of metastatic spread). > The combination of surgical resection and RFA provides the opportunity to achieve complete tumour removal. [122]
Transcatheter arterial chemoembolisation	***Transarterial hepatic chemoembolisation (TACE)*** > Liver metastases are highly vascular with an arterial supply that if occluded will lead to ischemia. > TACE has been developed based on the principle that ischemia of tumour cells increases sensitivity to chemotherapeutic substances. > Selective TACE with hepatic artery occlusion can be applied in the treatment of liver metastases from all types of neuroendocrine G1/G2 tumours,[123] but appears to benefit patients with pancreatic NETs. Median survival rates after TACE in patients with liver metastases is over 3 years with progression free survival of around 18 months. > Postembolisation syndrome (including nausea, vomiting, abdominal pain and fever) is the most common side effect, and symptoms usually last for 24–72 hours. > Major side effects include: gallbladder necrosis, hepatorenal syndrome, pancreatitis, liver abscess and formation of aneurysms. > The predominant benefit of the procedure is palliation of symptoms, with 70–90% of patients having high response rates in reduction of hormonal levels, symptoms and a reduction in tumour burden.[124] ***Drug Eluting Beads (DEB)*** > Deliver a chemotherapeutic agent directly to the tumour with controlled and sustained release from a bead. > Includes doxorubicin eluting beads (“DC beads”) that can be infused intraarterially for selective tumour targeting. > The procedure is contraindicated in the case of complete portal vein thrombosis and hepatic insufficiency. DEB should always be performed in experienced centres, as a common side effect (similar to conventional TACE) is post-embolisation syndrome.
Liver directed therapy with 90Yt-SirSpheres[125]	> Selective intra-arterial radionuclide therapy (SIRT) with Yttrium-90 (Y-90) microspheres is also known as radioembolisation and delivers high doses of radiation to hepatic tumours with manageable healthy liver exposure. > This treatment modality, which is most beneficial in patients with good liver reserve and low Eastern Cooperative Oncology Group (ECOG)

Treatment	Details
	performance status, has led to improved time to liver progression and extended overall patient survival. > Prior to the treatment, a technetium-99m (Tc-99m) macroaggregated albumin (MAA) scan is performed to map the area targeted for treatment and ensure no significant shunting occurs- especially to lungs and abdominal viscera such as stomach/duodenum. > Eligibility: o Adequate liver function o Pre-treatment visceral angiography to define and occlude non-target arteries. > Exclusion criteria: o Severe liver dysfunction o Life threatening major extra hepatic metastases o Expected survival < 3 months.

10.3 CHEMOTHERAPY AND OTHER TREATMENTS FOR GEPNETs

Chemotherapy

Chemotherapy has had a limited role in the treatment of GEP NETs. It is mainly used in patients with progressive and metastatic pancreatic GEP NETs after failure of other treatment modalities such as SSAs. There is no evidence to support use in adjuvant settings (after complete resection of the disease).

Tumour grade is useful for selecting systemic treatments. Chemotherapy may be more beneficial in high grade or poorly differentiated tumours. Patients with progressive tumours on standard treatment should be offered participation in clinical trials (Table 10.4)

Table 10.4 Chemotherapy for GEP NETs

Tumour type	Details	Regimen
High-grade	> Poorly differentiated with high proliferative/mitotic indices [>20 mitoses/10 HPF; Ki-67 index >20%] > Usually metastatic at presentation	> Cisplatin or carboplatin with etoposide > Likelihood of tumour response 42–65% > Duration of response 8–9 months > Median survival 15–19 months[126,127]
Low-grade	> Well-differentiated > Sometimes have an aggressive clinical course > Metastatic tumours with low mitotic/proliferative indices [<2 mitoses/10 HPF; Ki-67 index <3%] > Moderately differentiated (low grade malignant) tumours with intermediate mitotic/proliferative indices > Intermediate grade NETs with octreotide non-avid but FDG PET positive lesions may require	> SSAs may be considered as earlier-line systemic therapy in metastatic octreotide-avid non-pancreatic NETs, whereas targeted agents may be preferred in metastatic pancreatic NETs, prior to chemotherapy. > Streptozocin based regimens have been traditionally used in the majority of patients with pancreatic NETs. > Several newer chemotherapy regimens (dacarbazine, temozolomide and thalidomide or capecitabine) have shown

Tumour type	Details	Regimen
	cytotoxic chemotherapy regimens traditionally used in high grade NETs.	promising activity. > The addition of capecitabine (an oral 5-FU prodrug) to temozolomide has shown promising activity in previously untreated pancreatic NETs.

Systemic therapies

Systemic therapies that may be used in the treatment of GEP NETs (Table 10.5).

Table 10.5 Systemic therapies for GEP NETs

Therapy	Detail
Interferon alpha	> May have a role in control of hypersecretion symptoms in combination with SSAs when the symptoms are not sufficiently controlled with SSAs
Targeted therapies	> Agents targeting the vascular endothelial growth factor (VEGF) axis (e.g. sunitinib) and its downstream serine/threonine kinase mammalian target of rapamycin (mTOR) (e.g. everolimus) have shown a significant activity in recently published reports of randomised studies. > Includes anti-angiogenic agents and mammalian target of rapamycin (mTOR) pathway inhibitors. > Evidence supporting the use of targeted therapies is provided in Appendix K.

Somatostatin analogues (SSA)

The role of SSAs for the amelioration of symptoms of the carcinoid syndrome from functional GEP NETs is well established.

Definite indications of SSAs in the management of GEPNETs include:

- treatment of patients with symptomatic carcinoid syndrome.
- Prevention or treatment of carcinoid crisis as part of the perioperative management of patients with GEP NETs. [128] Prophylactic cover with SSAs is preferred in patients considered at risk of carcinoid crisis undergoing surgery. Some patients may also be at risk when commencing peptide receptor radionuclide therapy or chemotherapy.
- option for patients with progressing well-differentiated metastatic midgut NETs, regardless of the presence or absence of the carcinoid syndrome.
- treatment of symptomatic vasoactive intestinal peptide secreting tumours (VIPomas).

Further information on the role of SSAs in GEP NET management can be found in the *Guidelines for the Diagnosis and Management of GEP NETs* from the Clinical Oncological Society of Australia (COSA).

Targeted radionuclide therapy

Targeted radionuclide therapies may be used in the treatment of GEP NETs (Table 10.6).

Table 10.6 Targeted radionuclide therapies for GEP NETs

Treatment	Details
Peptide Receptor Radionuclide Therapy (PRRT)	> Uses radiolabeled SSAs coupled to peptides with beta, Auger, or alpha emitters that cause DNA damage through their particulate emission. > PRRT can be considered in both functioning and non-functioning GEP NETs with positive SRS, irrespective of the primary tumour site.
177Lu-DOTA- Octreotate (LuTate)	> Has been shown to improve survival and markedly improve quality of life with a very low incidence of adverse effects.[129] > Eligibility criteria: o inoperable locally-advanced or unresectable metastatic NET o significant SSR expression on SSR scan (Krenning grade 3-4, i.e.> liver uptake) o no evidence of macroscopic , octreotide-negative, areas of metabolically active disease o if high Ki-67 (>10%) or intense FDG uptake: has had (or will have) a trial of chemotherapy o hormone-related symptoms uncontrolled by SSA, when eligible o gastrinoma: symptoms uncontrolled by PPI o phaeochromocytoma/paraganglioma/neuroblastoma: has failed or unsuitable for I-131 MIBG o if previously treated with PRRT, evidence of therapeutic benefit > Plus at least one of these criteria: o Symptoms related to hormonal secretion or tumour burden (including pain, weight loss or organ dysfunction), not controlled by conventional therapy o Evidence of disease progression within the last 12 months, including: o New lesion(s) on SSR scan o RECIST criteria on CT (20% increase in sum of longest diameters of up to 5 target lesions) o Progressive Chromogranin-A levels; <100: at least 50% increase or >100: at least 25% increase > More information on 177Lu-DOTA- Octreotate (LuTate) side effects are provided in Appendix L.
Other Radio-nuclide Peptide Agents	> Historically, Iodine-131MIBG, Indium-111 Octreotide and Yttrium-90 Octreotate have also been used in the treatment of octreotide positive neuro-endocrine tumours.

Radiation therapy

Although GEPNET's are radiosensitive tumours, localised radiotherapy is usually reserved for symptomatic regions requiring an intensive dose.

This is usually delivered as 20 Gy in 5# (fractions) to the area of concern.

10.4 FURTHER INFORMATION

- **Clinical Oncological Society of Australia**: www.cosa.org.au
- **Endocrine Surgeons of Australia**: www.endocrinesurgeons.org.au
- **Australian Gastrointestinal Trials Group**. The largest Australian group conducting trials into gastrointestinal cancers. www.gicancer.org.au
- **Gastroenterological Society of Australia** Website. www.gesa.org.au
- **NETSIG- NET Specialist Interest Group**/Australia. www.netsig.com.au
- **Guidelines for the diagnosis and management of gastroenteropancreatic neuroendocrine tumours** (GEP NETs): http://wiki.cancer.org.au/australia/COSA:NETs_guidelines/Liver directed therapies

RECOMMENDATIONS

- SSAs have a role in progressive NET to improve tumour control.
- Systemic therapy (chemotherapy and biological agents and PRRT) have definite roles in NET although there are differences between PNET and non-PNET.
- Options for NET are mostly unfunded in a traditional sense. Funding mechanisms for treatments must be explored to allow access
- The use of HRQoL measures in clinical practice, such as the European Organisation for the Research and Treatment of cancer Quality of Life Questionnaire C30 is recommended
- It is recommended that there be funding for a state based service for the provision of radiopeptide therapy for those patients deemed suitable for this therapy by the GEP-NET MDM

11. COMPLEMENTARY THERAPIES

Many people with a cancer diagnosis use complementary therapies as an adjunct to conventional cancer treatment, usually to assist in the management of symptoms and side-effects of treatment and to improve quality of life.

The South Australian Cancer Clinical Network recommends health professionals take guidance from the available national principles, and refer patients to reputable resources such as the Cancer Council Helpline for further information.

Complementary and alternative therapies are a diverse group of practices and products not considered part of evidence based, conventional medicine. The term Complementary and Alternative Medicine (CAM) is frequently used to describe this group of therapies; **however it is important to distinguish between complementary and alternative therapies.**

- Complementary therapies may be used together with conventional medicine.
- Alternative therapies are used instead of conventional medicine.
- There is no evidence to support the use of alternative therapies in the treatment of cancer. This Chapter of the cancer pathway provides recommendations for health professionals on the use of complementary therapies as an adjunct to conventional cancer treatments.

11.1 THE USE OF COMPLEMENTARY THERAPIES

In Australia, the use of complementary therapies by people with cancer is rapidly increasing. Their use can be of concern to health professionals who are uncertain of evidence for their benefit. This concern is coupled with confusion over professional standards for CAM providers, availability and access to complementary medicines, different varieties of medicines available and the associated costs.

The South Australian Cancer Clinical Network has endorsed the Clinical Oncological Society of Australia (COSA) position statement *'The use of complementary and alternative medicine by cancer patients'.*

The comprehensive statement **provides guidance on the use of CAM for health professionals involved in the management of patients with cancer,** including key principles of care (See Box 11.1), discussing CAM, evidence, risks/benefits, harm reduction and reporting adverse events.[130]

Box 11.1 Key principles for the use of complementary medicine[89]

- Patient-centred care
- Shared decision-making
- Respect for the patient's right to make their own decisions about their healthcare
- Effective communication through the provision of a supportive environment that encourages patients to communicate how they are managing their health, including the use of any CAM
- Avoiding prejudice
- Application of risk minimisation principles when a patient chooses to use CAM
- Obligation:
  - providing care to a patient choosing to use CAM does not mean the health professional condones the patient's decision
  - health professionals are not obliged to provide treatments against their medical judgement when providing care for a patient who chooses to use CAM.

11.2 DISCUSSING COMPLEMENTARY THERAPIES WITH PATIENTS AND/OR CAREGIVERS

Health professional should actively ask patients about their use of CAM to avoid interactions with conventional treatments. When asking a patient about CAM, it is important to remember that many patients may refer to complementary therapies as traditional or natural therapies, herbal supplements, bush medicines or Chinese traditional medicine.

Discussing the evidence

- Health professionals discuss the process of developing evidence for medicines and the value of evidence based clinical studies compared with other sources of information. Health professionals should encourage patients to consider the evidence supporting the use of their chosen CAM.[89]
- Referral of a patient to another health professional with CAM expertise may be appropriate.[89]

Discussing implications

- Health professionals should encourage open communication with their patients regarding use of CAM in order to anticipate the potential of drug interactions. [89]
- Health professionals should discuss the possibility of CAM treatment failure in a similar way as they would discuss possible failure of conventional medicine. [89]

Keeping a record

- Health professionals should document all discussions they have with their patients about CAM including any advice, type of CAM, CAM provider, patient's reasons for taking CAM and perceived benefits. [89]

Reporting harmful CAM and CAM providers

- Some complementary therapists, such as Chinese medicine practitioners, are regulated by national legislation and registers. This can make choosing a practitioner safer.[89]
- Where there are concerns of CAM services/products or practitioners the SA Health and Community Services Complaints Commissioner may be contacted.

11.3 FURTHER INFORMATION

- Cancer Council, **Understanding Complementary Therapies- A guide for people with cancer, their families and friends** available online or by phoning the Cancer HelpLine 131120.
- Cancer Council Victoria, **Evidence supporting complementary therapies**: http://www.cancervic.org.au/about-cancer/types-treatments-trials/about_alternative_treatments
- Memorial Sloan Kettering Cancer Center (US), **'About Herbs, Botanicals and Other Products':** www.mskcc.org/mskcc/html/11570.cfm

RECOMMENDATIONS

- The guiding principles should provide the framework for all complementary and alternative therapies discussions with patients and their carers.
- All patients with cancer should be specifically asked about their use of CAM.
- Discussions and patient and family responses to questions about CAM use should be recorded in the clinical record.

12. FOLLOW-UP CARE

Follow-up care after diagnosis and treatment of a GEP NET is intended to evaluate the efficacy of a treatment, enable early detection of recurrence or secondary tumours, identify prognostic and risk factors at a population level, and allow for on-going monitoring of physical and psychosocial supportive needs.

The aim of follow-up care is to provide individualised follow up and surveillance. All members of the MDT have a role in planning and providing ongoing follow up care. A follow-up plan is recommended to streamline follow-up and avoid duplication of care by multiple specialists.

12.1 POST-TREATMENT FOLLOW-UP

There is currently no high-level evidence on which to base advice about medical follow-up after treatment for GEP NETs.

Follow-up investigations should include:

- clinical history
- physical examination
- biochemical parameters/ CgA determination
- conventional imaging.

If a patient's status shows a significant clinical change, a complete reassessment is required, and more frequent follow-up tests may be required. If the risk of recurrence is low: follow-up is at the discretion of the clinician.[131]

E-NETs (2012) evaluation and follow-up recommendations have been used to develop consensus guidelines in this document. A general guide is provided below (Table 12.1).

Table 12.1 A general guide to the follow up of GEP NETs

Tumour type		Follow up procedure
Gastric NETs	Type 1	> Endoscopy every 12 months (every 24 months for non-recurring cases). > Monitoring of iron and vitamin B12 is required.
	Type 2	> Endoscopy is repeated yearly.
	Type 3	> Imaging and CgA is measured every 6 months for the first 2 years, and yearly for the next 3 years.[132]
Duodenal NETs	Well-differentiated, asymptomatic duodenal NET; completely removed at endoscopy	> Endoscopy, abdominal CT scan, and plasma CgA levels at 6, 24 and 36 months.
	Post-surgical resection	> Multislice CT scan, SRS and CgA levels at 6 and 12 months, then yearly for at least 3 years.
	Unresectable, advanced	> Re-evaluation at 3–6 month intervals with CgA levels,

Tumour type		Follow up procedure
	metastatic disease	multislice CT scan and /or ultrasound and SRS, depending on clinical scenario. > Patients with MEN-1 and -2 syndromes are usually seen every 6–12 months for control of medical symptoms, and follow up investigations for tumour assessment, and require extended surveillance.[133]
Colonic NETs	All colonic NETs with lesions >2cm	> Endoscopy/scan/serum marker in the first year. > For G3 patients, follow-up is recommended every 4–6. months in the first year, and at least annually thereafter.
Functional Pancreatic NETs[134]	Benign or asymptomatic	> Follow-up at 3–6 months, and then followed every 12 months > Biochemical studies (e.g. vitamin B12, ionized calcium, gastrin) and tumour imaging (CT scans or MRI). > When clinically indicated, SRS is recommended 6 months after surgery.
	Malignant, asymptomatic	> Follow-up at 3 to 6 monthly intervals with tumour imaging (CT scans or MRI) > Serum CgA, according to the clinical scenario.
	Rare functioning tumours (e.g. VIPoma, glucagonoma, somatostatinoma)	> Follow-up every 3–6 months in metastatic disease and yearly in patients without metastatic disease, using specific markers coupled with CT scan or MRI and SRS (when clinically indicated).
Pancreatic non-functioning NETs	Adjusted to the type of tumour (G1, G2 or G3) and the stage of disease (radically resected or advanced disease).	> Suggested surveillance may involve EUS, PET/CT using 68Ga-DOTA-TOC/-NOC/-TATE, and serum CgA every 3 to 6 months, or according to clinical scenario.[135]
Appendiceal NETs	Appendectomy for lesion < 2 cm with no evidence of serosal invasion or lymph node metastases	> No follow-up required, or as clinically indicated.
	Larger tumours, metastases or additional risk factors (R1 resection, tumour size>2cm)	> Follow-up after 6 and 12 months postoperatively, and then annually.
	Goblet cell carcinomas	> Clinical, biochemical and imaging every 3-6 months > As GCC have a higher risk of distant metastases, a chest CT scan is added to the workup. > A CT scan of the abdomen and pelvis or MRI of the abdomen and pelvis with SRS may also be considered.
	R0/R1 resected NET	> Imaging every 3–6 months (CT or MRI) if the focus is

Tumour type		Follow up procedure
metstases from foregut, midgut, hindgut and unknown primary	G1/G2	on monitoring therapy. > Patients may be imaged at 12 monthly intervals unless there is clinical or biochemical evidence of disease progression
	NEC G3	> Imaging every 2–3 months. > Somatostatin receptor imaging should be included in the follow-up and is recommended after 18–24 months if expression of somatostatin receptor 2a has been proven on the tumour cells.

RECOMMENDATIONS

> Relevant multidisciplinary team members should complete a treatment summary, which includes a documented plan for follow-up. The care plan should ideally be discussed with the patient (and family/caregivers) and used as a living working document.

> All patients with disease progression/progressive symptoms should be referred to the SA GEP NET MDM for discussion and consideration of tailored interventions and to review plans for ongoing best supportive care.

13. CANCER RECURRENCE

The need for heightened awareness and screening for recurrence for GEP NETs is important, as one quarter of patients will develop a second non-endocrine malignancy (e.g. breast, colon or lung cancer). All patients with recurrence require a referral to the MDT meeting for discussion.

13.1 MANAGEMENT OF RECURRENT DISEASE

Treatment for recurrence of GEP NETs can be either **curative in intent** or focused on **palliation/disease control**. The referring specialist or nominated specialist (surgeon, medical oncologist or nuclear medicine specialist) has responsibility for managing treatment of recurrence within the multidisciplinary team. There should be active involvement by the patient's GP and early review by a palliative care team.

Clinical evaluation and patient wishes will determine the intent of treatment.

Neuroendocrine tumours frequently develop slowly, and many years can elapse from first presentation to disease recurrence or disease progression / progressive symptoms. The insidious nature and longevity of NETs resembles management chronic illness models. Metastatic GEP NET is complicated and requires ongoing close monitoring with regular review at the GEP NET MDT when there are disease progression/progressive symptoms.

Recurrence can be extremely challenging, confronting and met with more pessimism than the original diagnosis. Clinicians need to ensure that patients are referred to the appropriate supportive care professionals at this time.

All patients with disease progression/progressive symptoms should be referred to the NET cancer MDT meeting for discussion and consideration of investigation and treatments options and to review the plan for ongoing best supportive care.

13.2 FURTHER INFORMATION

- Chapter 10: **Treatment**
- Chapter 14: **Palliative care**

RECOMMENDATIONS

- A clear documented surveillance plan should be completed with an identified specialist for all patients following completion of treatment for GEP NETs. The surveillance plan should be provided to the patient and their GP.
- All patients with recurrent GEP NETs should be referred to an MDT meeting for discussion and consideration of interventions, and to review the plan for ongoing best supportive care.

14. PALLIATIVE CARE

Palliative care aims to improve the quality of life of patients and their families facing life-threatening illnesses, through the prevention and management of symptoms and pain.

A patient-centred palliative approach should be embedded in all cancer care.

14.1 PALLATIVE INTERVENTIONS AND CARE

The World Health Organisation defines palliative care to be 'an approach which improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'.[136]

The European Society of Medical Oncology (ESMO) defines palliative care as 'care that aims to optimise the comfort, function and social support of the patient and family when cure is not possible'.[137]

A palliative approach should be embedded in all cancer care. Care should be patient-centred and focused on symptom control at all stages of the disease. A palliative approach 'encourages a focus on pain and symptom management, and prompts more open communication about end-of-life issues'.[138]

Provision of palliative care

All professionals caring for cancer patients should **assess palliative and supportive care needs in initial treatment planning** and throughout the illness.

Specialist palliative care teams work in consultation with a patient's primary health providers to arrange:

- provision of relief from symptoms and symptom control
- physical, social, psychological and spiritual support for patients and their carers when these needs cannot be met by primary care teams.[139]

Specialist palliative care teams work across a range of health care services, from the acute setting to hospice or in the community.

Specialist palliative care teams will have varying involvement in patient care, depending on the stage of a patient's disease. As the patient nears end of life, the specialist palliative care team may become the primary specialist service involved in patient care, working alongside a GP and other primary care providers. The transition to care primarily led by the specialist palliative care team is best done in a coordinated fashion between the specialist groups, so that the patient understands the reason for transition, how it will occur and ensures the patient, and their family/carers continues to feel well supported.

Referral to specialist palliative care services

A person is eligible for referral to specialist palliative care services if:

- they have progressive, life limiting illness
- they, or their decision maker, is aware of, understands and has agreed to a palliative care referral
- the primary goals of patient care are to control symptoms, maximise function, maintain quality of life and provide comfort.

If a patient does not meet the three eligibility criteria outlined above, the referrer should contact the palliative care service to discuss the referral with a member of the specialist palliative care team.

Referral to a specialist palliative care service can be initiated by health care professionals, patients, carers or family members when:

- the patient requires a palliative care assessment and provision of service information
- symptoms and/or concerns exceed the capacity, resources, knowledge or skills of the primary care provider
- there is difficulty maintaining care at place of residence
- the patient requires terminal care (patient is in the last few weeks of life).

14.2 ADVANCE CARE PLANNING

Advance care planning enables an individual to express their wishes about his or her future health care. Advance directives are based on values of respect, dignity and autonomy. Conversations about the focus of care and the treatment options available should be held early in the course of disease while the patients have the ability to be involved.

Information contained within a patient's advanced care plan will need to be provided to all health professionals involved in their care including the specialist palliative care team. If a patient does not have a plan in place, the palliative care team can provide support in establishing one with the patient and/ or their decision maker. Further information can be found in Chapter 4.

14.3 END OF LIFE CARE

As the end of life approaches, all efforts are made to allow patients to spend their remaining time in the place of their choice, whether this is in their home, hospital or inpatient hospice unit. Health professionals should be mindful of the possibility that this preference may change close to the end of life.

Quality of life in people with advanced cancer is affected by symptoms, loss of function and curtailment of activity, physical effects of treatment, and psychosocial needs.[140]

Patients with metastatic disease have a significantly greater unmet need for assistance with physical aspects of daily living compared with the needs of patients without evidence of active disease.[141]

The physical burden faced by patients at the end of life can have a major effect on their emotional wellbeing, and emotional wellbeing of their family/carers. This may be exacerbated by existential and spiritual issues arising from facing death.

Distress can arise as patients and carers are confronted with their own mortality. Existential concerns are reported to be at least as important as the physical, psychological and social supportive care needs of patients and their family/carers in determining quality of life.[142]

14.4 FURTHER INFORMATION

- **Palliative Care Australia:** www.palliativecare.org.au
- **Palliative Care Council of South Australia:** www.pallcare.asn.au
- **Caresearch:** www.caresearch.com.au
- **National palliative care service directory:** http://pallcare.gky.com.au/c/pc?a=apps&ap=bd&sc=search
- Respecting Patient Choices, **Advanced Care Planning** www.respectingpatientchoices.org.au/
- National Comprehensive Cancer Network, **Clinical Practice Guidelines in Oncology-Palliative Care:** http://www.nccn.org
- **Appendix G**: The listing of cancer resources and services contains a **list of Palliative Care services**

14.5 KEY RECOMMENDATIONS

- A palliative approach should be a core principle of care for all treating clinicians
- Palliative care referral should be made early in the course of disease for people with complex and unmet needs
- All patients and their families and/or caregiver should have access to specialist palliative care services if required
- All patients and their families and/or care giver(s) require information regarding bereavement support services, while some will require specific assessment and support.

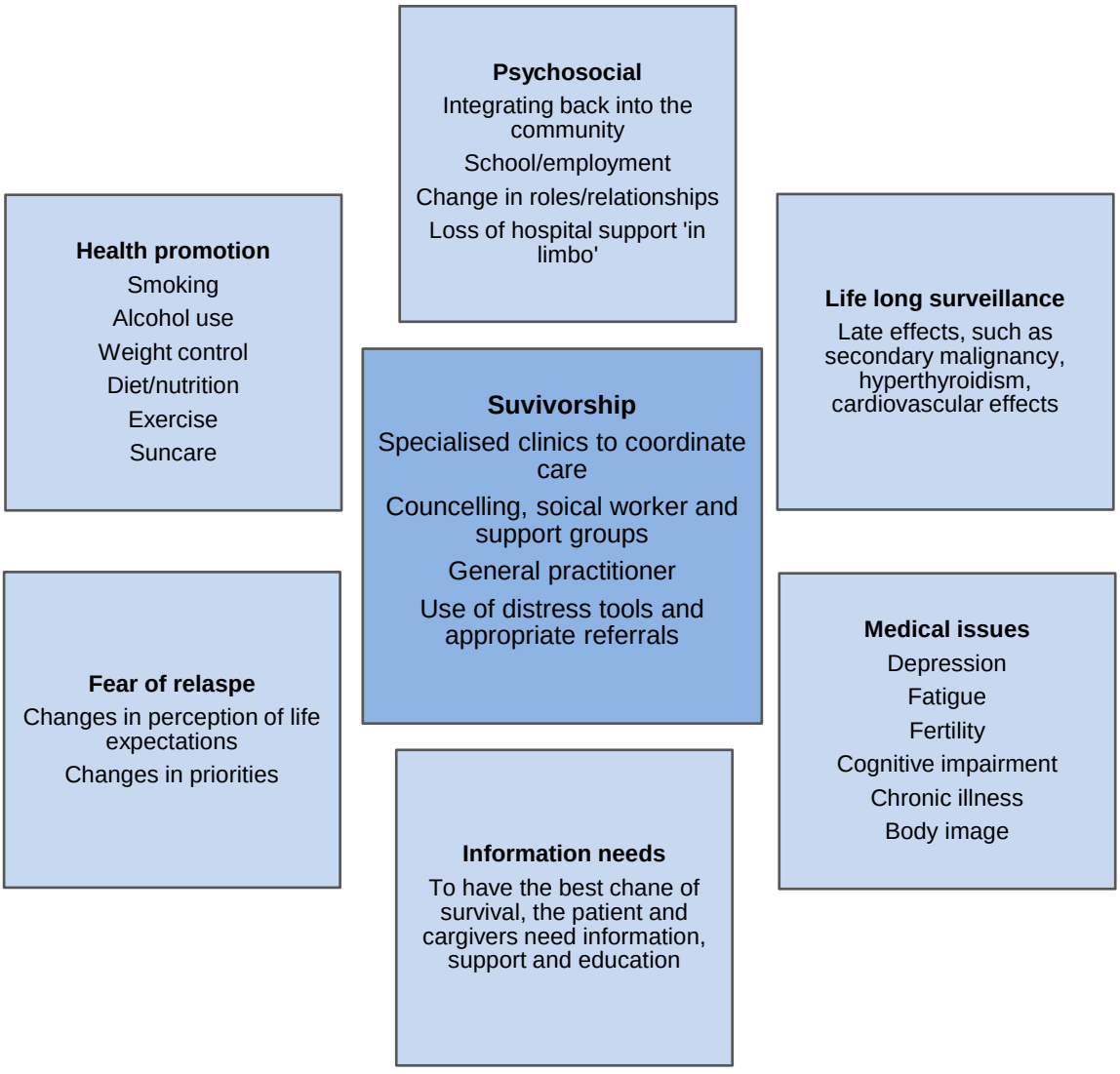
15. SURVIVORSHIP

The USA National Cancer Institute describes survivorship in cancer as covering the 'physical, psychosocial, and economic issues of cancer, from diagnosis until the end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancers, and quality of life. Family members, friends, and caregivers are also part of the survivorship experience'.[109]

15.1 OVERVIEW OF SURVIVORSHIP

Survivors face many issues affecting quality of life, including socioeconomic, psychological, functional and family domains.[149] As many of these domains are integrated, a problem in one area may affect other domains. For example, a survivor may experience a decline in their functional status, restricting family and work related responsibilities, in turn affecting their socioeconomic status and psychological wellbeing.

Figure 15.1 Aspects of survivorship



15.2 SURVIVORSHIP AND PATIENT NEEDS

An increase in the number of people surviving cancer has led to an increase in the number of people requiring cancer follow-up care.[143]

It has become apparent that follow-up services are not meeting the needs of patients. In particular, traditional routine medical follow-up frequently fails to meet the supportive care needs of people following completion of treatment for cancer, often resulting in feelings of abandonment during the transition from cancer 'patient' to cancer 'survivor'.

Survivorship support plans

It is important to ensure that survivor's needs are identified and plans made to meet them from an early stage. The benefits of a survivorship support plan are detailed in Box 15.1.

Box 15.1 Benefits of a survivorship support plan

- A vehicle for communication between treating physicians and local health providers.
- Help specialists and primary care physicians address questions that patients raise, perhaps years after treatment.
- Allows the patient to make informed health choices and promote healthy lifestyles in an attempt to reduce other co morbid conditions.
- Allows the patient to take some responsibility for their care. It may also ensure adherence to follow-up recommendations.
- Can support and facilitate moving the focus of care back to the community.
- Early detection of health complications that can be ameliorated

Due to the complexity of survivorship needs, it is important that survivorship support plans are implemented and coordinated addressing both medical and psychosocial aspects of care.

The planning process is not limited to doctors, and should be seen as a **quality-related multidisciplinary team activity.** Specialist nurses are in a unique position to assist with survivorship planning and provide the coordination of survivorship care. Through nurse led clinics, advanced nursing practice roles such as the nurse practitioner, advanced nurse clinical practice consultant and nurse clinical practice consultant can work alongside medical practitioners, benefiting both clinicians and patients.[150] Survivorship plans should be dynamic and working documents, updated as patient circumstance changes and additional research becomes available.

The key elements of a survivorship support plan are detailed in Box 15.2.

Box 15.2 Key elements of a survivorship support plan

- Patient diagnosis, age at diagnosis/treatment and stage.
- Treatment protocol/plan and exposures – including dates of therapy.
- Toxicities/morbidities experienced during therapy and potential long term toxicities.
- Guidelines for required screening for both recurrence and toxicities.
- Assessment of psychosocial/vocational/educational/financial needs.
- Recommended preventative behaviours/ interventions e.g. weight control, diet/nutrition, exercise, alcohol use, smoking, sun care, complementary medicine use, osteoporosis prevention, and immunisations.
- Information on the availability of community based psychosocial services e.g. an online searchable database of local resources according to postcode and/or links to national/international websites providing survivorship information and services.
- Contact information of the treating hospital and individual providers.
- Identification of a key contact and coordinator of continuing care.

Establishing partnerships with primary health providers, such as GP's, local community health services, is required to achieve quality survivorship care in the health care issues for this growing population.

Other **requirements for the implementation of survivorship planning** include:

- coordination of plans to ensure cohesive and efficient care, including an identified survivorship coordinator, i.e. specialist nurses such as nurse practitioners, nurse clinical practice consultants and advanced nurse clinical practice consultants
- time to create and deliver plans
- training of health professionals (inclusive of specialists) in needs of survivors and how to act on care plan recommendations.
- research to expand the evidence base.
- recognition of cancer as a chronic condition.

15.3 FURTHER INFORMATION

- **Peter MacCallum Cancer Centre Cancer.** Australian Cancer Survivorship Centre providing information for those who have successfully completed cancer treatment provides an example of a survivorship care plan template
- **Cancer Council Victoria.** Currently developing a 'comprehensive survivorship package' including: DVD, booklet and a question prompt list, SCP for patient and for GP, Nurse-led 'end of treatment' session, and telephone-based follow up.
- **The Warwick Foundation.** Provides support to young adults with cancer aged 18-40, with a particular emphasis on their social and emotional wellbeing.
- **Oncolife:** Information about potential late effects of cancer treatment and survivorship care plans. All information is based on published, evidence-based guidelines whenever possible, and lacking those, consensus-based guidelines.
- **Cancer Survivor Toolbox**: www.**cancer**advocacy.org/**toolbox**
- Macmillan Cancer Support, **The National Cancer Survivorship Initiative Vision:** http://www.ncsi.org.uk/
- **Flinders Cancer Centre and the ACRF Cancer Prevention Unit:** http://www.fcic.org.au
- Journey Forward, for information on **survivorship research and care plan**: http://www.asco.org

RECOMMENDATIONS

- Relevant multidisciplinary team members should regularly review and update the monitoring plan.
- Establishment of partnerships between cancer specialists and primary health care providers such as the GP can help to facilitate improvements in achieving quality survivorship care.

APPENDIX A: GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOUR PATHWAY RECOMMENDATIONS

GEP NETs IN SOUTH AUSTRALIA

1. The SA NET database requires investment in administrative and clinical support allowing all treatment outcomes to be reported, reviewed and measured.

2. The development of neuroendocrine tumour treatments requires cell lines for ongoing genetic and molecular studies. Funding is needed to be sought to support ongoing research in this area.

MULTIDISCIPLINARY AND COORDINATED CARE

3. All patients with a NET diagnosis should have access to a NET specialist nurse coordinator throughout their cancer journey. Patients should be referred to a NET specialist nurse coordinator at the point of diagnosis/consultation with specialist

4. The booklet “Neuroendocrine Tumours: A Guide for Nurses” is recommended as a valuable tool for general and specialist nurses caring for NET patients in SA. Treatment options will need to be amended for local context.

5. Cancer Council resources should be used as standard practice, and include the brochure ‘A multidisciplinary team approach to cancer care’.

SUPPORTIVE CARE

6. All patients diagnosed with neuroendocrine tumours have access to culturally appropriate care and effective communication throughout the cancer pathway

7. Health professionals should be trained in supportive care screening to encourage inclusion of supportive care issues as part of multidisciplinary care.

8. The NCCN Distress Thermometer in automated electronic (touch-screen) format which may be used to screen patients with results scored and transcribed so that information is readily available to guide the consultation. QUICATOUCH and or similar programs can be effective in monitoring patients and increasing the number of timely and appropriate referrals for psychological treatment.

SPECIFIC SUPPORTIVE CARE

8. At risk patients should receive early nutritional intervention by an experienced Dietitian in the management of NETs.

PREVENTION AND MINIMISING RISK

9. Health promotion strategies should promote the importance of a healthy lifestyle for all South Australians.

SCREENING AND EARLY DETECTION

10. The following patients should be referred for genetic testing; apparently sporadic enteropancreatic tumours, bronchial or thymic NETs (patients under 30), all Phaeochromocytomas or Paragangliomas.

11. Improved education and awareness campaigns directed to the General Practitioner will hopefully improve the timely diagnosis of NETs. The utilisation of the UK NET Foundation Treatment Pathway Toolkit with localised SA content is recommended.

12. Clear referral pathways for availability for specialists in NET management and membership to SA

GEP-NET MDM (e.g. endocrinology services, medical oncologists, surgeons) should be web based. This will assist in providing information on available services and guidelines for GP's for the management of NETs.

DIAGNOSIS AND STAGING

13. The cost of CgA is not covered by Medicare. For patients not treated in a public hospital, there will therefore be an out-of-pocket cost for this test, currently about $30. CgA is a key element of investigation, and testing should be available in South Australia , with Medicare reimbursement

14. CgA results should be available in accessible electronic format within 14 days.

15. Patient samples of Serum CgA should be measured in the same lab consistently (and over time) to reduce potential for variability in results.

16. That all South Australians have timely access to radionuclide peptide imaging agents, including Ga-68 labelled SSAs, which are considered to be the most sensitive radio-nuclide agents for the diagnosis, staging/restaging and assessment of response to therapy

17. To increase access of patients with neuroendocrine tumours to appropriate imaging by:

- the Medicare descriptor for OctreoScan Scintigraphy be modified to allow use of imaging to assess suitability for unlabelled and Radio-labelled SSAs therapy
- the MBS be modified to allow re-imbursement for the use of other radio-nuclide imaging agents in neuroendocrine assessment, including Gallium-68 labelled SSAs and lutetium-177 octreotate.

PRESENTATION AT THE MDM

18. GEP NET-MDM meeting should be appropriately resourced including a MDM coordinator and/or administrative support

19. Development of an action plan for long term support of research of NETs at a national level is required .Adaptation of the Cancer Council of Victoria's "Forgotten Cancers Project" to the SA environment is recommended. This project aims to raise the profile and understanding of NETs, and will help to advocate for Federal funding

20. Web based information for the SA NET-MDM and contact details should be linked to SA NET Audit

21. All patients with a NET diagnosis should be discussed prospectively at a multidisciplinary meeting within 8 weeks of a confirmed diagnosis

22. A copy of the treatment plan, including any revisions made following patient discussion, should be sent to the referring GP within 7 working days. A copy should also be placed in the patient's case file, and also sent to the referring clinician.

23. Where possible, patients should be offered clinical trial enrolment.

TREATMENT

24. SSA's have a role in progressive NET to improve tumour control

25. Systemic therapy (chemotherapy and biological agents and PRRT) have definite roles in NET although there are differences between PNET and non-PNET

26. Options for NET are mostly unfunded in a traditional sense. Funding mechanisms for treatments must be explored to allow access.

27. The use of HRQOL measures in clinical practice, such as European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 is recommended.

28. It is recommended that there be funding for a state based service for the provision of radiopeptide therapy for those patients deemed suitable for this therapy by the GEP-NET MDM

COMPLEMENTARY THERAPIES

29. The guiding principles should provide the framework for all complementary and alternative therapies discussions with patients and their carers.

30. All patients should be specifically asked about their use of complementary and alternative therapies (CAM) at all points of their cancer journey. This communication will help prevent adverse events and increase overall knowledge of the potential advantages and limitations of CAM therapies with conventional therapies

31. Discussions and patient and family responses to questions about CAM use should be recorded in the clinical record.

FOLLOW-UP CARE

32. Relevant multidisciplinary team members should complete a treatment summary, which includes a documented plan for follow-up. The care plan should ideally be discussed with the patient (and family/caregivers) and used as a living working document.

33. All patients with disease progression/progressive symptoms should be referred to the SA GEPNET MDM for discussion and consideration of tailored interventions and to review plans for ongoing best supportive care.

CANCER RECURRENCE

34. A clear documented surveillance plan should be completed with an identified specialist for all patients following completion of treatment for GEP NETs. The surveillance plan should be provided to the patient and their GP.

35. All patients with recurrent GEP NETs should be referred to an MDT meeting for discussion and consideration of interventions, and to review the plan for ongoing best supportive care.

PALLIATIVE CARE

36. A palliative approach should be a core principle of care for all treating clinicians

37. Palliative care referral should be made early in the course of disease for people with complex and unmet needs

38 All patients and their families and/or caregiver should have access to specialist palliative care services if required

39. All patients and their families and/or care giver(s) require information regarding bereavement support services, while some will require specific assessment and support.

SUPPORTIVE CARE

40. Relevant multidisciplinary team members should regularly review and update the monitoring plan.

41. Establishment of partnerships between cancer specialists and primary health care providers such as the GP can help to facilitate improvements in achieving quality survivorship care.

APPENDIX B: KEY PRINCIPLES OF CANCER CARE

Underpinning the cancer pathway are key principles that support each stage of the pathway.

Patient centred care

- Patients and their families/care givers are encouraged to be involved as active participants in care planning and decision making. Ultimately treatment decisions rest with the patient or designated person. This requires information and discussion to be provided in their preferred language and in a manner that is sensitive to their culture.

Safe and high quality care

- Cancer care is complex, involving a range of specialist providers and health professionals with varied clinical expertise. To ensure safe and high quality cancer care it is essential for health professionals to possess the technical skills and experience to undertake the relevant aspects of cancer care and have access to appropriate infrastructure to support such care.

Multidisciplinary care

- Best practice in cancer care involves multidisciplinary treatment planning and multidisciplinary care delivery.
- Effective multidisciplinary approaches in the management of patients with cancer have demonstrated positive outcomes, including increased survival, a greater understanding that a comprehensive team is providing care, a greater likelihood of receiving care that is in accordance with clinical practice pathways (including psychosocial and practical support), increased access to information for patients and increased patient satisfaction with care.

Supportive care

- Patients with cancer have psychological and social needs that are frequently undetected and unmet, and have the potential to cause long-term distress.
- Supportive care includes the acknowledgement of all domains of patient needs – physical, psychological, social, informational and spiritual – that may be required to support the patient and their families/caregivers.

Care co-ordination

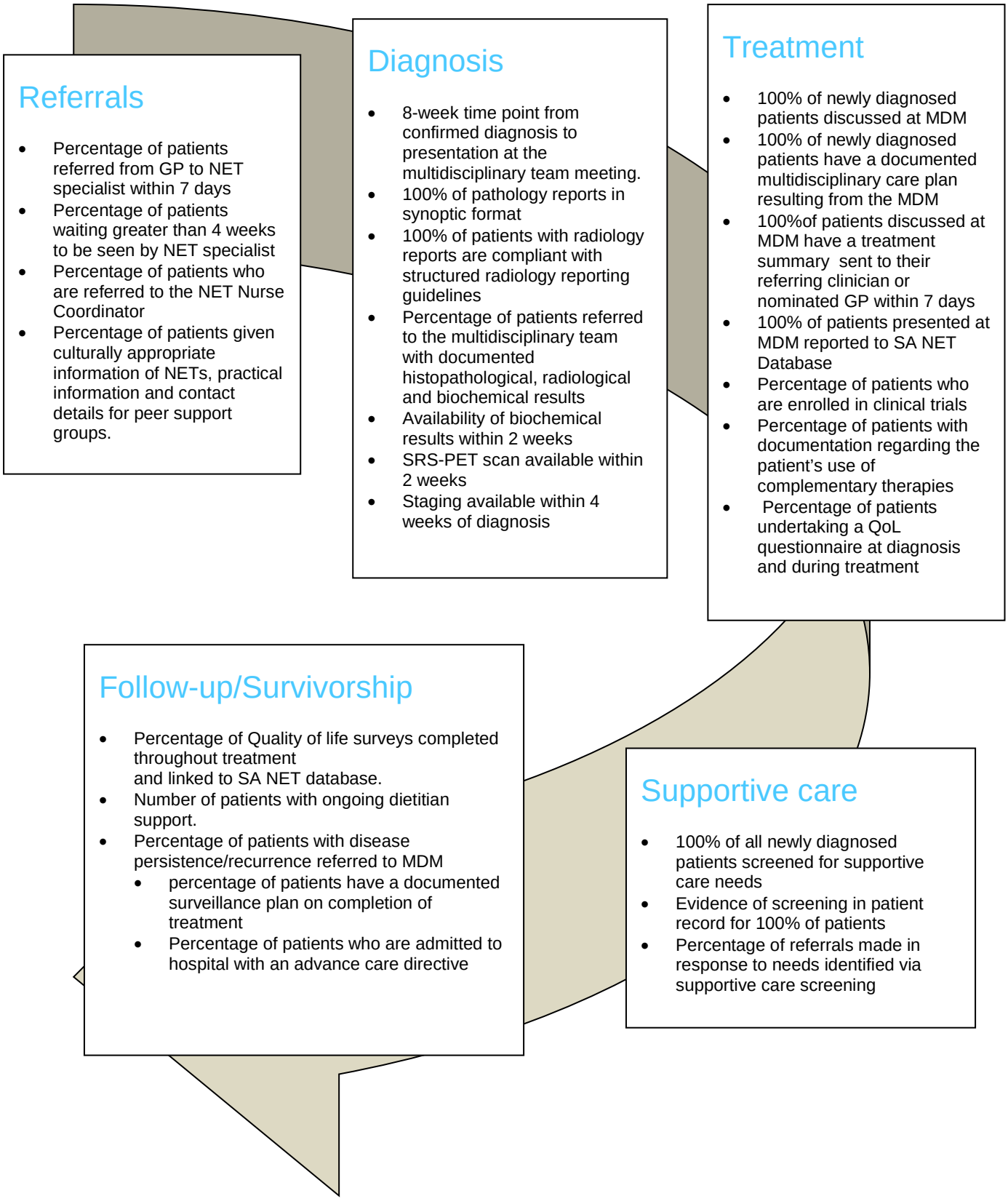
- Patients require co-ordination of their health care. A variety of strategies have been shown to improve co-ordination of care and these include multidisciplinary team meetings, clinical protocols, access to cancer nurse specialists and utilisation of appropriate performance indicators.

APPENDIX C: RECOMMENDED PATIENT INFORMATION LINKS

Organisation	Website
The Unicorn Foundation	www.unicornfoundation.org.au
Clinical Oncology Society of Australia *Guidelines for the diagnosis and management of gastroenteropancreatic tumours (Wiki Platform)*	http://wiki.cancer.org.au/australia/COSA:NETs_guidelines/Short_and_Long-Acting_Somatostatin_Analogues_(SSA)
United Kingdom and Ireland Neuroendocrine Tumour Society (UKINETs)	www.ukinets.org
Cancer Council South Australia	http://www.cancersa.org.au/

APPENDIX D: SAFETY AND QUALITY

Below are the key quality indicators representing all the stages of Neuroendocrine Tumour care: including referral, diagnosis, treatment, supportive care, post treatment follow-up and survivorship. (Based on Performance Indicator Framework for SA Cancer services, Communio 2010)



APPENDIX E: BENEFITS AND PRINCIPLES OF MULTIDISCIPLINARY CARE

BENEFITS OF MULTIDISCIPLINARY CARE

- Increased provision of evidence-based care in accord with clinical practice pathways (where available) with implications for both clinical outcomes and cost effectiveness
- All treatment options are considered and treatment plans are individualised to each patient
- Improved referral pathways
- Decreased variation in care
- Increased referrals for psychosocial support
- Increased discussion of patient eligibility for clinical trials
- Enhanced clinical education opportunities
- Opportunity for health professionals to interact.

Positive outcomes identified for patients include:

- Increased patient satisfaction with care
- Increased survival when care is managed by a multidisciplinary team
- Increased access to information for patients, particularly psychosocial and practical support
- Increased perception by the patient that care is being managed by a team

MULTIDISCIPLINARY CARE PRINCIPLES

1. A team approach [144]

- There is an established multidisciplinary team that comprises relevant core disciplines, including allied health and psychosocial health specialists.
- The general practitioner is regarded as a team member and effective communication processes between the multidisciplinary team and the general practitioner are established.
- Effective communication processes exist with access and referral links between all core and non-core team members.

2. Communication among team members[145]

- All the core team members regularly attend multidisciplinary team meetings (MDM) to provide input into diagnostic, treatment, supportive and palliative care planning.
- Processes are in place for communication for treatment recommendations and care plans.
- The OACIS or EPAS clinical summary (or alternative summary) letter enables electronic communication of treatment recommendations and care plan between core MDM members and members of the treating team. Summaries and letters need to be communicated in a timely manner to the patient's GP and private practitioners.

3. Access to the full range of therapeutic modalities for all patients, regardless of geographical remoteness or size of institution[146]

- All patients regardless of where they live will have information about and access to relevant treatment and services.

- Clinical trial involvement is considered for all eligible patients who will be undergoing cancer treatment.

4. Provision of care in accord with agreed standards/pathway[2]

- Informed decision making is guided by current best practice principles.
- All relevant diagnostic results, reports and pathology and radiology images are available for MDM.
- Professional development activities for all MDM members are offered and supported.

5. Involvement of patients in decisions about their care[3]

- Informed consent is obtained prior to a MDM.
- Patients are informed of the MDM care and billing processes through Medicare for their treatment planning
- Patients are informed of the MDM; recommendations and provided with information about all aspects of their treatment.
- Patients are routinely provided with suitable information about and access to supportive care services.

APPENDIX F: FACTSHEET FOR GENERAL PRACTITIONERS

EARLY DETECTION, INVESTIGATION AND REFERRAL

The following is a guide to assist general practitioners gain awareness of the varied clinical presentation and behaviour of NETs. A greater awareness and incorporation of suspicion of NETs into initial evaluation of patients, prompting earlier referral to specialists for appropriate diagnostic testing, will allow for earlier treatment and better control over symptoms.

Gastrointestinal System NETs

Site	Presentation
Stomach	Small gastric NETs rarely cause symptoms and often are detected as a result of investigations of problems arising in connection with atrophic gastritis (e.g. pernicious anaemia, B12 deficiency). Larger tumours are likely to cause upper GI bleeding, resulting in iron deficiency anaemia, or can cause epigastric pain, and are typically found during endoscopic ultrasound.
Duodenum	Majority are diagnosed when the patient presents with symptoms suggesting a gastric-duodenal ulcer. Abdominal pain is a common symptom, and is described as; dull, burning, aching, and is often relieved by eating.
Jejunum/ileum	NETs of the ileum and distal jejunum are often slow growing and are asymptomatic in the early stages. When diagnosed they are often larger than 2cm and have metastasised to regional lymph nodes and the liver. Patients often present with abdominal pain, which may be due to the tumour or fibrosis surrounding the tumour. Bowel obstruction is often the first sign of metastatic disease. Carcinoid syndrome symptoms such as diarrhoea, flushing symptoms of reduced cardiac function, and asthma like symptoms may also occur.
Appendix	Have non-specific symptoms, and do not cause carcinoid syndrome. They rarely metastasise to regional lymph nodes (unless they reach >2.5cm), and never to the liver. The most common clinical presentation is acute appendicitis, followed by abdominal pain and a mass.
Colon and Rectum	Approximately 50% of patients are asymptomatic and the tumour is often discovered chance during routine colonoscopy. Local symptoms include changed stool pattern, rectal bleeding, anorexia and weight loss. Metastases are often found in the liver and regional lymph nodes

Bronchopulmonary System NETs

Site	Presentation
Lung	Hormone related symptoms are not common, but a small number of patients may experience 'carcinoid syndrome' symptoms. Clinical presentation includes a cough, wheeze, shortness of breath and haemoptysis in 50% of patients due to the highly vascular nature of lesion. Recurrent pneumonia can occur due to the symptoms listed.
Pancreas	Patients often develop symptoms caused by the tumour invading surrounding organs e.g. pain and jaundice. PNETs are divided into 2 groups; 1) Functioning with a recognisable syndrome Insulinoma- symptoms are variable and may be intermittent. Possible symptoms include hypoglycaemia. Symptoms of hypoglycaemia reflect a lack of glucose in the CNS resulting in; confusion and disorientation, altered consciousness and symptoms due to sympathetic overdrive (trembling, sweating without exercising, heart palpitations, sweating, and relief with eating) Diagnosis is based clinically and biochemically on basis of Whipple's triad.
Gastrinoma	Patients generally present with recurrent, multiple or ectopic peptic ulceration, and unexplained secretory diarrhoea. Abdominal pain, nausea, vomiting, diarrhoea and weight loss are other symptoms; associated syndrome is Zollinger-Ellison syndrome.
Glucagonoma	Presents characteristically as necrotic migratory erythema (a rash found particularly in groin region) and is often diagnosed by a dermatologist. There is associated glossitis and stomatitis, anaemia and weight loss. Clinically significant hyperglycaemia (causing fatigue, blurred vision, frequently urinating, dry mouth) occurs in only half of such patients. Otherwise known as 4D syndrome; dermatosis, diarrhoea, DVT and depression.
Somatostatinoma	Salient features are diabetes, diarrhoea/steatorrhoea, gallbladder disease, hypochorhydria, weight loss.
VIPoma	Severe watery diarrhoea potentially leading to hypokalaemia or hypochlorhydria (collection of symptoms known as WDHA), weakness and ongoing fatigue; associated syndrome is Verner-Morrison syndrome. Non-functioning with no recognisable syndrome, and often presents with localised symptomology resulting from a mass.
Pancreatic polypeptidoma (PPoma)	Clinical symptoms include pain, jaundice, mass, obstructive symptoms and weight loss.

APPENDIX G: PRINCIPLES OF SUPPORTIVE CARE

Supportive care is an 'umbrella' term used for all health services (generalist and specialist) that may be required to support people with cancer and their families and/or care givers

Research indicates that people with cancer who receive appropriate information and psychosocial interventions have lower rates of anxiety, mood disorders, nausea, vomiting, pain, as well as a greater knowledge and understanding about their disease and treatment. The type and degree of interventions to meet the supportive care needs for patients and their caregivers will vary throughout the cancer journey; many patients' needs will be met adequately through the provision of general information, while some patients will require specialised intervention.[147]

The spectrum of supportive care includes:

- management of physical symptoms and side effects across the cancer continuum from diagnosis through treatment to post treatment care
- management of psychosocial issues
- enhancing rehabilitation
- secondary cancer prevention
- promoting healthy lifestyles with health risk reductions strategies
- monitoring functional status
- survivorship support and care
- end of life care

PROVIDERS OF SUPPORTIVE CARE

All members of the multidisciplinary team have a role in the provision of supportive care. In addition the patient may have support from family, friends, support groups, volunteers and other community-based organisations.

ACHIEVING BEST PRACTICE IN SUPPORTIVE CARE[148]

Supportive care service provision requires an initial assessment and identification of the patient's specific needs. This is achieved through regular discussion and systematic review of the patient and their care givers. Regular reassessment is essential, as needs frequently change throughout the cancer journey.

This review process assists in identifying those patients who are experiencing significant levels of distress and are at higher risk of psychological morbidity, and facilitates appropriate referral for further assessment and specific interventions. The Australian Clinical practice guidelines for the psychosocial care of adults with cancer and the National Comprehensive Cancer Network's clinical practice guidelines for distress management recommend the use of a validated screening tool such as the Distress Thermometer.[149,150]

ESTABLISHING A SUPPORTIVE CARE MODEL

As a range of professionals and services provide supportive care, it is important to have in place:

- Patient's and carers have their supportive care needs systematically identified as part of a multidisciplinary best-practice approach to cancer care
- A detailed assessment of supportive care needs will help identify those patients who require more specific one-one intervention and follow-up

- A clear referral pathway to specialised supportive care services
- A skilled workforce with the ability to assess patient needs, deliver support and/or enable referral onto specialist supportive care providers at suitable points in the patient's cancer journey
- Promotions of supportive care as integral components of cancer service delivery, including information about the range of professional services available so that patients can self-refer of self-identify a need.
- Adequate communication between health services, to enhance referral and linkage of supportive care services.[4]

Other specific information needs may include:

- assistance with smoking cessation may be required; this is particularly relevant prior to surgery to reduce the like hood of post-operative complications[4]
- Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities have specific informational needs that require culturally appropriate resources (Aboriginal Cancer Care Co-ordinators/ local Aboriginal Health Service may be able to assist patients and caregiver(s) in their region).

COMMUNICATION WITH PATIENT AND CARE GIVERS

Patients require verbal and written information that is culturally appropriate and may require access to a qualified interpreter (accredited by the National Accreditation Authority for Translators and Interpreters (NAATI). Information required includes details about the disease, preventative actions, the reasons for and likely effects of diagnostic procedures, treatment options (including known risks and potential adverse effects), and information about effective coping strategies. Patients and carers should receive both individual support and guidance and well-produced, culturally appropriate information leaflets, or quality web –based information.

It is recommended that health care providers ask patients if they want additional information and discuss how much they wish to be involved in decisions about treatment. Determine the patient's needs and preferences regarding information about treatment, and encourage family members, care givers and/or others who may provide support to the patient during consultations. Specific instructions for self- care may enable patients and family members to maintain their desired level of independence throughout the cancer care journey.[151]

All health professionals involved should know what information has been given to each patient. A record of this, along with the patient's preferences for information and involvement in decision-making, should be included in the notes and given to the patient's general practitioner, together with a comprehensive summary of the management plan. Communication needs to be effective, with fast and efficient links.

APPENDIX H: CANCER RESOURCES AND SERVICES IN SOUTH AUSTRALIA

Cancer resources

Organisation	About	Resources	Wesbite
Resources for the general population			
Cancer Australia	Cancer Australia works to reduce the impact of cancer and improve the well-being of those diagnosed by ensuring that evidence informs cancer prevention, screening, diagnosis, treatment and supportive care.	> **Factsheets and statistics sheets** on different cancer types > **Links** to supportive care and survivorship services	http://canceraustralia.gov.au/
Cancer Council South Australia	An independent, non-profit organisation driving research into cancer and supporting South Australians affected by cancer.	> Services include **information resources** on cancer, its treatment, side effects, and medical terminology, support services such as counselling, self-care programs, accommodation and research. > CCSA also provides **links to other reliable cancer information websites**, along with an online library.	www.cancersa.org.au
Cancer Council Helpline	Nurses and health counsellors available via a telephone support service. Cancer Connect - for telephone peer support from people who have had cancer experiences.	> Telephone help line : 13 11 20 > Email: chl@cancersa.org.au	
Cancer Council Australia	The leading independent funders of cancer research in Australia (through National and state-based organisations). Provide evidence-based, up to date information for consumers.	> **Fact sheets on a variety of cancer issues** including early detection, diagnosis and treatment, living with cancer and lifestyle advice.	www.cancer.org.au
Health insight	*healthinsite* is a non-commercial, government-funded health	> **Fact sheets** on a variety of health conditions	http://www.healthinsite.gov.au/

Organisation	About	Resources	Wesbite
	information service, operated by Healthdirect Australia. It aims to improve the wellbeing of all Australians by providing easy access to quality health information and services.	> **Tips for healthy living** at different stages of life	
Resources for Aboriginal and Torres Strait Islander population			
Australian Indigenous Health Info Net	A national website with information for both the public and health professionals. It promotes knowledge and information sharing on all health issues relevant to ATSI people.	> **Fact sheets** on a variety of health conditions > **Information on prevention and risk factors**	www.healthinfonet.ecu.edu.au
A Cancer Journey	A Cancer Story for Remote Indigenous Patients In the NT	An information DVD available in the following languages; English, Kriol,murrinh-Patha, Yolngu-Matha, Warlpiri, Pitjantjatjatjara	wwwcancercouncilnt.com.au

CANCER SERVICES

Organisation	Location	Website
Services for Aboriginal and Torres Strait Islanders		
Aboriginal Health Liaison Units located in Adelaide hospitals.	Royal Adelaide Hospital Aboriginal Health Team North Terrace, Adelaide	http://www.rah.sa.gov.au/aboriginal_health/intro.php
	The Queen Elizabeth Hospital Aboriginal Liaison Officers Woodville Road Woodville, SA	
	Lyell McEwin Hospital, Muna Paidendi Aboriginal Health Team Haydown Road, Elizabeth Vale	
	Flinders Medical Centre Aboriginal Health Unit (Karpa Ngarrattendi)	http://www.flinders.sa.gov.au/community/default.asp?web=community&group=abhealth&id=AAP_PBAz_z
	Women's and Children's Hospital Aboriginal Health Unit	http://www.wch.sa.gov.au/services/az/other/aboriginal/
A list of Community Health services in SA is available at the following web sites: http://www.caesa.org/commhealth.html http://www.caesa.org/acsd.htm http://www.rah.sa.gov.au/aboriginal_health/downloads/FINAL_RAH_ATSI_Brochure.pdf		
Services for culturally and linguistically diverse populations		
Migrant Health Service *Provides information and health services that are culturally appropriate. For example access to bilingual nurse, doctors and counsellors*	21 Market Street, Adelaide 5000	>
Migrant Resource Centre of South Australia	59 King William Street	http://www.mrcsa.com.au/

Organisation	Location	Website
Multicultural Communities Council of SA (MCC)	113 Gilbert Street, Adelaide 5000	www.multiwebsa.org.au
Multicultural SA	Interpreting and Translation Centre 24 Flinders Street, Adelaide 5000	www.multicultural.sa.gov.au
Translating and Interpreting Service (TIS)	Casseldon Place, 2 Lonsdale Street, Melbourne VIC 3000	
Services for Women		
Women's Health Statewide Information Service *Services include women's health line and counselling*	64 Pennington Terrace, North Adelaide 5006	www.whs.sa.gov.au

PALLIATIVE CARE SERVICES

Palliative care services are available throughout South Australia. Up to date contact information can be found on the Palliative Care Council of SA website (link below).

Organisation	Location
Palliative Care Council of SA Inc	www.pallcare.asn.au
Statewide Services **Paediatric Palliative Care**	www.wch.sa.gov.au/services/az/divisions/paedm/pallcare/index.html

Metropolitan services

- Northern Adelaide Palliative Care
- Central Adelaide Palliative Care
- Southern Adelaide Palliative Care

Country services

For country referrals to palliative care, please direct to your local community health service. The exception is for referrals to the Inner North, Lower North and Yorke Peninsula areas. These are to be directed to Health Link. Phone: 1800 003 307; Fax: 8561 2142.

- Adelaide Hills Palliative Care (Mt Barker)
- Inner North Palliative Care (Barossa/Gawler)
- Ceduna Palliative Care
- Kangaroo Island Palliative Care
- Lower North Palliative Care (Clare)
- Murray Mallee Palliative Care (Murray Bridge)
- Naracoorte Palliative Care
- Port Augusta Palliative Care
- Port Lincoln Palliative Care
- Port Pirie Palliative Care
- Riverland Palliative Care (Barmera)
- South Coast Palliative Care (Victor Harbor)
- South East Palliative Care (Mt Gambier)
- Whyalla Hospital Palliative Care
- Yorke Peninsula Palliative Care (Wallaroo)

APPENDIX I: REFERRAL FOR PSYCHOSOCIAL CARE

It is important to screen patients for elevated distress and emotional concerns at every medical appointment, but particularly at times **of increased vulnerability** e.g. at time of diagnosis, prior to commencement of treatment or at the end of treatment, discharge from hospital, surveillance appointments and recurrence / progression of disease.
It is common for people who are experiencing increased distress to have difficulty recalling and remembering information. To assist in reducing anticipatory anxiety, be sure the patient understands their disease and treatment options. Refer the patient to education materials and advise patients and their families that times of transition may bring increased vulnerability to distress.

Before referring for psychosocial care please consider the following:

- Is the person and/or family member experiencing an acute exacerbation in distress following a period of increased vulnerability? (as listed above)
- Is the person's distress directly related to:
  - Sadness associated with loss of usual good health
  - Preoccupation with thoughts about illness and treatment
  - worry about future
  - worry about the impact the illness is having on their family
  - relationship or family issues
- Are there significant practical concerns for person? (e.g. financial stress, transport issues, power of attorney, end of life decisions, etc)

⬇

- Is the person experiencing chronic elevated distress that is impacting on pain or symptom control or on their normal functioning or ability to complete cancer treatment
- Has a past history of mental health concerns
- Has trauma history or symptoms (i.e. PTSD)
- Is experiencing severe anxiety related to their medical condition
- Is hyper vigilant, experiencing panic attacks or highly irritable
- Appears to be depressed or reporting suicidal ideation
- Is describing illness specific fears and phobias (i.e. needle phobia, hypochondriaisis)
- Is exhibiting behaviours that are challenging to manage (i.e. aggression)
- Is reporting issues with body image or sexuality concerns
- Is concerned by chronic disruption to sleep, appetite and/or concentration

⬇

- Is the person's primary presentation psychiatric in nature?
- Are there imminent risk issues? (e.g. suicidal plan/intent or agression)
- Does the person have a previous psychiatric history or do they have current psychiatric input?
- Is there evidence of a thought disorder or psychosis?
- Is the person non-compliant?
- Are there signs or symptoms of suspected delirium?

⬇

- Does the person appear to have borderline cognitive status?
- Is there uncertainty about the nature and extent of cognitive issues?
- Is there difficulty identifying or distinguishing possible diagnoses/aetiologies?
- Has the person experienced any particular event that may impact on their cognitive function? e.g. brain injury, cancer metastases to brain).
- If the person is over the age of 65, has the person been triaged to Geriatric Medicine for formal assessment?

⬇

Consider consulting or referring to these Disciplines:

Social Work

- Supportive counselling for patient and family
- Linking with external psycho-social supports
- Support groups and/or individual counselling
- Family meetings
- Grief counselling

Clinical Psychology

Dependent on the presenting complaint, psychological intervention may include a combination of formal assessment, cognitive behavioural therapy, hypnotherapy, management suggestions, and other relevant therapeutic interventions.

Psychiatric Referral

- Formal Psychiatric Assessment and Review (e.g. history/medications)
-

Clinical Neuropsychological

- Formal Neuropsychological Assessment

APPENDIX J: ADDITIONAL SUPPORTIVE CARE INFORMATION

NUTRITIONAL CONSIDERATIONS FOR SYMPTOMATIC PATIENTS WITH NETS

Research is ongoing for development of nutritional guidelines for patients with Neuroendocrine Tumours. Studies have shown that for some patients certain foods and drinks can 'trigger' symptoms such as abdominal pain, diarrhoea and flushing. Some common examples discussed by patients are large meals and alcohol. Patients with carcinoid syndrome are advised to minimise their alcohol intake. The types of foods/drinks that cause this reaction are individual in nature and the most reliable method of identifying possible' trigger foods' is with a food and symptom diary. A diary can be completed by the patient over a 2 week period. All food, drink and medication are documented alongside all symptoms experienced and their timings. The diary can be reviewed by the dietitian (with the patient) to help identify potential 'trigger foods' and to ensure that the diet is nutritionally balanced. Suggestions are then made about any necessary changes required to both diet and medication (with physician input). It is essential that a dietitian is involved in this discussion to ensure that vital food groups are not removed from the diet to prevent any nutritional deficiencies.

General points

1. Adopt general healthy eating principles- Australian guide to healthy eating (AGHE), Cancer Council of Australia

2. Diet should be based on regular meals, with moderate portion of food at each meal

3. Reducing the 'load' of amines in the diet may help with symptoms (particularly flushing). It is not necessary to avoid all foods that contain amines – Refer to Box 1 as a guide for 'trigger foods' high in amines.

4. Foods high in serotonin DO NOT cause high levels of serotonin in the blood. Therefore there is no need to avoid foods in serotonin to control symptoms of carcinoid syndrome.

5. Avoid unnecessary food restrictions

6. A dietitian will discuss individualised nutritional strategies to cope with symptoms and effects of treatment (e.g. fatigue, weakness, weight loss and diarrhoea).

(Scarfe K, "Nutrition and NETs" Northern Sydney Local Health Network, NSW)

CARCINOID HEART DISEASE

Carcinoid heart disease occurs in approximately 50% of patients with "carcinoid syndrome", and is consequent on the release of vasoactive hormones (such as serotonin, histamine, tachykinins and prostaglandins) released into the systemic circulation by metastatic carcinoid tumours in the liver[152]. The characteristic pathological findings are endocardial plaques of fibrous tissue involving primarily the right heart (tricuspid and/or pulmonary) valves, and possibly also the right cardiac chambers, vena cavae, pulmonary artery and coronary sinus. Inactivation of the vasoactive substances by the lungs protects the left side of the heart. The fibrous plaques result in distortion of the heart valves leading to either stenosis, or more commonly, regurgitation. Left-sided valvular pathology occurs in less than 10 percent of patients with cardiac involvement, and is almost always associated with an atrial right-to-left shunt (such as a patent foramen ovale) or a primary bronchial carcinoid[153]. Cardiac (intra-myocardial) metastases of carcinoid tumours can occur but are extremely rare[154].

1. Clinical Presentation

The clinical manifestations of carcinoid heart disease are often subtle early in the course of the disease. In addition, moderate to severe tricuspid and pulmonary valve disease may be well tolerated for many months. Early symptoms of right-sided valvular heart disease include fatigue and dyspnoea on exertion. Right-sided heart failure with worsening dyspnoea, oedema, ascites and eventual cardiac cachexia occur with progressive disease. Prognosis is poor, with median survival in patients with carcinoid heart disease only 1.6 years, compared to 4.6 years in those carcinoid syndrome patients without cardiac involvement[155].

2. Diagnosis and Screening

All patients with suspected carcinoid syndrome should undergo careful cardiac examination for murmurs, JVP elevation or peripheral oedema. The auscultatory findings may be subtle, as the murmurs of tricuspid and pulmonary valve disease may be difficult to detect due to the low pressure in the pulmonary circulation. In such patients, elevation of the jugular venous pressure with a prominent "v" wave is often the earliest finding. Screening ECG is often unhelpful as 30-50% of ECGs are normal in carcinoid heart disease; abnormalities are often non-specific such as diffuse mild ST changes, sinus tachycardia, and most commonly, P pulmonale or right bundle branch block[156]. Similarly, the chest X-ray is usually normal.

The two key investigations for the diagnosis of carcinoid heart disease are 24 hour urinary excretion of 5-hydroxy-indole acetic acid (5-HIAA) and transthoracic echocardiography. In a large series of patients with carcinoid heart disease, the mean 24 hour urinary excretion of 5-HIAA was approximately 10-fold higher than the reference range, and other studies have shown a correlation between urinary 5-HIAA excretion and greater cardiac disease activity[157].

Extent and severity of cardiac involvement is one of the main predictors of clinical outcome in patients with carcinoid syndrome. This is best assessed with echocardiography, which pays a central role on the diagnostic and prognostic evaluation of this condition. A baseline transthoracic echocardiogram is recommended in all carcinoid syndrome patients, and should be repeated if any clinical features of carcinoid heart disease subsequently arise. Right atrial and ventricular dilatation is noted in 90% of patients with carcinoid heart disease[158]. The tricuspid valve leaflets and subvalvular structures (chordae tendineae and papillary muscles) are often thickened, shortened and retracted, leading to incomplete coaptation and usually moderate to severe tricuspid regurgitation in 90% of cases[159]. The pulmonary valve may also be thickened and retracted, leading to pulmonary regurgitation (in 80%) and/or stenosis (in 50%)[160]. The combination of tricuspid regurgitation and pulmonary stenosis is particularly problematic as the latter further exacerbates the former leading to profound right heart failure. Left sided involvement is only occasionally seen, and rarely severe. Long-standing tricuspid and pulmonary valve disease leads to progressive right ventricular overload and elevation in right ventricular diastolic pressures.

3. Treatment

Carcinoid heart disease with advanced symptoms (NYHA class III or IV) portends a particularly poor prognosis and the median survival is only 11 months; most die within one year because of progressive heart failure[161]. The principles of management of carcinoid heart disease can be divided into the treatment of right heart failure, treatment of the underlying carcinoid tumours to reduce secretion of tumour products, and surgical treatment of valvular pathology.

Heart failure therapy: General measures include salt and water restriction, monitoring of fluid balance and weight, and compression stockings. Loop diuretics are required in almost all patients, and if additional diuresis is needed, the judicious co-administration of a thiazide diuretic may be successful[162]. However, diuretics may lead to a further reduction in left-sided cardiac output, which in

turn worsens fatigue. Digoxin is often added to assist right ventricular contractility, although data on its effectiveness in pure right heart failure are limited. [163]

Anti-tumour therapy: Therapy with long-acting somatostatin analogues or PRRT leads to both a measurable biochemical improvement and observable clinical improvement with respect to systemic symptoms such as flushing and diarrhoea. Although progression of valvular disease can be slowed, existing valve lesions do not generally regress, even with steep declines in 5-HIAA excretion. [164]

Valve surgery: Patients with carcinoid heart disease usually die of progressive right heart failure consequent on severe tricuspid valve regurgitation rather than carcinomatosis.[165] Valve surgery is often the only effective treatment for carcinoid heart disease and should be considered for symptoms of increasing right heart failure or declining right ventricular function in patients whose metastatic carcinoid disease and symptoms of carcinoid syndrome are well-controlled. Peri-operatively, optimal control of the carcinoid symptoms is required, often with large doses of octreotide, to avoid an anaesthesia-induced carcinoid crisis.[166]

Valve surgery should be performed soon after the onset of cardiac symptoms, as worsening right heart function increases the risk of surgery. Tricuspid valve replacement is the operation of choice, together with pulmonary valve replacement in selected cases. Balloon valvuloplasty is not recommended for pulmonary stensosis because of the co-existence of tricuspid and pulmonary valve regurgitation. Although mechanical valves are durable and unaffected by the vasoactive peptides, the need for anti-coagulation can be problematic particularly in patients requiring further surgery for their carcinoid disease, or in those with widespread liver disease due to risk of bleeding. [167] Hence bio-prosthetic valves are usually preferred; although these are prone to fibrosis as well, leading to premature degeneration, the life expectancy of the patient is often less than that of the new valve.[168]

Despite high surgical mortality (10-20%), valve replacement surgery can provide an increase in both longevity and quality of life in selected patients[169] [170] However higher surgical mortality rates of up to 63% have been reported in older patients over the age of 60. [171]

Summary

Carcinoid heart disease, almost exclusively related to fibrous infiltration of the right heart valves, occurs in approximately 50% of patients with carcinoid syndrome. All patients with carcinoid syndrome should undergo baseline echocardiography. The presence of significant cardiac involvement leads to a much poorer prognosis, with median survival of only nineteen months. Medical options other than judicious use of diuretics are limited. Valve replacement surgery can alleviate intractable symptoms and improve survival, and should be considered for patients with symptoms of right heart failure whose metastatic carcinoid disease and carcinoid syndrome symptoms are well controlled.

APPENDIX K: NEUROENDOCRINE TUMOUR MULTIDISCIPLINARY TEAM

1. Objectives of the MDM meeting are:

1. To ensure evidence-based treatment recommendations are being made with respect to patient management as clinical circumstances dictate.
2. To facilitate the referral, presentation and discussion of all new patients diagnosed with neuroendocrine tumours in South Australia at the Multidisciplinary Team meeting.
3. To maintain documentation of treatment recommendations for each patient, and communicate these to relevant team members including the referring physician, primary physician, and patient's medical chart.
4. To provide an opportunity to discuss: enrolment of particular patients in clinical trials and research activities (including clinical audit).
5. To obtain data documenting time from initial patient presentation to diagnosis to treatment for each patient.
6. To provide an educational environment for multidisciplinary team members, fellows, registrars and interns and visiting clinicians.
7. To contribute to a complete database of NET's diagnosed in South Australia.

2. Consent

All patients must be made aware that their case will be presented at the multidisciplinary team meeting for discussion and consent to this process. Consent may be either verbal or written and it must be noted in the patient's clinical health record and/or on the multidisciplinary meeting referral form.

(Patient information brochure on multidisciplinary team meetings is available)

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3. SA GEP-NET MDM MEETINGS IN SOUTH AUSTRALIA

-HOW TO REFER TO AN MDM MEETING

Refer to Contact Details on GEP-NET proforma for patients

-LOCATION AND TIMES

Cancer Council South Australia

202 Greenhill Road

Eastwood SA 5063

Time: 1800-1930

Frequency: currently every 6 weeks

Referral form GEPNET MDT Meeting

Please Return to:
David Moffat: david.moffat@imvs.sa.gov.au
Moses Beh: mosesbeh@gmail.com
Michael Kitchener: bronton@internode.on.net
CC:Gabby Cehic: gabby.cehic@health.sa.gov.au

PATIENT DETAILS

Name: _____ ***DOB:***_____-_____

Hospital: _____

URN:_____

DOCTOR DETAILS

Treating Doctor:_____

Phone/Email:_____

DIAGNOSIS AND CLINICAL SYNOPSIS

_____

_____

_____

PATHOLOGY

Date of biopsy: _____ ***Date of surgery:***_____

Which service:

- ☐ Pathology SA (IMVS/QEH/LMH)
- ☐ Pathology SA (FMC)
- ☐ APP
- ☐ Clinpath
- ☐ Healthscope/Gribbles
- ☐ Other:_____

Description of specimen:

_____

_____

BIOCHEMISTRY

	DATES								
Chromogranin A									
5HIAA									
Other:									

IMAGING

DATE	SERVICE							LOCATIONS							
	CT	*MRI*	*NM*				*Other*	Bensons	Dr Jones & Partners	Radiology SA	RAH	QEH	LMH	FMC	Other
			WB	^{111}In	^{177}Lu	^{FDG}PET									

SPECIFIC QUESTION(S) FOR MEETING:

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4. The South Australian GEPNET MDM Background and Future Considerations

This State based multidisciplinary meeting began in April 2009.

It was a response to both a state based need for a meeting in which such patients could be discussed, as well as to the recently created Australian NET guidelines, (COSA endorsed) which strongly encouraged the formation of MDM's in each State.

FORMAT:

Cases are presented, usually by the treating clinician, with review of relevant Histopathology and Imaging. Most disciplines are usually present at most meetings. The meetings are currently 6 weekly.

The overall aim of the multidisciplinary meeting is to enable a formal mechanism for multidisciplinary input into treatment planning and ongoing management and care of patients with NETs. Treatment decisions are the responsibility of the primary clinician responsible for the patient.

CHAIRPERSON:

The role of the chairperson is to co-ordinate the dates of the meeting decide which patients are selected to be presented at the meeting, run the meeting and ensure a summary of the discussion/recommendations is written up and distributed to the referring clinician within 2 weeks.

The inaugural Chairperson remains in this role. All support from pathology, imaging and nuclear medicine are prepared and presented by clinicians who do receive financial or administrative support for MDM.

A small amount of temporary secretarial support became available in August 2012. This is currently on a trial basis, with no dedicated financial support available at this time.

PATHOLOGY

The inaugural Pathologist has provided all the pathology support since the meeting began. All cases are prepared and presented in a power point format.

IMAGING:

Structural Imaging- Based on the data provided on the proforma completed by the clinicians, the relevant imaging is reviewed and presented, again in Power point format.

The inaugural Nuclear Medicine specialist reviews and presents the Nuclear Medicine scans

Radiology and Nuclear Medicine Scans from both public hospitals and private practices need to be sourced, obtained and converted into a suitable format for presentation at the Meetings for all patients. Time frame for storage of scans also needs to be formalised.

Case Discussion

Only patients whose referring clinician (or their delegate) is present at the meeting will be discussed. The referring clinician is responsible to ensure that all necessary patient clinical information is available for the meeting. The referring clinician provides the Chair with the appropriate clinical summary and investigation/diagnostic test results prior to the MDM Meeting. Late inclusions to the agenda are acceptable. In this instance it is the responsibility of the presenting clinician to ensure all appropriate clinical results are available to the meeting.

Case presentation and discussion will include the patient's clinical condition and any relevant psychosocial aspects impacting on clinical management.

The Chair will summarise the recommendations made from the discussion before moving to the next case.

OUTCOME:

For each patient, a case synopsis is written up along with a summary of the discussion and recommendations. This is provided to the treating clinician, usually within 1-2 weeks of the meeting. A copy of the summary and treatment recommendation will be distributed to the referring clinician who will subsequently notify the patient and patient's GP, other relevant MDM members, and the original copy will be filed into the patient's medical record.

CURRENT DIFFICULTIES:

1. Increasing patient numbers translates to additional workload for those presenting the meeting- all of which is unsupported. With the number of cases now capped at 8, this has resulted in some cases being deferred to later meetings. This has at times been met with frustration and disappointment by the referring clinicians.

2. Increasing the frequency of the meetings will place a significant strain on resources as those currently involved with chairing, and presenting imaging and pathology would not be able to maintain an increased workload without assistance.
3. Monitoring of MDM Key performance indicators:
4. Increasing discussion relating to a change of venue. A suitable alternative is yet to be found. Many patients are managed in private and the new venue will need to accommodate this.
5. Ongoing Pharma support- If this is to cease, this will be associated with an additional administrative burden.

FUTURE CONSIDERATIONS:

- Venue and Time of Meetings to currently to remain unchanged as it provides a good forum for open discussion and easily reached by nearly all.
- The potential for two or three sites with telelinks may be considered but will need infrastructure support, and a move closer to working hours may ultimately be considered if access is improved, e.g. 5-6pm Business Case to source a NET coordinator who could take on the administrative role.
- In the current economic climate, it is very unlikely that state government funding will be made available for this and that alternatives will need to be considered.
- Public donations
- MDM Medicare billing into a specific fund that can be accessed for this purpose
- Pharma Administrative support
- Rotate the Chair/Pathology and Imaging roles. To date, there have been no new “volunteers”. This could be overcome if dedicated time was assigned to these roles, especially from within SAMI (for imaging review) and SA pathology (histopathology support.)
- This is a reasonably specialised field and the number of suitably qualified specialists is limited
- Also competing with time demands from other MDM’s

APPENDIX L: ADDITIONAL TREATMENT INFORMATION

DEBULKING OF NON-HEPATIC DISEASE

Debulking surgery can be considered for control of symptoms that are resistant to medical management. Surgery should be considered to prevent intestinal obstruction or ischaemic complications. Before debulking is undertaken, appropriate staging should be done to exclude significant volume of extra-hepatic disease.

There are several scenarios where surgery should be considered in the presence of unresectable metastatic disease:

For patients with midgut NETs, palliative surgery to prevent intestinal obstruction or ischaemic complications secondary to desmoplastic mesenteric reaction offers the best chance of symptom control and has increased survival in highly selected case comparisons.

Palliative surgery should also be considered for large bowel obstruction.

Resection of primary disease leaving hepatic metastatic disease only may be indicated if it can be safely performed. This allows therapy to be directed at the hepatic metastases alone.

Resection of pancreatic disease may be indicated for local complications of obstruction or bleeding. Each patient needs to be treated on their own merits. Otherwise there is no evidence to support debulking of locally advanced non-functioning pancreatic tumours.

TARGETED THERAPIES

a) Anti-angiogenic agents

Several VEGF and VEGFR tyrosine kinase inhibitors have been studied mostly in pancreatic NETs. Significant reduction of tumour blood flow and improvement of PFS at week 18 (95% vs 68%; p=0.02) was noted with bevacizumab (monoclonal anti-VEGF Ab) when compared to pegylated interferon alpha.[172] When combined with temozolomide, bevacizumab was associated with a high disease control rate (PR+SD) in both pancreatic and non-pancreatic NETs (94% and 92%, respectively). As expected there were more partial responses observed in pancreatic NETs (24% vs 0).[173] An impressive, although unconfirmed, PR rate (60%) was reported in a small number of patients with progressive NETs with combination of bevacizumab and FOLFOX. However, patients with high grade tumours were also included in analysis.[174]

Sunitinib, a multikinase inhibitor (VEGFR, PDGFR, RET, c-Kit), achieved overall objective response rate of 16.7% in pancreatic and 2.4% in non-pancreatic NETs in an early study. In that study, median time to progression however, was longer in non-pancreatic then pancreatic NETs (10.2 and 7.7 months respectively), although one year survival rates were similar for both cohorts. [175] A recently published report of randomised trial of sunitinib versus placebo which enrolled patients with progressing advanced pancreatic

neuroendocrine tumours has shown a significant improvement in progression free survival (11.4 vs 5.5 months, hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; p<0.001).[176] With longer term follow up, the overall survival improvement which was initially observed is no longer statistically significant, although a trend towards survival benefit is still suggested.[177]

b) Mammalian target of rapamycin (mTOR) pathway inhibitors

Evidence of mTOR involvement in pathogenesis of NETs is suggested by association of germline mutations in the mTOR pathway with NETs. Both of the currently available mTOR inhibitors, temserolimus and everolimus (RAD001) have been studied in patients with NETs.

Temserolimus has shown a modest objective response rate of 5.6% in a phase II study but higher baseline levels of phosphorylated mTOR (p=0.01) predicted for a better response. An increase in pAKT and decrease in phosphorylated mTOR after the treatment correlated well with increased time to progression.[178]

Everolimus showed a promising ORR (20%) and median PFS (60 weeks) in initial phase II study. 179In a follow-on international phase II study (RADIANT-1) patients with advanced pancreatic NETs progressing after chemotherapy, were divided into two strata, everolimus alone (n=115) or everolimus plus octreotide (n=45) on the basis of whether the patients were receiving octreotide at study entry. The median PFS for patients receiving everolimus or everolimus and octreotide were 9.7 and 16.7 months, respectively. An early biomarker response (30% decrease or normalisation of CgA or NSE at week 4) correlated with superior PFS. 180Everolimus (RAD001) has been shown to significantly improve progression free survival in metastatic pancreatic neuroendocrine tumours in a randomised phase III trial (RADIANT-3) compared to placebo (11 versus 4.6 months, hazard ratio for disease progression and death, 0.35; 95% CI 0.27 to 0.45; p<0.001), although no overall survival improvement was observed. 181Crossover to everolimus in the placebo arm was allowed in the study, which does make overall survival difficult to interpret. Benefit is also suggested in a similar randomized study in patients with non-pancreatic neuroendocrine tumours and a history of the carcinoid syndrome, in which patients were treated with Sandostatin LAR with or without everolimus. 182Although this study did not meet its primary end point of an improvement in central review evaluated progression-free survival (hazard ratio 0.77, but p=0.026, above pre-set cut off of 0.0246), there was still a clinically meaningful 5.1 month progression-free survival difference between arms, and progression free-survival by investigator review was significantly improved; interpretation of the overall survival results are also complicated by crossover."

In metastatic well and intermediate differentiation pancreatic neuroendocrine tumours, the clear improvement in outcomes observed with the use of agents such as sunitinib and everolimus may make these agents preferable to chemotherapy earlier in the course of managing these patients.

Phase II trials of combining chemotherapy as a radiosensitiser with LuTate are ongoing.

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