An Roinn Sláinte
Department of Health

Diagnosis, staging and treatment of patients with oesophageal or oesophagogastric junction cancer

National Clinical Guideline No. 19

Summary August 2019

National Patient Safety Office
Oifig Náisiúnta um Shábháilteacht Othar

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

This National Clinical Guideline has been developed by the National Cancer Control Programme (NCCP) Guideline Development Group, within the Health Service Executive (HSE).

Using this National Clinical Guideline

This summary should be read in conjunction with the full version National Clinical Guideline. The full version is available at: https://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/. The complete list of appendices can be found in the full version. Only the relevant appendices are in this summary and the same numbering has been retained in both versions. This summary National Clinical Guideline applies to adults (18 years or older) with newly diagnosed oesophageal or oesophagogastric junction (OGJ) cancer, or, those that have a suspected diagnosis of oesophageal or OGJ cancer in a hospital setting.

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with oesophageal or OGJ cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with oesophageal or OGJ cancer and their significant others. Effort has been made to make this document more user-friendly, a list of medical abbreviations used throughout the guideline can be found in Appendix 8: Glossary of terms and abbreviations.

Disclaimer

NCEC National Clinical Guidelines do not replace professional judgment on particular cases, whereby the clinician or health professional decides that individual guideline recommendations are not appropriate in the circumstances presented by an individual patient, or whereby an individual patient declines a recommendation as a course of action in their care or treatment plan. In these circumstances the decision not to follow a recommendation should be appropriately recorded in the patient's healthcare record.

Users of NCEC National Clinical Guidelines must ensure they have the current version (hardcopy or softcopy) by checking the relevant section in the National Patient Safety Office on the Department of Health website: https://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/

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Membership of the Guideline Development Group

The Guideline Development Group was chaired by Professor John Reynolds, Upper Gastrointestinal Consultant Surgeon, St. James's Hospital, Dublin. This National Clinical Guideline is supported by the National Cancer Control Programme (NCCP).

Membership nominations were sought from a variety of clinical and non-clinical backgrounds so as to be representative of all key stakeholders within the Health Service Executive. Guideline Development Group members included those involved in clinical practice, administration including research and librarian services, and education.

Due to the nature of this disease and its treatment, the patient's life expectancy and the duration of guideline development, the NCCP felt that it was not appropriate to include patients as active members of the Guideline Development Group. Patients contributed via a focus group forum at The Oesophageal Cancer Fund (OCF) National Patient Support meeting held in April 2018. The NCCP recognise the importance of patient input and their role as key stakeholders in informing quality improvements in our healthcare system. This approach assisted in capturing the patient experience and aided discussion on important quality of life issues.

Name	Title/position	Role on guideline group
Professor John Reynolds	Consultant Surgeon, SJH	Chair and writing member
Radiology		
Dr Ciaran Johnston	Consultant Radiologist, SJH	Writing member
Dr Catherine Dewhurst	Consultant Radiologist, MUH	Writing member
Dr Peter MacEneaney	Consultant Radiologist, MUH	Contributor (until February 2015)
Dr Stephen Power	Radiology Specialist Registrar, MUH	Writing member
Dr Nuala Healy	Radiology Specialist Registrar, SJH	Contributor (until December 2017)
Pathology		
Dr Cian Muldoon	Consultant Histopathologist, SJH	Writing member
Professor Elaine Kay	Consultant Histopathologist, BH	Writing member
Dr Ciara Ryan	Consultant Histopathologist, SJH	Writing member
Dr Stephen Finn	Consultant Histopathologist, SJH	Contributor (until February 2015)
Surgery		
Mr Will Robb	Consultant Surgeon, BH	Contributor
Mr Narayanasamy Ravi	Consultant Surgeon, SJH	Writing member
Mr Raymond Kennedy	Consultant Surgeon SJH	Contributor (until February 2015)
Dr Claire Donohue	Surgical Specialist Registrar, SJH	Writing member
Gastroenterology		
Professor Dermot O'Toole	Consultant Gastroenterologist, SJH	Writing member
Medical oncology		
Dr Derek Power	Consultant Medical Oncologist, CUH	Contributor
Dr Greg Leonard	Consultant Medical Oncologist, UHG	Contributor
Dr Anne Horgan	Consultant Medical Oncologist, UHW	Contributor

Radiation oncology		
Dr Brian O'Neill	Consultant Radiation Oncologist, SLRON	Writing member
Dr Moya Cunningham	Consultant Radiation Oncologist, SLRON	Contributor
Dr Astrid Billfalk-Kelly	Radiation Oncology Specialist Registrar, SLRON	Contributor (until December 2017)
Patients representative groups		
Oesophageal Cancer Fund (OCF)	Patient representatives	Focus Group
Project management		
Ms Keira Doherty	Project Manager, NCCP	Writing member
Ms Evelyn O'Shea	Project Manager, NCCP	Writing member (until February 2015)
Research		
Dr Eve O'Toole	Guideline Methodologist, NCCP	Writing member/Guideline lead
Ms Louise Murphy	Research Officer, NCCP	Writing member/Research
Ms Deirdre Love	Senior Research Officer, NCCP	Contributor (until December 2016)
Dr Helena Gibbons	Senior Research Officer, NCCP	Writing member (from September 2017)
Dr Niamh Kilgallen	Senior Research Officer, NCCP	Writing member (from December 2017)
Library		
Ms Nicola Fay	HSE Librarian, HSE Midlands	Literature search
Ms Margaret Morgan	HSE Librarian, HSE East	Literature search
Mr Gethin White	HSE Librarian, HSE East	Literature search
Ms Marie Carrigan	HSE Librarian, SLRON	Literature search
Ms Maura Flynn	HSE Librarian, HSE Midlands	Literature search
Mr Brendan Leen	HSE Librarian, HSE South	Literature search
Health economist		
Ms Rebecca Moore	Health Economist, TCD	Writing member

Key:	
SJH	St. James's Hospital
MUH	Mercy University Hospital
BH	Beaumont Hospital
CUH	Cork University Hospital
UHG	University Hospital Galway
UHW	University Hospital Waterford
SLRON	St. Luke's Radiation Oncology Network
NCCP	National Cancer Control Programme
HSE	Health Service Executive
TCD	Trinity College Dublin

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1 Background

1.1 Impact of oesophageal cancer in Ireland

Cancer is a major healthcare challenge. Each year in Ireland, approximately 22,641 people are diagnosed with invasive cancer (excluding non-melanoma skin cancer) (National Cancer Registry Ireland (NCRI), 2018b). Cancer is the second leading cause of death in Ireland after diseases of the circulatory system. Deaths from cancer averaged about 8,875 deaths per year during 2013-2015, representing about 30.7% of all deaths in 2016 (NCRI, 2018b). Oesophageal cancer was ranked the sixth most common cause of cancer deaths in Ireland 2013-2015, with an average of 387 deaths annually from 2013-2015 (NCRI, 2018b).

Cancer incidence data from the NCRI and population projections from the Central Statistics Office (CSO) have been combined by the NCRI to estimate the number of new cancer cases expected in five year bands from 2020-2045. The total number of new invasive cancer cases (including non-melanoma skin cancer) is projected to increase by 84% for females and 111% for males between 2015 and 2045, based only on changes in population size and age distribution (demography).

The incidence of oesophageal cancer in Ireland is projected to rise. By 2045 cases of oesophageal cancer are projected to increase by 60% in females and 103% in males (model median estimate projection) (NCRI, 2019).

The National Cancer Strategy 2017-2026 (Department of Health (DoH), 2017) was published on the 5th of July 2017 and focuses on prevention, early diagnosis, treatment and quality of life and works towards improving the treatment, health & wellbeing, experiences and outcomes of those living with and beyond cancer.

1.2 Cancer centres, multidisciplinary teams and Hospital Groups

In Ireland, there are nine hospitals designated as cancer centres which includes one paediatric cancer centre. As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

Following the 2006 National Cancer Strategy (Department of Health and Children (DoHC), 2006), the National Cancer Control Programme (NCCP) was set up to implement its recommendations. These nine regional cancer centres were designated to support implementation.

The NCCP engages regularly with the individual cancer centres and with Hospital Group structures. Discussion of performance data, improvement plans, and resources including manpower, service planning and development takes place at regular review meetings between the NCCP and senior management at cancer centre and Hospital Group level. This provides an opportunity to share good practice from other cancer centres, if relevant. Where resource issues are identified, these are included in the service planning process. As specific issues arise in hospitals, these are managed by senior hospital management.

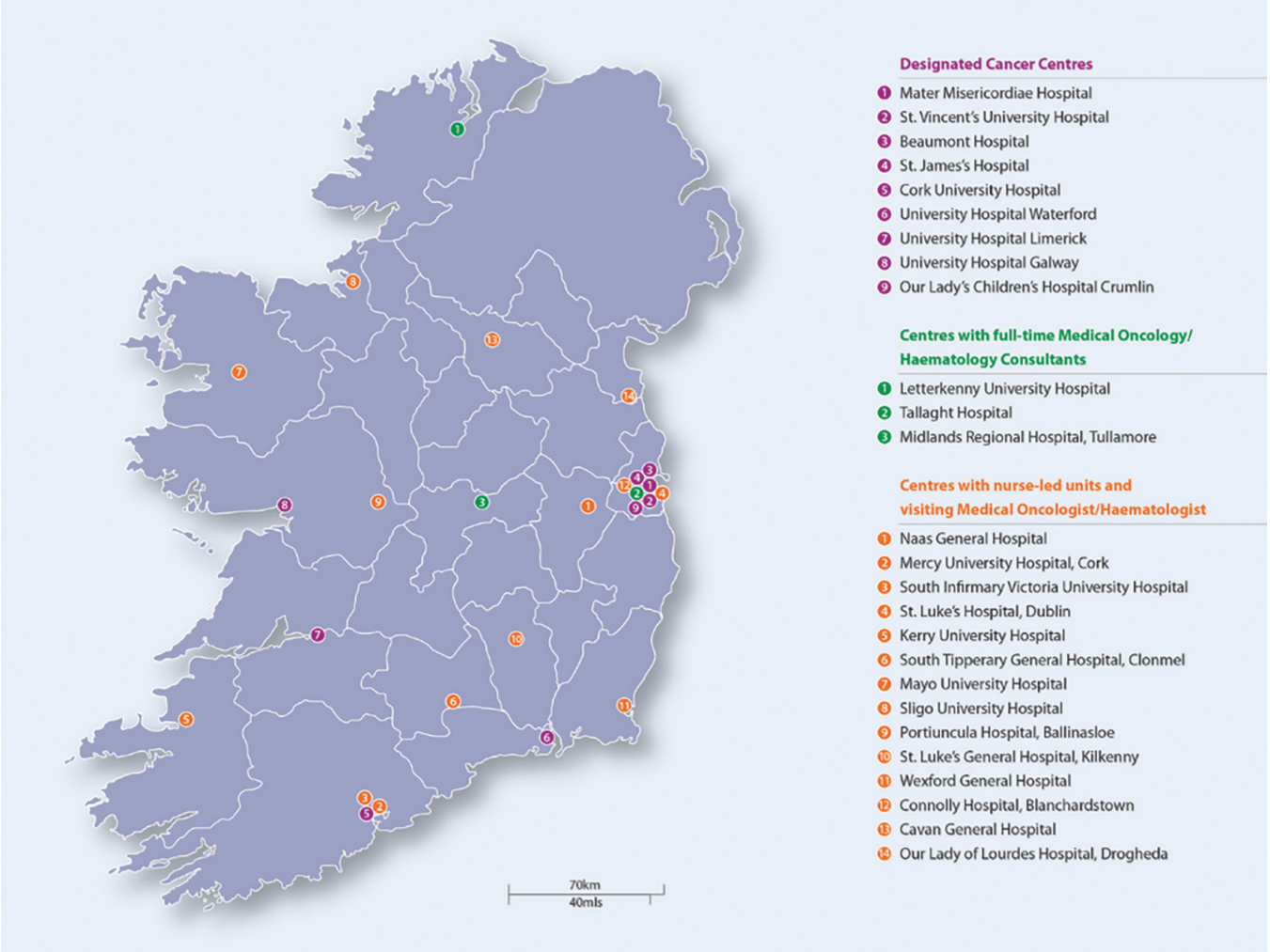

Figure 1: Cancer services in Ireland

Recommendation 13 of the National Cancer Strategy 2017-2026 (DoH, 2017) states "Patients diagnosed with cancer will have their case formally discussed at a multidisciplinary team meeting. The NCCP, working with the Hospital Groups, will oversee and support multidisciplinary team composition, processes and reporting of outcomes".

A multidisciplinary team is a group of healthcare workers who are members of different disciplines each providing specific services to the patient. The team members independently treat various issues a patient may have, focusing on the issues in which they specialise. While the multidisciplinary team consists of clinical staff involved in clinical decision making, diagnosis and treatment aspects of care, nursing, pharmacy and allied health professionals are also involved in the day to day management of the patient. For patients with oesophageal/OGJ cancer, the core multidisciplinary team membership who should be involved in their care is specified in clinical question 2.4.10. Any multidisciplinary team meeting held to discuss patients with oesophageal/OGJ cancer should align itself regarding location and composition to the National Cancer Strategy recommendation 13.

The hospitals in Ireland are organised into seven Hospital Groups. The services delivered include inpatient scheduled care, unscheduled/emergency care, maternity services, outpatient and diagnostic services. The Chief Executive of each Hospital Group reports to the National Director for Acute Services and is accountable for their Hospital Group's planning and performance under the HSE Accountability Framework. The establishment of the Hospital Groups allows for better utilisation of hospital resources which are governed by agreed patient protocols and pathways.

1.3 Centralisation of services

Cancer patients should have access to high quality care staffed by appropriate specialists to ensure optimal treatment and improve patient outcomes. Recommendation 21 of The National Cancer Strategy 2017-2026 states "The NCCP will draw up a plan setting out which number/location of designated cancer centres in which surgery will take place for the various tumour types. Timescales for the implementation of the plan will be included for each tumour type" (DoH, 2017). The NCRI (2019) report showed that oesophageal cancer patients survival improvements appeared most marked among patients first treated or diagnosed in a designated surgical centre.

The National Cancer Strategy 2017-2026 has set a target that 95% of cancer surgeries will be conducted in approved centres by 2020. It is acknowledged throughout the implementation plan for this guideline, that service centralisation of oesophageal cancer services is required in order to implement a number of its recommendations. The NCCP, in consultation with the Department of Health, is currently undertaking a programme of work in relation to cancer surgery centralisation with a view to obtaining Ministerial approval. Funding for centralisation of cancer surgeries will be sought through normal service planning processes and is not relevant to the budget impact analysis for this guideline.

1.4 Context and scope of this National Clinical Guideline

The National Cancer Strategy (DoHC, 2006) recommended that national, tumour site-specific, multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The purpose of developing these guidelines is to improve the quality of care received by patients.

The National Cancer Strategy 2017-2026 (DoH, 2017) recommendation 37 states that "The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards".

A Guideline Development Group was established to develop evidence-based guidelines for the diagnosis, staging and treatment of patients with oesophageal or OGJ cancer. The guideline development process is described in detail in Section 3: Development of a National Clinical Guideline. This National Clinical Guideline will improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.

This guideline focuses on the diagnosis, staging, and treatment of patients with oesophageal or OGJ cancer. It does not include recommendations covering every detail of diagnosis, staging, and treatment nor does it include specific guidance on nutritional intervention, physical rehabilitation or full multidisciplinary team management of patients with oesophageal cancer or OGJ cancer. It focuses solely on areas of clinical practice that are known to be controversial or uncertain, where there is variation in practice, where there is new or emerging evidence, or where there is potential for most impact. The aims and objectives of this guideline, along with the clinical question which addresses each one, are explicitly stated in Section 3.3 Aims and objectives.

2 National Clinical Guideline

2.1 Summary of clinical recommendations, practical considerations around patient care and summary of budget impact analysis

Here follows a list of all the recommendations in this guideline, along with the grade of that recommendation. The grade reflects the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence and grading systems used are documented in Appendix 9: Levels of evidence & grading systems.

A list of practical considerations around patient care was generated through collaboration with patient representatives from the Oesophageal Cancer Fund (OCF) following a focus group meeting.

Section	Recommendation	Grade of recommendation
Radiology	**2.2.1.1** **Early-stage** In patients with early-stage oesophageal/OGJ cancer, OGD plus diagnostic CT followed by EUS is recommended.	**B**
	2.2.1.2 **Early-stage** In patients with early-stage oesophageal/OGJ cancer who have had an OGD, diagnostic CT and EUS, PET-CT may be considered following discussion at a multidisciplinary team meeting.	**C**
	2.2.1.3 **Advanced-stage** In patients with advanced-stage oesophageal/OGJ cancer, OGD plus diagnostic CT is recommended.	**B**
	2.2.1.4 **Advanced-stage** In patients with advanced-stage oesophageal/OGJ cancer, if no metastatic disease is identified on CT, further evaluation with PET-CT is recommended. If no metastatic disease is identified on PET-CT, further evaluation with EUS is recommended.	**B**
	2.2.1.5 **Advanced-stage** In patients with advanced-stage oesophageal/OGJ cancer, if metastatic disease is identified on CT, there is generally no role for further imaging with PET-CT.	**B**

Section	Recommendation	Grade of recommendation
Pathology	**2.3.1.1** For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends the use of the AJCC 8th edition for pathological staging.	**A**
	2.3.1.2 For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends standardised reporting using the current dataset guidelines published by the Royal College of Pathologists, UK.	**A**
	2.3.2.1 For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends that every lymph node identified is examined.	**D**
	2.3.3.1 In resected oesophageal/OGJ cancer specimens the distance from the tumour to the circumferential resection margin (CRM) should be stated microscopically and in millimetres to one decimal point.	**B**

Section	Recommendation	Grade of recommendation
Surgery & Gastroenterology	**2.4.1.1** In patients with oesophageal/OGJ cancer careful clinical assessment with respect to operative fitness including discussion in the context of an upper gastrointestinal multidisciplinary meeting should be performed. Patients with clinical or physiological evidence of cardiac or respiratory disease should be assessed by appropriate medical specialists.	**D**
	2.4.2.1 In patients with locally advanced oesophageal adenocarcinoma involving the abdominal oesophagus or junction staging laparoscopy is recommended.	**B**
	2.4.3.1 **Classification** OGJ tumours should be classified as type I (distal oesophagus), type II (cardia) and type III (proximal stomach).	**C**
	2.4.3.2 **Surgical approach** In patients with OGJ cancer the operative strategy should ensure that adequate in vivo longitudinal (oesophagectomy 5 cm; extended gastrectomy 3 cm) and radial resection margins (R0) are achieved with lymphadenectomy appropriate to the histological tumour type and its location.	**B**

Section	Recommendation	Grade of recommendation
	2.4.3.3 **Surgical approach** Type III OGJ tumours should be treated by transhiatal extended total gastrectomy.	**B**
	2.4.3.4 **Surgical approach** Type II OGJ tumours should be treated by transhiatal/transthoracic oesophagectomy or extended total gastrectomy.	**B**
	2.4.3.5 **Surgical approach** Type I OGJ tumours should be treated by transthoracic oesophagectomy or transhiatal in selected cases.	**B**
	2.4.4.1 **Barrett's related neoplasia** In patients with early oesophageal/OGJ cancer endoscopic resection (ER) should be considered the therapy of choice for neoplasia associated with visible lesions and T1a adenocarcinoma.	**B**
	2.4.4.2 **Ablative therapy for flat high-grade dysplasia (HGD) and residual Barrett's after endoscopic resection** In the presence of HGD or intramucosal cancer without visible lesions (flat HGD/intramucosal cancer), these should be managed with radiofrequency ablation (RFA).	**A**
	2.4.4.3 **Squamous cell neoplasia (superficial lesions)** In patients with early oesophageal/OGJ cancer endoscopic resection is recommended for staging and/or treatment of visible lesions.	**C**
	2.4.4.4 In patients with early oesophageal/OGJ cancer the Guideline Development Group does not recommend radiofrequency ablation treatment for squamous cell neoplasia in Western populations.	**D**
	2.4.5.1 In patients with locally advanced oesophageal cancer, transthoracic oesophagectomy is recommended.	**A**
	2.4.5.2 In patients with oesophageal cancer with high operative risk, transhiatal oesophagectomy can be considered as it has reduced respiratory morbidity compared to transthoracic oesophagectomy.	**A**
	2.4.5.3 For patients with OGJ tumours which can be resected with R0 margins and a lower mediastinal and nodal dissection, a transhiatial approach can be considered.	**B**

Section	Recommendation	Grade of recommendation
	2.4.5.4 For patients with locally advanced oesophageal cancer, transthoracic oesophagectomy may be of benefit where positive lymph nodes are present (1-8 nodes) or predicted compared with node negative patients.	**B**
	2.4.6.1 In patients with oesophageal/OGJ cancer, the Guideline Development Group recommends two-field lymphadenectomy.	**B**
	2.4.7.1 In patients with oesophageal/OGJ cancer all surgical approaches, including open, hybrid, and MIO can be considered.	**A**
	2.4.7.2 In patients with oesophageal/OGJ cancer, MIO appears to have advantages with respect to pulmonary morbidity, in particular the risk of pneumonia.	**B**
	2.4.7.3 In patients with oesophageal/OGJ cancer there is no evidence of superiority of MIO or hybrid procedures on oncological outcomes compared with open surgery.	**D**
	2.4.8.1 In patients with oesophageal/OGJ cancer, the use of enhanced recovery after surgery (ERAS) programmes should be considered, as they are compatible with favourable morbidity, mortality and length of stay.	**C**
	2.4.9.1 Oesophageal/OGJ surgery should be performed by surgeons who attend a specialist multidisciplinary team meeting in a designated oesophageal cancer centre with outcomes audited regularly.	**B**
	2.4.10.1 Patients with oesophageal or OGJ cancer (both invasive and non-invasive) should be discussed at a multidisciplinary team meeting, this improves decision making and management and by inference has an impact in overall survival.	**B**

Section	Recommendation	Grade of recommendation
Palliative Care	**2.5.1.1** For patients with cancer, early provision of palliative care can improve patient outcomes.	**C**
	2.5.1.2 Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	**D**

Practical considerations around patient care
• For all patients with oesophageal/OGJ cancer, early referral to a specialist dietitian should be considered.
• Consider referral of oesophageal/OGJ cancer patients to a physiotherapist.
• Consider referral of oesophageal/OGJ cancer patients to psycho-oncology and/or a medical social worker for psychological support.
• Patients with oesophageal/OGJ cancer should have access to a Clinical Nurse Specialist (CNS) as a single point of contact to co-ordinate patient education and care requirements that impact on quality of life.
• Post-treatment referral to a speech and language therapist should be considered for patients with oesophageal/OGJ cancer.

Summary of Budget Impact Analysis	
Subgroup	**Cost of implementation**
Radiology	€513,836
Pathology	€0
Surgery & Gastroenterology	€395,200
Palliative Care	€0
Total cost of implementation	**€909,036**

2.2 Radiology

The following are responsible for implementation of the radiology recommendation:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical Question 2.2.1

For patients with oesophageal/OGJ cancer, what is the utility of CT, PET-CT and EUS for T, N, and M staging and survival outcomes?

Evidence summary
A number of retrospective studies addressed this clinical question (Wani et al., 2015, Findlay et al., 2015, Shin et al., 2014, Cuellar et al., 2014, Dhupar et al., 2014, Noble et al., 2009).

The Guideline Development Group found the quality of the studies was low.

Standard workup for diagnosing a patient with oesophageal cancer, includes OGD (oesophagogastro duodenoscopy) and biopsy followed by staging contrast enhanced computed tomography (CT) thorax, abdomen and pelvis (TAP).

Suspected early-stage (0-I) oesophageal cancer
If suspected early-stage (0-I) on CT (Figure 2), patients can be referred for endoscopic ultrasound (EUS) for more accurate T and locoregional N staging.

The NICE (2018) guidelines recommends that patients with suspected T1 oesophageal cancer are offered endoscopic mucosal resection for staging.

While there is a paucity of evidence regarding the use of positron emission tomography – computed tomography (PET-CT) in staging early oesophageal cancer, the available evidence suggests limited utility of PET-CT in staging early tumours particularly in adenocarcinoma subtypes (Cuellar et al., 2014, Noble et al., 2009).

Sensitivity and positive predictive value for the identification of nodal disease was 0% and accuracy was 82% in a small population of early-stage patients with adenocarcinoma (Cuellar et al., 2014). In a large study by Wani et al., PET-CT did not result in an improvement in survival for patients with in-situ and locoregional adenocarcinoma or in-situ squamous cell carcinoma (Wani et al., 2015), arguing against its routine use in this population.

The current literature does not provide sufficient data to accurately quantify the number of patients over- or under-staged on PET-CT compared to EUS and CT for early-stage patients.

Suspected advanced-stage (II-IV) oesophageal cancer
If suspected advanced-stage (II-IV) on CT (Figure 2), patients can be referred for PET-CT and subsequently EUS, if no metastatic disease on PET-CT for accurate N and M staging.

Wani et al. (2015) demonstrated a survival benefit following PET-CT in patients with advanced-stage adenocarcinoma and squamous cell oesophageal cancer. Receipt of PET-CT was a significant predictor of improved one- (HR, 0.57; 95% CI, 0.51-0.64; p<.0001), three- (HR, 0.66; 95% CI, 0.60-0.73; p<.0001), and five-year survival (HR, 0.67; 95% CI, 0.62- 0.74; p<.0001).

The Dhupar et al. paper comparing nodal positivity on CT, PET-CT and EUS demonstrated reduced survival in patients with positive nodes on imaging (Dhupar et al., 2014).

The Findlay et al. study showed that PET-CT altered management in 23% of cases and identified unsuspected metastasis in 13% of cases (Findlay et al., 2015).

PET-CT was found to be helpful in planning management in 174 cases (91%), changed staging in 65 cases (34%), and management in 50 cases (26%). The overall sensitivity of PET-CT in detecting distant metastases was 91% and its specificity was 94% (Noble et al., 2009).

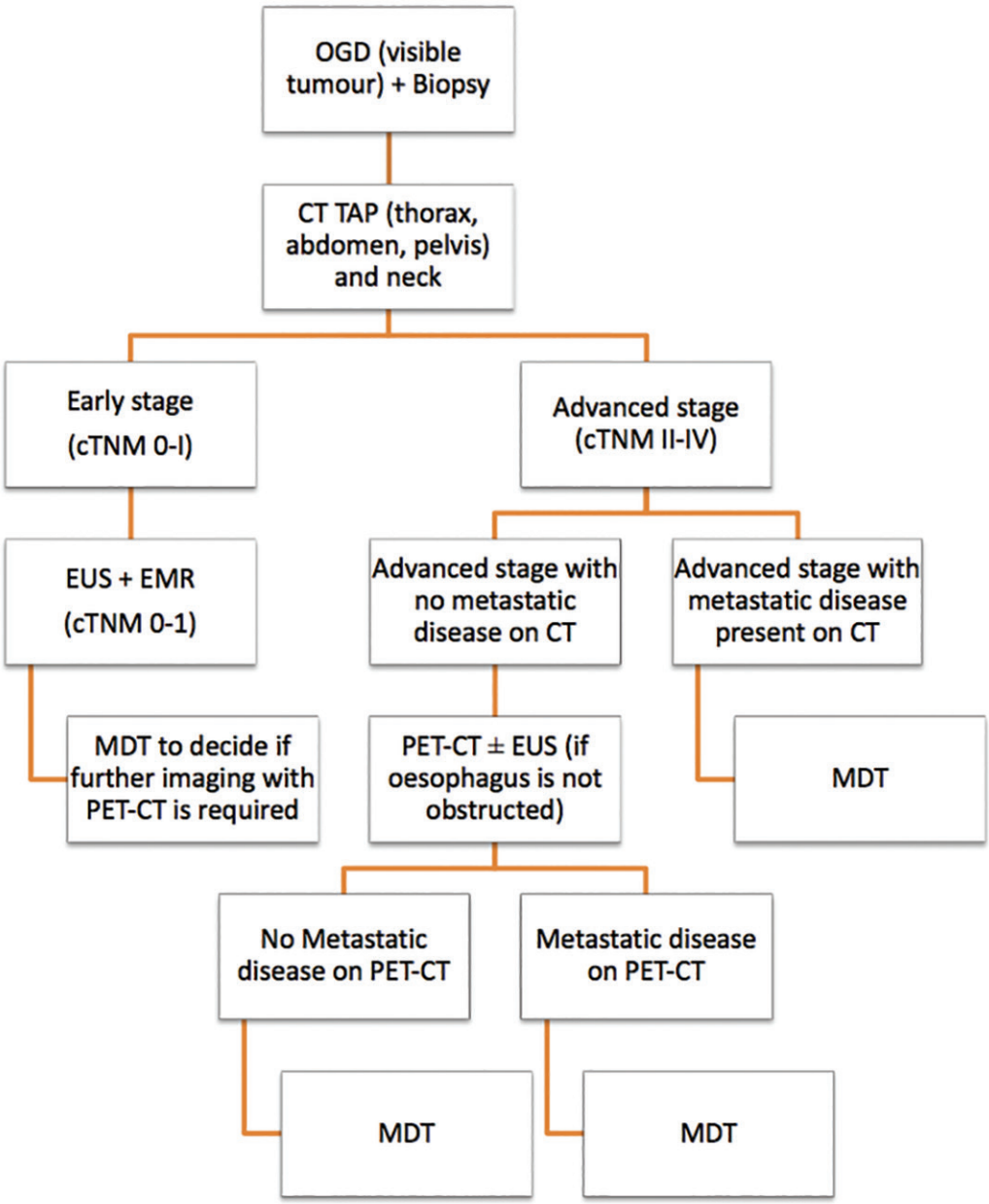

Figure 2: Algorithm for sequence of imaging modalities for diagnosis and staging early and advanced oesophageal cancer using the AJCC 8th edition (Amin, 2017) (Source: NCCP Oesophageal Guideline Development Group)

Recommendation 2.2.1.1	Grade of recommendation
Early-stage In patients with early-stage oesophageal/OGJ cancer, OGD plus diagnostic CT followed by EUS is recommended.	**B**

Recommendation 2.2.1.2	Grade of recommendation
Early-stage In patients with early-stage oesophageal/OGJ cancer who have had an OGD, diagnostic CT and EUS, PET-CT may be considered following discussion at a multidisciplinary team meeting.	**C**

Recommendation 2.2.1.3	Grade of recommendation
Advanced-stage In patients with advanced-stage oesophageal/OGJ cancer, OGD plus diagnostic CT is recommended.	**B**

Recommendation 2.2.1.4	Grade of recommendation
Advanced-stage In patients with advanced-stage oesophageal/OGJ cancer, if no metastatic disease is identified on CT, further evaluation with PET-CT is recommended. If no metastatic disease is identified on PET-CT, further evaluation with EUS is recommended.	**B**

Recommendation 2.2.1.5	Grade of recommendation
Advanced-stage In patients with advanced-stage oesophageal/OGJ cancer, if metastatic disease is identified on CT, there is generally no role for further imaging with PET-CT.	**B**

Good Practice Point
Patients diagnosed with oesophageal cancer outside a tertiary referral centre, should be referred to a tertiary centre for multidisciplinary team meeting discussion and further investigations, following OGD and CT.

Good Practice Point
PET-CT is not routinely indicated in patients with stage IV oesophageal cancer.

2.3 Pathology

The following are responsible for the implementation of pathology recommendations:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.3.1

What constitutes the minimum data to be included as standard on pathology reports of resected oesophageal/OGJ specimens?

Evidence summary

The Guideline Development Group have reviewed the evidence that supports the continued assessment of parameters that are required for accurate pathological staging as per the AJCC 8th edition (Rice et al., 2016a, Rice et al., 2016b, Rice et al., 2017). The Guideline Development Group recommends the use of the AJCC 8th edition for pathological staging.

The Guideline Development Group recommend standardised reporting using the current dataset guidelines published by the Royal College of Pathologists, UK.

For local resection specimens, nodal status does not apply.

The Guideline Development Group recommend the use of the Mandard classification system for tumour regression grade (Mandard et al., 1994).

Recommendation 2.3.1.1	**Grade of recommendation**
For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends the use of the AJCC 8th edition for pathological staging.	**A**

Recommendation 2.3.1.2	**Grade of recommendation**
For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends standardised reporting using the current dataset guidelines published by the Royal College of Pathologists, UK.	**A**

Clinical question 2.3.2

Is there a minimum number of lymph nodes that should be identified and evaluated from a resected specimen from a patient with oesophageal/OGJ cancer in order to ensure accurate pathological staging?

Evidence summary

Five retrospective studies address this clinical question (Samson et al., 2017, Groth et al., 2010, Bollschweiler et al., 2006, Wu et al., 2016, Hanna et al., 2015) and were deemed as low quality by the Guideline Development Group.

There is currently no robust evidence to determine the number of lymph nodes that should be identified and evaluated.

The higher the number of lymph nodes examined the less likely the patient is to be understaged. The point at which the optimum number of nodes is reached is unclear.

Recommendation 2.3.2.1	Grade of recommendation
For patients with oesophageal/OGJ cancer, the Guideline Development Group recommends that every lymph node identified is examined.	D

Good Practice Point

In the absence of more robust evidence, if fewer than 15 nodes are identified re-examination of the specimen for lymph nodes is recommended.

Clinical question 2.3.3

In resected oesophageal/OGJ cancer specimens how should an involved (positive) circumferential resection margin (CRM) be defined?

Evidence summary

This question was addressed in two guidelines (The Royal College of Pathologists (RCPath), 2007, College of American Pathologists (CAP), 2016), two meta-analyses (Wu et al., 2014, Chan et al., 2013) and several prospective and retrospective studies (Lee et al., 2015, Ahmad et al., 2013, Hulshoff et al., 2015, Okada et al., 2016, Markar et al., 2016, Ghadban et al., 2016, O'Neill et al., 2013).

Having a positive margin defined by RCPath or CAP clearly correlated with poor survival. The status of CRM influences the decision to treat. On the basis of the evidence the definition of a positive margin remains undefined. The clinical significance of a distance to CRM of 0-0.99 mm remains uncertain.

Until such a time as a clear definition emerges, the distance from the tumour to the CRM should be stated in the report as an absolute measurement.

Recommendation 2.3.3.1	Grade of recommendation
In resected oesophageal/OGJ cancer specimens the distance from the tumour to the circumferential resection margin (CRM) should be stated microscopically and in millimetres to one decimal point.	**B**

2.4 Surgery and Gastroenterology

The following are responsible for the implementation of surgery and gastroenterology recommendations:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.4.1

In patients undergoing oesophageal surgery with curative intent does a detailed physiological assessment or exercise testing assessment accurately select/predict patients who are higher risk of peri-operative mortality/severe morbidity?

Evidence summary
A guideline (Allum et al., 2011), a systematic review (Dutta et al., 2010), three prospective studies (Moyes et al., 2013, Bosch et al., 2011, Dutta et al., 2011) and two retrospective studies (McCulloch et al., 2003, Bartels et al., 1998) addressed this clinical question.

Up to half of all patients with oesophageal cancer may not be fit for resection surgery (McCulloch et al., 2003). Complications can be reduced by removing those patients at greatest risk from the surgical cohort (Bartels et al., 1998).

Tools such as risk scoring systems or pre-operative physiological testing, which could augment clinical judgement regarding operative fitness would be of benefit in clinical practice.

Scoring systems for risk prediction specifically for patients with oesophageal cancer have been developed but have not been independently validated and may overestimate mortality risk and underestimate morbidity risk (Bosch et al., 2011, Dutta et al., 2011, Dutta et al., 2010).

Cardiopulmonary exercise testing (CPX) is a dynamic non-invasive objective test that evaluates the ability of the cardiorespiratory system to adapt to a sudden increase in oxygen demand. The ramped exercise test is performed on a cycle ergometer with ECG monitoring and analysis of expired carbon dioxide and oxygen consumption. (Allum et al., 2011)

In the only study that specifically examines the use of CPX in patients prior to oesophagogastric surgery, the previously recommended anaerobic threshold of <11ml/min/kg and/or with significant myocardial ischaemia on CPX (Older et al., 1993) had poor sensitivity (45%) and specificity (30%). In this cohort of 180 patients the anaerobic threshold cut-off value (9ml/min/kg) with best predictive ability was not accurate enough for use in routine clinical practice (sensitivity of 74%; specificity of 57%) (Moyes et al., 2013).

In a study of 91 patients who had undergone transthoracic oesophagectomy, maximum oxygen uptake during exercise correlated well with postoperative cardiopulmonary complications (Nagamatsu et al., 2001). FVC (forced vital capacity) <80% or FEV1 (forced expiratory volume in one second) <70%, predicts complications. The authors concluded that transthoracic oesophagectomy can safely be performed on patients with a maximum oxygen uptake of at least 800 ml/min/m^2. This conclusion has been disputed in a study of 78 consecutive patients who had CPX testing prior to oesophagectomy, where CPX testing was found to be only of limited value in predicting postoperative cardiopulmonary morbidity (Forshaw et al., 2008). Limitations of CPX testing can occur in patients with reduced lower limb function related to osteoarthritis or limb dysfunction. (Allum et al., 2011)

Recommendation 2.4.1.1	**Grade of recommendation**
In patients with oesophageal/OGJ cancer careful clinical assessment with respect to operative fitness including discussion in the context of an upper gastrointestinal multidisciplinary meeting should be performed. Patients with clinical or physiological evidence of cardiac or respiratory disease should be assessed by appropriate medical specialists.	**D**

Good Practice Point
There are no specific risk scoring systems, exercise or physiological assessments which adequately predict operative risk.

Clinical question 2.4.2

What are the indications for staging laparoscopy for oesophageal cancer and OGJ cancer patients?

Evidence summary

Three guidelines (National Comprehensive Cancer Network (NCCN), 2018, Allum et al., 2011, National Institute for Health and Care Excellence (NICE), 2018) and a systematic review (Richardson and Khan, 2012) addressed this clinical question.

There was international consensus that staging laparoscopy may be useful in the staging of locally advanced oesophageal tumours in select patients, especially those with Siewert type II and type III OGJ tumours (Allum et al., 2011, NCCN, 2018). The NICE guideline (2018) adds that staging laparoscopy should only be considered for patients with oesophageal/OGJ cancer when it will help guide ongoing management.

Richardson and Khan (2012) conducted a systematic review to investigate if staging laparoscopy provides useful additional staging information in patients with radiologically-staged resectable disease undergoing an oesophagectomy for an OGJ tumour. The review included five retrospective studies (Heath et al., 2000, Bonavina et al., 1997, Romijn et al., 1998, Krasna et al., 2002, de Graaf et al., 2007). There were no RCTs included and the five retrospective cohort studies had small patient numbers, did not include patients undergoing neoadjuvant therapy and addressed OGJ cancer only. The review concluded that as an additional tool following radiological staging of OGJ tumours, staging laparoscopy does appear to detect previously occult peritoneal metastases as well as liver metastases and lymph nodes and these findings do in turn lead to changes in management in over ten percent of patients. However, it was noted that although staging laparoscopy does appear to be superior to radiological imaging alone in detecting occult disseminated disease, it was still associated with a false negative rate of approximately 5%. The procedure is also associated with some morbidity and its efficacy in changing management in the era of routine PET scanning remains to be evaluated.

Recommendation 2.4.2.1	**Grade of recommendation**
In patients with locally advanced oesophageal adenocarcinoma involving the abdominal oesophagus or junction staging laparoscopy is recommended.	**B**

Good Practice Point

There is no relevant literature to support the use of staging laparoscopy in squamous cell carcinoma.

Good Practice Point

Access to staging laparoscopy should be timely (10 working days) to avoid unnecessary treatment delay.

Clinical question 2.4.3

Does classification of OGJ cancers into Siewert classification change the treatment options (plan) for patients?

Evidence summary

A guideline (Allum et al., 2011), three randomised studies (Johansson et al., 2004, Hulscher et al., 2002, Sasako et al., 2006), including a five year follow-up (Omloo et al., 2007), four prospective studies (Siewert et al., 2006, Barbour et al., 2008, Grotenhuis et al., 2013, Siewert et al., 2000) and five retrospective studies (Reynolds et al., 2010, Curtis et al., 2014, Barbour et al., 2007, Leers et al., 2009, Pedrazzani et al., 2007) addressed this clinical question.

The term OGJ tumour was redefined in the 8th edition of the AJCC/UICC staging classification system: adenocarcinomas with epicentres no more than 2 cm from the gastric cardia (Siewerts type II) are staged as oesophageal adenocarcinomas, and those extending further are staged as stomach cancers (Siewerts type III) (Rice et al., 2017). The junction (cardia) is defined endoscopically by where gastric rugal folds meet the end of the tubular oesophagus. This classification, first proposed by Siewert et al. is used to subdivide OGJ tumours into type I, II, and III (Siewert et al., 2000) (Table 1).

Table 1: Siewert classification subdivision of OGJ tumours

Siewert classification	
Type I	The centre of the cancer or more than two thirds of identifiable tumour mass is located >1 cm proximal to the anatomical cardia;
Type II	The centre of the cancer or the tumour mass is located in an area extending 1 cm proximal to the gastro-oesophageal junction to 2 cm distal to it;
Type III	The centre of the tumour or more than two thirds of identifiable tumour mass is located >2 cm below the gastro-oesophageal junction.

Although some single centre series suggest differences in tumour biology between types (Siewert et al., 2006, Reynolds et al., 2010, Curtis et al., 2014) with improved overall survival in type I tumours, perhaps related to reduced nodal involvement or less margin involvement, there are no large scale population-based studies to allow a definitive statement on biological differences to be made.

Staging

There have been several reports of difficulties with accurate application of Siewert staging pre-operatively with discrepancies between endoscopic typing versus pathologic typing noted in both randomised controlled trials (Hulscher et al., 2002), prospective studies (Grotenhuis et al., 2013) and in large retrospective studies (Leers et al., 2009). This is largely due to bulky tumours obscuring the landmarks making assignment of type impossible or due to the tendency to label those tumours found at pathological analysis to be type II, as type I at endoscopy. Lymph node involvement is thought to differ according to Siewert type (Siewert et al., 2000), leading to the proposal that different surgical approaches are warranted with each type of tumour.

Extent of lymph node involvement

For adenocarcinomas, most surgeons accept the need for an adequate abdominal lymphadenectomy as the predominant route of lymphatic spread in lower third tumours is in a caudal direction (Pedrazzani et al., 2007). The extent of mediastinal lymphadenectomy, particularly in the upper half of the mediastinum, remains unclear.

Experience from Munich has shown in type II OGJ tumours that the pattern of lymph node involvement is mediastinal (2.1%), paraoesophageal (15.6%) and intraabdominal (56-72%) (Siewert et al., 2000). The most widely practiced operation is the two-phase Ivor Lewis operation with a laparotomy followed by a right thoracic approach with the anastomosis high in the chest. Some surgeons favour a third stage with a cervical incision to create the anastomosis at this level. (Allum et al., 2011)

This may be an important consideration to gain adequate clearance in tumours arising from or extending into the mid or upper oesophagus.

Surgical approach

In a large Dutch randomised study (n=220), a 14% non-significant (p=0.33) difference in survival was evident in a subset of patients with adenocarcinoma of the distal oesophagus (type I tumours). Notably, patients with one to eight positive lymph nodes on pathological assessment had improved locoregional disease-free survival if operated via the transthoracic route (64% vs. 23% for transhiatal). Although retrospective non-matched studies have indicated a survival benefit from a radical thoracic oesophagectomy compared with transhiatal oesophagectomy. A post-hoc subgroup analysis from the Dutch randomised trial identified improved local control in node positive patients, there is no level I data from the Dutch and other smaller randomised studies based on intention-to-treat in support of the oncological superiority of the transthoracic approach (Johansson et al., 2004) for type I or II tumours.

The approach to cardia, subcardia (type III) and some type II OGJ cancers can be via an extended total gastrectomy or oesophagogastrectomy. The aim is to ensure adequate local clearance, appropriate lymphadenectomy and an uncomplicated anastomosis with low morbidity. Barbour and colleagues have reported that an ex vivo proximal margin of >3.8 cm of normal oesophagus (which equates to 5 cm in vivo) is associated with a minimal risk of anastomotic recurrence and is an independent predictor of survival (Barbour et al., 2007). Lymphadenectomy should include a formal dissection of D2 and posterior mediastinal, perioesophageal nodes. A randomised comparison of transhiatal and left thoracoabdominal extended total gastrectomy for type III tumours was halted after interim analysis as the left thoracoabdominal approach was highly unlikely to have a superior overall survival than transhiatal oesophagectomy and was associated with greater morbidity (Sasako et al., 2006). The authors postulated that this reflected the greater physiological insult associated with thoracotomy. Thus, for these tumours, a transhiatal, extended total gastrectomy should be considered with an oesophagogastrectomy the alternative if an adequate proximal margin cannot be achieved. Non-randomised comparative health related quality of life (HRQoL) data add further support for this approach (Barbour et al., 2008).

Although ongoing application of Siewert grading is recommended, there is a lack of evidence regarding its suitability to guide treatment decisions particularly with respect to selection of operative approach. Operative approaches should be individualised with respect to oncological factors such as tumour extent including submucosal spread, background Barrett's metaplasia, likely lymph node involvement, as well as patient comorbidities and preferences.

Recommendation 2.4.3.1	**Grade of recommendation**
Classification OGJ tumours should be classified as type I (distal oesophagus), type II (cardia) and type III (proximal stomach).	**C**

Recommendation 2.4.3.2	Grade of recommendation
Surgical approach In patients with OGJ cancer the operative strategy should ensure that adequate in vivo longitudinal (oesophagectomy 5 cm; extended gastrectomy 3 cm) and radial resection margins (R0) are achieved with lymphadenectomy appropriate to the histological tumour type and its location.	**B**

Recommendation 2.4.3.3	Grade of recommendation
Surgical approach Type III OGJ tumours should be treated by transhiatal extended total gastrectomy.	**B**

Recommendation 2.4.3.4	Grade of recommendation
Surgical approach Type II OGJ tumours should be treated by transhiatal/transthoracic oesophagectomy or extended total gastrectomy.	**B**

Recommendation 2.4.3.5	Grade of recommendation
Surgical approach Type I OGJ tumours should be treated by transthoracic oesophagectomy or transhiatal in selected cases.	**B**

Clinical question 2.4.4

In patients with early oesophageal (including high-grade dysplasia only)/OGJ cancer what is the evidence supporting endotherapy (resection and/or ablative measures) with regard to efficacy and long-term outcomes?

Evidence summary
Two clinical guidelines addressed this clinical question (Allum et al., 2011, NCCN, 2018).

Current evidence on the efficacy and safety of endotherapy in patients with Barrett's oesophagus with either low-grade dysplasia (LGD) or no dysplasia is inadequate in quality and quantity and the balance of risks and benefits is not clear. Therefore, the Guideline Development Group agreed to address early oesophageal cancer and high-grade dysplasia (HGD) only.

Overview of Endotherapy
Endoscopic therapy has become an integral part of the multidisciplinary management of oesophageal and gastric cancer. The UK NICE guidance recommends that such procedures need to be carefully audited in high-volume tertiary referral centres with access to an oesophageal and gastric cancer surgeon, should be performed by appropriately trained staff, and patient care must be managed through a multidisciplinary team meeting (NICE, 2010a, NICE, 2010b). Endoscopic mucosal resection (EMR) and endoscopic submucosal resection (ESD), photodynamic therapy (PDT) mucosal ablation using lasers (photothermal), electrocoagulation, argon plasma coagulation (APC) and radiofrequency ablation (RFA) (thermal) have all been employed to remove dysplasia and early cancer. Most techniques are now being used in combination to eradicate local disease and address any field change abnormality (Li et al., 2008, Pech et al., 2008, Sugano, 2008). It is important to emphasise that patients must have reversal of the underlying abnormality with reflux control and *H. pylori* eradication and have repeat endoscopic surveillance to detect metachronous or recurrent tumours. (Allum et al., 2011)

Aims of Endoscopic therapy
The goal of endoscopic therapy [by endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and/or ablation] is the complete removal or eradication of early-stage disease (pTis, pT1a, selected superficial pT1b without LVI) and pre-neoplastic tissue (Barrett's oesophagus). (NCCN, 2018)

Suggested treatment – Early-stage disease
Early-stage disease, Tis, also known as high-grade dysplasia (HGD), needs to be fully characterised, including evaluating presence of nodularity, lateral spread and ruling out multi focal disease, as well as ruling out lymph node metastases by EUS in selected higher risk cases. This is important to permit decisions on endoscopic therapy with ablative methods such as RFA, cryoablation, PDT and/or endoscopic resection (ER) (Shaheen et al., 2009, Shaheen et al., 2010, Overholt et al., 2007, Pech et al., 2008). Areas of nodularity or ulceration should be resected rather than ablated. Completely flat, small lesions (≤2 cm) of squamous cell HGD/Tis (carcinoma in-situ) and Barrett's oesophagus associated with flat HGD should be treated by ER as it provides more accurate histologic assessment of the lesion. Larger flat lesions (>2 cm) can be treated effectively by ER, but this is associated with greater risk of complications. Such lesions can be effectively treated by ablation alone, but there is very limited data on treating squamous cell HGD by ablation alone (Shaheen et al., 2009, Shaheen et al., 2010, Bergman et al., 2011, Pech et al., 2014, Shaheen et al., 2011, Chadwick et al., 2014). (NCCN, 2018)

Lesions that are found to be pathologically limited to the lamina propria or muscularis mucosae (pT1a), or the superficial sub mucosa (pT1b), in the absence of evidence of lymph node metastasis, LVI, or poor differentiated grade can be treated with full ER (Nentwich et al., 2014, Leggett et al., 2015, Lee et al., 2013). However, a thorough and detailed discussion regarding comparative risk or oesophagectomy

vs. potential for concurrent nodal disease should be undertaken, preferably between patient and surgeon, especially in cases with larger tumours or tumours with superficial submucosal invasion. Ablative therapy of residual Barrett's oesophagus should be performed following ER (Pech et al., 2014). Complete eradication of Barrett's oesophagus can also be performed with more aggressive application of EMR (widefield EMR) or ESD at the initial intervention, if necessary to completely resect an area of superficial tumour or mucosal nodularity less than or equal to 2 cm in maximal dimension (van Vilsteren et al., 2011). (NCCN, 2018)

Endoscopic therapy is considered "preferred" for patients with limited early-stage disease (Tis and T1a, less than or equal to 2 cm, and well or moderately differentiated carcinoma), because the risk of harbouring lymph node metastases, local or distant recurrence, and death from oesophageal cancer is low following endoscopic therapy (Pech et al., 2014). (NCCN, 2018)

Endotherapy for squamous cell cancer
The level of evidence for ablation of squamous cell carcinoma (SCC) after ER is low. However, additional ablation may be needed if there is multifocal HGD/carcinoma in-situ elsewhere in the oesophagus. Ablation may not be needed for lesions that are completely excised (Bergman et al., 2011, van Vilsteren et al., 2011, Becker et al., 2011). (NCCN, 2018)

Long-term outcome
The long-term outcome remains to be determined. Some series have suggested a 10% recurrence rate that may need to be addressed in further studies; this underlines the need for surveillance in a specialist centre (Cotton et al., 2017).

Recommendation 2.4.4.1	**Grade of recommendation**
Barrett's related neoplasia In patients with early oesophageal/OGJ cancer endoscopic resection (ER) should be considered the therapy of choice for neoplasia associated with visible lesions and T1a adenocarcinoma.	**B**

Recommendation 2.4.4.2	**Grade of recommendation**
Ablative therapy for flat high-grade dysplasia (HGD) and residual Barrett's after endoscopic resection In the presence of HGD or intramucosal cancer without visible lesions (flat HGD/ intramucosal cancer), these should be managed with radiofrequency ablation (RFA).	**A**

Recommendation 2.4.4.3	**Grade of recommendation**
Squamous cell neoplasia (superficial lesions) In patients with early oesophageal/OGJ cancer endoscopic resection is recommended for staging and/or treatment of visible lesions.	**C**

Recommendation 2.4.4.4	Grade of recommendation
In patients with early oesophageal/OGJ cancer the Guideline Development Group does not recommend radiofrequency ablation treatment for squamous cell neoplasia in Western populations.	**D**

Good Practice Point
Barrett's related neoplasia requires expert pathological assessment and this should be performed in high-volume centres.

Good Practice Point
All assessments for endotherapy should be performed in high-volume centres with expert multidisciplinary team specialists.

Good Practice Point
Endoscopic resections should be done in high-volume surgical centres.

Good Practice Point
The long-term outcome following endotherapy remains to be determined. Some series have suggested a 10% recurrence rate that may need to be addressed in further studies; this underlines the need for ongoing surveillance in a specialist centre.

Clinical question 2.4.5

In patients with oesophageal/OGJ cancer treated with surgery, is there evidence that transhiatal oesophagectomy is inferior to transthoracic oesophagectomy with respect to post-operative outcomes or long-term cancer outcomes?
a) Oesophageal cancer
b) OGJ cancer

Evidence summary
A meta-analysis (Boshier et al., 2011) and one high quality randomised controlled trial (Hulscher et al., 2002) with a five year follow-up (Omloo et al., 2007) addressed this clinical question.

The meta-analysis (Boshier et al., 2011) included 59 studies comparing transthoracic with transhiatal oesophagectomy. It concluded that there was no difference in five-year survival. However, significant heterogeneity exists between the included studies, and the extent of lymphadenectomy and reported surgical quality appears suboptimal in both groups. More patients with advanced cancer undergo transthoracic resection, another source of bias. The finding of equivalent survival should therefore be viewed with caution. Only through adequate surgical quality and standards of reporting may the true benefit of these operations be determined (Boshier et al., 2011).

These overall caveats notwithstanding, the Dutch multicentre randomised controlled trial reported by Hulscher et al. (2002) and updated by Omloo et al. (2007) provides important data on this question exclusively for adenocarcinoma of the oesophagus and OGJ. 220 patients were randomised to transhiatal or en-bloc transthoracic resection. The in-hospital mortality rate was similar, 2% and 4%, respectively, but the incidence of pulmonary complications was significantly ($p<0.001$) lower in the transhiatal group (27% vs. 57%). Omloo et al. (2007) conducted a five-year follow-up demonstrating survival was 34% and 36% in the transhiatal and transthoracic groups, respectively ($p=0.71$). A 14% non-significant ($p=0.33$) difference in survival was evident in a subset of 90 patients with adenocarcinoma of the distal oesophagus (Siewert type I tumours). Notably, patients with one to eight positive lymph nodes on pathological assessment had improved locoregional disease-free survival if operated via the transthoracic route (64% vs. 23% for transhiatal).

Although retrospective non-matched studies have indicated a survival benefit from a radical thoracic oesophagectomy compared with transhiatal oesophagectomy (Johansson et al., 2004) and post-hoc subgroup analysis from the Dutch randomised trial identified improved local control in node positive patients, there is no level I data from the Dutch and other smaller randomised studies based on intention-to-treat in support of the oncological superiority of the transthoracic approach.

In the absence of level I evidence, the standard of care internationally is to perform an en-bloc transthoracic resection for locally advanced intra-thoracic oesophageal tumours, and transhiatal approaches are generally reserved for patients with early tumours (high-grade dysplasia or T1a), or patients with more advanced distal tumours that are considered high-risk for surgery, in particular from respiratory comorbidity.

Recommendation 2.4.5.1	**Grade of recommendation**
In patients with locally advanced oesophageal cancer, transthoracic oesophagectomy is recommended.	**D**

Recommendation 2.4.5.2	Grade of recommendation
In patients with oesophageal cancer with high operative risk, transhiatal oesophagectomy can be considered as it has reduced respiratory morbidity compared to transthoracic oesophagectomy.	**A**

Recommendation 2.4.5.3	Grade of recommendation
For patients with OGJ tumours which can be resected with R0 margins and a lower mediastinal and nodal dissection, a transhiatial approach can be considered.	**B**

Recommendation 2.4.5.4	Grade of recommendation
For patients with locally advanced oesophageal cancer, transthoracic oesophagectomy may be of benefit where positive lymph nodes are present (1-8 nodes) or predicted compared with node negative patients.	**B**

Clinical question 2.4.6

In patients with oesophageal/OGJ cancer treated with surgery, is there evidence that three-field lymphadenectomy is superior to two-field lymphadenectomy with respect to post-operative outcomes or long-term cancer outcomes?
a) Squamous cell carcinoma
b) Adenocarcinoma

Evidence summary
Two meta-analyses (Ma et al., 2014, Ye et al., 2013), two randomised trials (Nishihira et al., 1998, Kato et al., 1991) and five retrospective studies (Dresner and Griffin, 2000, Peyre et al., 2008a, Peyre et al., 2008b, Hölscher et al., 1995, Siewert et al., 2000) addressed this clinical question.

Lymph node involvement is the strongest predictor of survival in oesophageal cancer (Peyre et al., 2008b). It has also been established that the number of lymph nodes resected/analysed is an independent predictor of survival, even for node-negative patients, and a median of 23 nodes identifies a cut-off associated with improved outcomes (Peyre et al., 2008a). An international standard is the analysis of at least 15 nodes. A significant decline in survival is seen where there are four or more positive lymph nodes, with five year survival as low as 20% (Hölscher et al., 1995). Local disease control may be improved with radical lymphadenectomy, and better staging information is obtained through higher nodal yields from relevant fields (Dresner and Griffin, 2000). Good long-term results from a two-field lymphadenectomy with subtotal oesophagectomy have been reported for patients with oesophageal cancer but there have been no randomised trials demonstrating improved survival. In patients with squamous cell cancer of the oesophagus extended cervical and superior mediastinal lymphadenectomy does not demonstrate significant improvement in five year survival compared with standard resection and increases pulmonary complications and recurrent nerve injury (Nishihira et al., 1998).

In summary, for squamous cell cancer of the oesophagus, adequate lymphadenectomy in the abdomen and chest is logical, but there is no indication for neck dissection in the absence of involved nodes. For adenocarcinomas, most surgeons accept the need for an adequate abdominal lymphadenectomy as the predominant route of lymphatic spread in lower third tumours is in a caudal direction. The extent of mediastinal lymphadenectomy, particularly in the upper half of the mediastinum, remains unclear. Experience from Munich has shown in type II OGJ tumours that the pattern of lymph node involvement is mediastinal (2.1%), paraoesophageal (15.6%) and intraabdominal (56-72%) (Siewert et al., 2000). The most widely practiced operation is the two-phase Ivor Lewis operation with a laparotomy followed by a right thoracic approach with the anastomosis high in the chest. Some surgeons favour a third stage with a cervical incision to create the anastomosis at this level. This may be an important consideration to gain adequate clearance in proximal tumours.

Two meta-analyses (Ma et al., 2014, Ye et al., 2013) which include the two Japanese randomised trials that address this question to date (Kato et al., 1991, Nishihira et al., 1998) conclude the following. Ma et al. (2014) showed that three-field lymphadenectomy improves overall survival rate but has more complications. Due to high heterogeneity among included studies, definite conclusions are difficult to draw. This is supported by Ye et al. (2013) which concluded that given the lack of large sample randomised controlled studies, further evaluations are necessary.

Recommendation 2.4.6.1	**Grade of recommendation**
In patients with oesophageal/OGJ cancer, the Guideline Development Group recommends two-field lymphadenectomy.	**B**

Clinical question 2.4.7

In patients with oesophageal/OGJ cancer treated with surgery, is there evidence that minimally invasive oesophagectomy (MIO) (or laparoscopic assisted or hybrid or thoracoscopic oesophagectomy) is superior to open oesophagectomy with respect to post-operative outcomes or long-term cancer outcomes?

Evidence summary

A guideline (NICE, 2018), three meta-analyses (Kauppila et al., 2017, Lv et al., 2016, Yibulayin et al., 2016), two randomised controlled trials (Biere et al., 2012, Straatman et al., 2017) and a systematic review (Findlay et al., 2014) addressed this clinical question.

A meta-analysis by Kauppila et al. (2017) combined nine studies including 1,157 patients who had MIO and 907 patients who underwent open surgery. Patients reported better global quality of life, physical function, fatigue and pain three months after MIO compared with open surgery. No such differences remain at longer follow-up of six and 12 months.

Furthermore a meta-analysis by Lv et al. (2016) included 20 studies (four randomised controlled trials and 16 prospective studies) with 2,091 (35%) patients who underwent MIO and 3,934 (65%) patients who underwent open oesophagectomy. This meta-analysis concluded that patients undergoing MIO may benefit from reduced blood loss, less respiratory complications, and also improved overall survival condition compared with open oesophagectomy.

Yibulayin et al. (2016) found that MIO had less intraoperative blood loss, shorter hospital stay, and high operative time ($p<0.05$) than an open approach. MIO also had reduced incidence of total complications; (OR, 0.700, 95% CI, 0.626 to 0.781, $pV<0.05$), pulmonary complications (OR, 0.527, 95% CI, 0431 to 0.645, $pV<0.05$), cardiovascular complications (OR, 0.770, 95% CI, 0.681 to 0.872, $pV<0.05$), and surgical technology related (STR) complications (OR, 0.639, 95% CI, 0.522 to 0.781, $pV<0.05$), as well as lower in-hospital mortality (OR, 0.668, 95% CI, 0.539 to 0.827, $pV<0.05$). However, there was significant heterogeneity among a number of the outcomes (Yibulayin et al., 2016).

A systematic review by Findlay et al. (2014) included three meta-analyses (Sgourakis et al., 2010, Nagpal et al., 2010, Biere et al., 2012) and four systematic reviews (Gemmill and McCulloch, 2007, Decker et al., 2009, Verhage et al., 2009, Dantoc et al., 2012) all of which are largely based on retrospective and heterogeneous cohorts from individual centres. It concluded that MIO is at least comparable with open surgery, although the included studies were non-randomised and of poor quality. Due to the reporting bias, variations in surgical technique, and variations in the selection criteria of patients between case control studies, it is difficult to aggregate findings using the meta-analysis technique and, therefore to definitively state whether any differences found by meta-analysis are real.

Biere et al. (2012) demonstrated a reduction in pulmonary morbidity (infections) with MIO compared with open surgery and found that MIO reduced complications, blood loss, and length of stay (LOS), without oncological compromise. Consequently, MIO can be recommended within the context of appropriate expertise. In a follow-up study of the TIME trial no differences in disease-free and overall 3-year survival for open and MIO were found (Straatman et al., 2017).

It is important to note that the evidence did not address long-term cancer outcomes but focused on operative outcomes, although it did include surrogate markers of quality of cancer surgery which appear equivalent, but large prospective randomised trials are required to answer this question. The NICE (2018) guideline also stated that there is a general absence of high quality randomised controlled trials and recommend an open or minimally invasive oesophagectomy for surgical treatment of oesophageal cancer.

A recent open-label randomised controlled trial (Mariette et al., 2019) randomised 207 oesophageal cancer patients (middle or lower third of the oesophagus) to undergo transthoracic open oesophagectomy or hybrid minimally invasive oesophagectomy (hybrid procedure). At three-years, overall survival was 67% (95% CI, 57 to 75) in the hybrid-procedure group, as compared with 55% (95% CI, 45 to 64) in the open-procedure group; disease-free survival was 57% (95% CI, 47 to 66) and 48% (95% CI, 38 to 57), respectively. A total of 37 patients (36%) in the hybrid-procedure group had a major intra-operative or postoperative complication, as compared with 67 (64%) in the open-procedure group (OR, 0.31; 95% CI, 0.18 to 0.55; p<0.001). A total of 18 of 102 patients (18%) in the hybrid-procedure group had a major pulmonary complication, as compared with 31 of 103 (30%) in the open-procedure group.

Recommendation 2.4.7.1	**Grade of recommendation**
In patients with oesophageal/OGJ cancer all surgical approaches, including open, hybrid, and MIO can be considered.	**A**

Recommendation 2.4.7.2	**Grade of recommendation**
In patients with oesophageal/OGJ cancer, MIO appears to have advantages with respect to pulmonary morbidity, in particular the risk of pneumonia.	**B**

Recommendation 2.4.7.3	**Grade of recommendation**
In patients with oesophageal/OGJ cancer there is no evidence of superiority of MIO or hybrid procedures on oncological outcomes compared with open surgery.	**D**

Good Practice Point
A high-volume centre should encompass all modalities of surgical approaches.

Clinical question 2.4.8

In patients undergoing oesophageal surgery with curative intent, is there any evidence that enhanced recovery protocols improve post-operative outcomes?

Evidence summary

Two systematic reviews and three cost-effectiveness studies addressed this clinical question (Markar et al., 2014, Findlay et al., 2014, Pisarska et al., 2017, Wang et al., 2015, Gemmill et al., 2015).

Published reports on enhanced recovery after surgery (ERAS) for oesophagectomy suggest that it is feasible with acceptable levels of morbidity and mortality and that formalisation of care pathways improves outcomes.

The pooled analysis (n=1,240 patients) from one systematic review (Markar et al., 2014) suggest a benefit from the utilisation of an enhanced recovery protocol with a reduction in the incidence of anastomotic leak, pulmonary complications and length of hospital stay and no significant change in peri-operative mortality or readmission. However, due to the inherent heterogeneity of different enhanced recovery protocols included in the pooled analysis, the low quality of the studies included and the small number of events recorded in outcomes, caution must be taken in interpretation of these results as they are likely to be subject to bias.

With regards to cost-effectiveness, three relevant papers (Pisarska et al., 2017, Wang et al., 2015, Gemmill et al., 2015) focus on ERAS in oesophageal cancer and have shown that ERAS has a significant improvement in morbidity and a reduction in post-surgical length of stay in hospitals. ERAS causes no harm to the patient and the effects are also cost-saving. However more research would be helpful to strengthen the cost-effectiveness evidence and no specific costing has yet been undertaken in an Irish setting.

Regarding individual components of the ERAS programme, the following Table 2 presents the recommendations (adapted from Findlay et al., 2014).

Table 2: Components of ERAS for oesophagectomy, adapted from Findlay et al. (2014)

Preoperative	
Counselling	• Independent predictor of ERAS success, multimodal counselling is recommended.
Nutrition	• Patients with oesophageal cancer are prone to preoperative malnutrition, and this probably affects outcome. • Nutrition should be optimised preoperatively but evidence for immune-nutrients is conflicting. • Optimal fasting: 6 hours for solids (caution if dysphagia); 2 hours for clear fluids. • Oral and intravenous carbohydrate loading attenuates insulin resistance and hyperglycaemia.
Inspiratory muscle training (IMT)	• IMT improves inspiratory function after oesophagectomy but not outcome.
Operative	
Pre-emptive analgesia	• Pre-emptive (before incision) thoracic epidural reduces severity of acute pain.
Fluid therapy	• There have been no studies of goal directed vs. restrictive or liberal perioperative fluid protocols, but relative fluid restriction is optimal within ERPs.
Pyloric drainage	• Pyloroplasty reduces outlet obstruction but it is unclear whether this affects short term outcomes.
Chest drains	• Passive drainage may be as effective as active. Transhiatal or vacuum drainage cannot be recommended. • One drain may be as effective (similar morbidity, less pain) as two drains.
Postoperative	
Gastric conduit decompression	• Gastric conduit decompression via NG is recommended.
Nutrition	• High quality non-oesophageal evidence advocates early enteral nutrition (vs. late). • Enteral nutrition is favoured over parenteral. • Feeding jejunostomies are most commonly used but are associated with some specific complications. • The optimal timing of oral intake after oesophagectomy is unclear. • Studies assessing the role of routine imaging before commencing oral diet are low in quality and power.
Analgesia	• Thoracic epidural analgesia provides better pain relief than systemic opioids after thoracotomy. • Paravertebral block provides equivalent analgesia for thoracotomy, with fewer pulmonary complications and side effects but it has not been studied in thoracolaparotomy. • The optimal duration of thoracic epidural and paravertebral block is unclear, as is analgesia for minimally invasive oesophagectomy.
Mobilisation	• There is a lack of evidence as to the benefits of early mobilisation after oesophagectomy; however, it should be recommended.

Recommendation 2.4.8.1	Grade of recommendation
In patients with oesophageal/OGJ cancer, the use of enhanced recovery after surgery (ERAS) programmes should be considered, as they are compatible with favourable morbidity, mortality and length of stay.	**C**

Clinical question 2.4.9

In centres performing oesophageal surgery, is there evidence that volume (hospital or individual surgeon caseload) impacts on post-operative outcomes or long-term cancer outcomes?

Evidence summary

Current guidelines (NICE, 2018, Allum et al., 2011, NCCN, 2018), and two meta-analyses (Brusselaers et al., 2014, Wouters et al., 2012) addressed this clinical question. The evidence and principle is consistent across the literature, with reduced operative mortality and improved cancer outcomes associated with high-volume surgeons and hospitals.

There is international consensus that there is a highly significant relationship between lower in-hospital postoperative mortality and increasing surgeon and institutional patient volumes. (NICE, 2018, Allum et al., 2011, NCCN, 2018)

A recent meta-analysis by Brusselears et al. (2014) reported an 18–25% and 9–13% improved survival for high-volume hospitals and high-volume surgeons, respectively, compared with their low-volume counterparts. This difference in survival was not solely due to a decreased early postoperative mortality, since even after exclusion of early deaths, a 15% benefit was found.

Recommendation 2.4.9.1	Grade of recommendation
Oesophageal/OGJ surgery should be performed by surgeons who attend a specialist multidisciplinary team meeting in a designated oesophageal cancer centre with outcomes audited regularly.	**B**

Good Practice Point

Specialist centres should perform at least 50 resections (Guideline Development Group consensus) of the oesophagus/OGJ annually, with a minimum of 20 resections per surgeon. (Allum et al., 2011)

Good Practice Point

The individual surgeon and team outcomes should be audited against risk-adjusted international benchmarked standards.

Clinical question 2.4.10

In patients diagnosed with oesophageal and OGJ cancer, is there evidence that multidisciplinary team care improves quality of care?

Evidence summary
Two international guidelines (NCCN, 2018, Allum et al., 2011), a prospective study (van Hagen et al., 2013) and a retrospective study (Freeman et al., 2011) addressed this clinical question.

Patients diagnosed with either non-invasive (dysplasia, or early non-invasive cancers) or invasive oesophageal or OGJ neoplasms should be discussed at an upper gastrointestinal multidisciplinary team meeting and managed in a recognised upper GI multidisciplinary team setting. Patients should have the opportunity to discuss options in detail with experts from endoscopic and surgical disciplines.

Multidisciplinary team meeting
Multidisciplinary team management in oesophageal and oesophagogastric neoplasia leads to increased full and appropriate staging, improved decision making (in over 30% of cases) (van Hagen et al., 2013) and decreases the time between diagnosis and management (Freeman et al., 2011). Multidisciplinary team for treatment planning should comprise of: surgical oncologists, gastroenterologists, medical oncologists, radiation oncologists, radiologists and pathologists experienced in their field. The multidisciplinary clinical management team of the patient should in addition include specialist dietitians, pharmacy, psycho-oncology, physiotherapists and speech and language therapists.

Clinical Nurse Specialist
All patients newly diagnosed with oesophageal or gastric cancer should have access to a clinical nurse specialist for support; they have an integral role; consulting with medical, surgical and allied healthcare professionals in order to provide a co-ordinated approach to care, enhancing quality of care and patients' wellbeing. They should be available to the patient to advocate on their behalf and provide early and ongoing communication between the multidisciplinary team and the patient to ensure the patient is fully involved in all decisions and that their views and preferences are clearly understood by those involved in treatment planning. (Allum et al., 2011)

Data management
Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions. (NCCN, 2018)

Outcomes using adequate and accurate data capture should be reviewed on a regular basis. Periodic formal review of relevant literature is recommended.

Recommendation 2.4.10.1	Grade of recommendation
Patients with oesophageal or OGJ cancer (both invasive and non-invasive) should be discussed at a multidisciplinary team meeting, this improves decision making and management and by inference has an impact in overall survival.	**B**

Good Practice Point
In all patients with oesophageal/OGJ cancer, early referral to a specialist dietitian should be considered.

Good Practice Point
In patients with oesophageal/OGJ cancer who are deconditioned and/or have respiratory risk factors, early referral to physiotherapy should be considered.

Good Practice Point
In patients with metastatic oesophageal/OGJ cancer early involvement with palliative care should be standard of care.

Good Practice Point
All patients with oesophageal/OGJ cancer should have access to professional psycho-oncology support.

2.5 Palliative care

The following are responsible for the implementation of the palliative care recommendations:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.5.1

When should palliative care be introduced for patients with cancer?

Evidence summary

Palliative care is an approach that improves the quality of life of people and their families facing the problems associated with life-limiting 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 (World Health Organisation, 2014). It is a vital and integral part of all clinical practice.

When combined with standard cancer care or as the main focus of care, palliative care leads to better patient and caregiver outcomes. These include improvement in symptoms, quality of life (QoL), and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care (Smith et al., 2012).

No trials to date have demonstrated harm to patients and caregivers from early involvement of palliative care (Smith et al., 2012).

A 2013 literature review on the cost and cost-effectiveness of palliative care found that despite wide variation in study type, characteristics and study quality, there are consistent patterns in the results. Palliative care is most frequently found to be less costly relative to comparator groups, and in most cases, the difference in cost is statistically significant. (Smith et al., 2014)

Good clinical practice dictates that assessment of palliative care needs should be an ongoing process throughout the course of a patient's illness; assessments should be carried out at key transition points in the patient pathway, for example:

- At diagnosis of a life-limiting condition
- At episodes of significant progression/exacerbation of disease
- A significant change in the patient's family/social support
- A significant change in functional status
- At patient or family request
- At end of life (Health Service Executive (HSE), 2014).

Palliative care services should be structured in three levels of ascending specialisation according to the expertise of the staff providing the service (DoHC, 2001):

- Level one (Palliative Care Approach): Palliative care principles should be appropriately applied by all healthcare professionals.
- Level two (General Palliative Care): At an intermediate level, a proportion of patients and families will benefit from the expertise of healthcare professionals who, although not engaged full time in palliative care, have had some additional training and experience in palliative care.
- Level three (Specialist Palliative Care): Specialist palliative care services are those services whose core activity is limited to the provision of palliative care.

All patients should be able to engage easily with the level of expertise most appropriate to their needs.

Recommendation 2.5.1.1	**Grade of recommendation**
For patients with cancer, early provision of palliative care can improve patient outcomes.	**C**

Recommendation 2.5.1.2	Grade of recommendation
Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	**D**

3 Development of a National Clinical Guideline

3.2 Rationale for this National Clinical Guideline

The National Cancer Strategy (DoHC, 2006) recommended that national tumour site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care.

The National Cancer Strategy 2017-2026 (DoH, 2017) recommends: The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards.

The diagnosis, staging, and treatment of patients with oesophageal or OGJ cancer requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery, radiotherapy and chemotherapy.

The purpose of developing these guidelines is to improve the quality of care delivered to patients.

3.3 Aims and objectives

The overall objectives of the NCCP's National Clinical Guideline 'Diagnosis, staging and treatment of patients with oesophageal or oesophagogastric junction cancer' are outlined below, along with the clinical question number that addresses the specific aim.

The recommendations within this guideline relate to the clinical treatment of cancer and do not provide specific guidance on nutritional intervention, physical rehabilitation or full multidisciplinary management of patients with oesophageal cancer. The guideline is based on the best research evidence in conjunction with clinical expertise, and developed using a clear evidence-based internationally used methodology.

- Improvement in patient outcomes including potential for reduction in morbidity and mortality, improvement in quality of life (Clinical Questions 2.4.1, 2.4.3, 2.4.4, 2.4.5, 2.4.8, 2.4.9, 2.4.10, 2.5.1),
- Promotion of interventions of proven benefit and discouragement of ineffective interventions, improvement in standard of care (Clinical Questions 2.4.1, 2.4.3, 2.4.6, 2.4.5, 2.4.9, 2.5.1),
- Improvement in consistency of care, and reduce variation in practice (Clinical Questions 2.2.1, 2.3.1, 2.3.2, 2.3.3, 2.4.1, 2.4.2, 2.4.3, 2.4.4, 2.4.5, 2.4.8, 2.4.9, 2.4.10, 2.6.1, 2.5.1),
- To address areas of clinical care with new and emerging evidence (Clinical Questions 2.4.1, 2.4.4, 2.4.7, 2.5.1),
- Potential to have the most impact (on patients and resources) (Clinical Questions 2.4.1, 2.4.2, 2.4.5, 2.4.9, 2.4.10, 2.5.1)

3.4 Financial impact of oesophageal/OGJ cancer

A population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer is estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). Across the EU, the cost of cancer healthcare was equivalent to €102 per person, but varied substantially from €33 per person in Lithuania to €171 per person in Germany.

In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million in 2009. In 2009, drug expenditure accounted for a further €127

million while primary, outpatient and emergency care were estimated at €32 million, €30 million and €13 million respectively (Luengo-Fernandez et al., 2013). A recent productivity loss analysis carried out in an Irish context (Pearce et al., 2016) projected that from 2011-2030, premature death as a result of oesophageal cancer will cause a value of €233,866 lost production per household and an overall productivity loss per population of ~ €2.5 billion.

The resource implications of implementing the recommendations within the guideline were identified by the clinicians during meetings to discuss and develop the recommendations (See Appendix 6 of the full guideline: Economic assessment and implementation plan).

Healthcare investment of €909,036 is required to implement the recommendations contained in this guideline, however this does not include the cost for centralisation of services which will be sought through normal service planning processes. €513,836 is required to ensure availability of PET-CT and EUS to patients with oesophageal/OGJ cancer. Importantly, by implementing the recommendations of the radiology section, the use of PET-CT in early-stage oesophageal cancer may be reduced, resulting in a potential cost-saving. The pathology recommendations require no investment while surgical and gastroenterology recommendations require a budget of €395,200.

A number of recommendations identified within this guideline will not require further resourcing as the initiative is already funded in the National Service Plan (HSE, 2019). Certain recommendations made within the surgical section can be implemented by centralisation of services. This will take into consideration staffing, expertise, infrastructure and equipment requirements. By adopting novel surgical techniques as recommended, length of hospital stay could be reduced resulting in a cost-saving, which is currently unknown.

3.5 Guideline scope

3.5.1 Target population

Patients that are covered by this guideline are:

- Adults (18 years or older) with newly diagnosed oesophageal or OGJ cancer,
- Adults that have a suspected diagnosis of oesophageal or OGJ cancer.

3.5.2 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with oesophageal or OGJ cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients diagnosed with oesophageal or OGJ cancer and their significant others.

A list of medical abbreviations used throughout the guideline can be found in Appendix 8: Glossary of terms and abbreviations.

3.6 Conflict of interest statement

A conflict of interest form developed by the NCEC was signed by all Guideline Development Group members and the national/international reviewers. The Guideline Development Group was managed by the Chair to promote the highest professional standard in the development of this guideline. Any conflicts declared are detailed below and where a conflict arises, a Guideline Development Group member absents themselves from discussion pertaining to their area of conflict.

Table 9: Conflicts of interests declared by members of the Guideline Development Group

Guideline Development Group member	Detail of conflict declared
Dr Greg Leonard, UHG	Received sponsorship from Roche, Servier, Bayer and Merck pharmaceuticals and involved as part of tumour board

3.6.1 Governance

Governance of the guideline development process was provided by a multidisciplinary Guideline Steering Group which was chaired by the Director of the NCCP. Details of Guideline Development Group members are provided at the beginning of the document and details of the Guideline Steering Group members are available in Appendix 1 of the full guideline: Guideline Development Group terms of reference.

The Guideline Development Group was responsible for the development and delivery of the National Clinical Guideline and included representatives from relevant professional groups (radiology, pathology, surgeons, gastroenterologists, radiation oncologists and medical oncologists) with expertise in the diagnosis, staging and treatment of patients with oesophageal or OGJ cancer. The Guideline Development Group also included a project manager, a methodologist, research officers, a health economist and a number of clinical librarians.

3.7 Sources of funding

The guideline was commissioned and funded by the NCCP; however, the guideline content was not influenced by the NCCP or any other funding body. This process is fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.

3.8 Guideline methodology and literature review

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development which is available upon request. This manual adheres to the standards outlined in the NCEC Guideline Development Manual. Figure 3 outlines the stages of guideline development.

3.8.1 Step 1: Formulate the clinical questions

Guideline Development Group members met and through clinician led experience identified areas of new and emerging evidence, areas with identifiable variation in practice, or areas with potential to have impact on patient care. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.
To formulate the clinical questions, they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time

This process was carried out by discipline specific subgroups. The Guideline Development Group signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 14 clinical questions are listed in Appendix 2 of the full guideline: Clinical Questions in PICO format.

3.8.2 Step 2: Search methodology

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (See Appendix 4 of the full guideline: Systematic Literature Review Protocol). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools
- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to March 2018.

The search strategies for all clinical questions and the three economic questions in the budget impact analysis are available on request by contacting the NCCP at guidelines@cancercontrol.ie.

3.8.3 Step 3: Screen and appraise the evidence

International guidelines were appraised using the international, validated tool the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

Economic papers included in the Budget Impact Analysis (See Appendix 6 of the full guideline: Economic assessment and implementation plan) were appraised by a health economist using validated economic checklists developed by SIGN.

There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of this guideline? (external validity)

After literature appraisals were completed, the data selected for possible inclusion in the guideline were compiled in the data extraction tables by the research officers. The data extraction tables are available on request by contacting the NCCP at guidelines@cancercontrol.ie.

3.8.4 Step 4: Develop and grade the recommendations

The evidence which addressed each clinical question from international guidelines and primary literature was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN) was completed for each clinical question.

The following items were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
- What is the potential impact on the health system?
- What is the potential benefit versus harm to the patient?
- Are there resource implications?

The evidence summaries and recommendations were then written. Each recommendation was assigned a grade by the Guideline Development Group. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are documented in Appendix 9: Levels of evidence & grading systems.

Good Practice Points are intended to assist guideline users by providing short pieces of advice which may not have an evidence base, but which are seen as essential to good clinical practice (SIGN, 2015). The Good Practice Points presented in this clinical guideline were based on the clinical expertise of the Guideline Development Group. For the economic literature, key messages are presented in boxes entitled 'relevance to the guideline recommendations'.

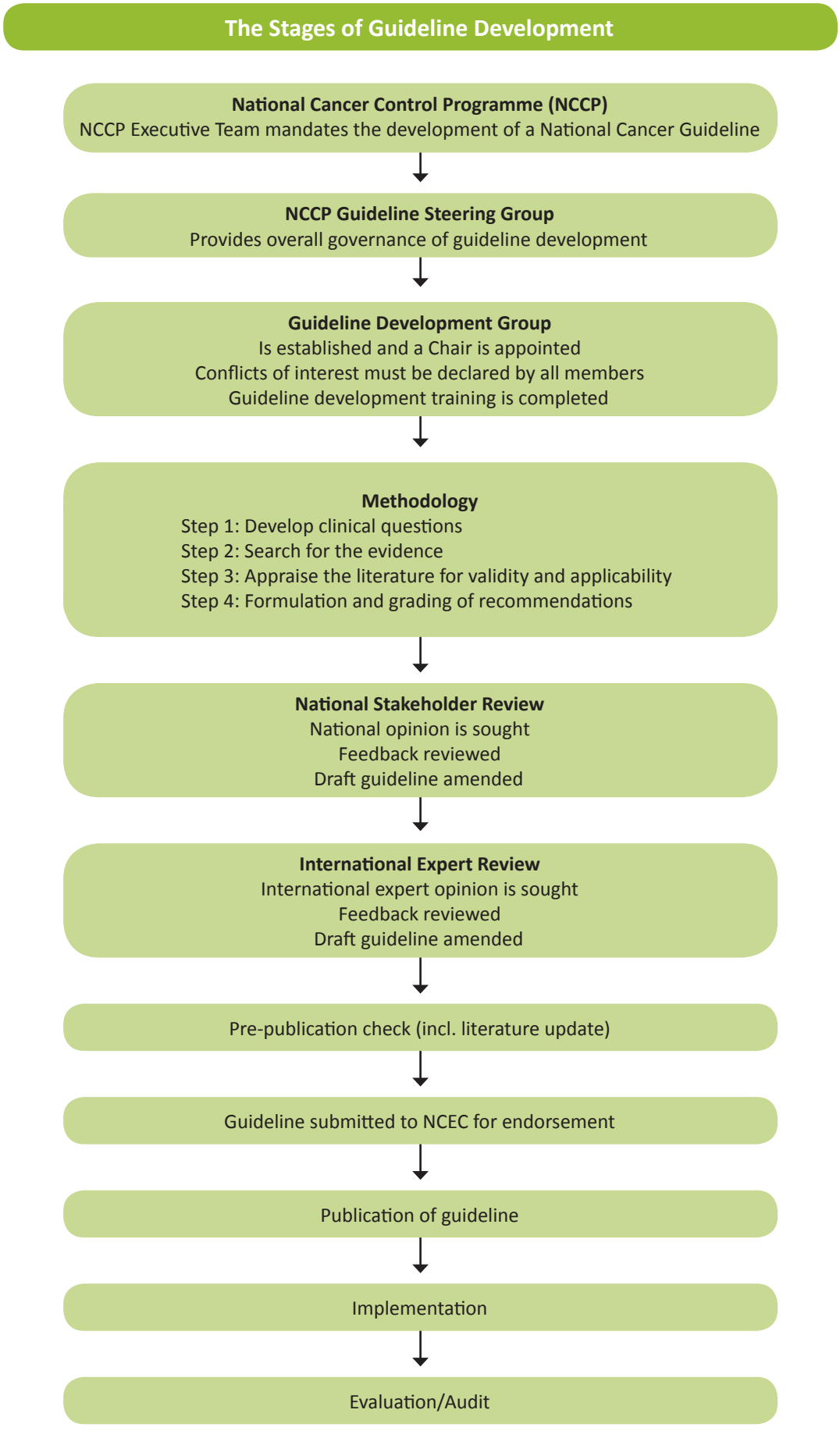

Figure 3: The stages of guideline development

3.9 Consultation process

The guideline was placed on the NCCP website and circulated for comment from the 24th of November 2017 to the 5th January 2018. Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided (see NCCP Methodology Manual) along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments. A list of the stakeholders including groups, organisations and committess can be found in Appendix 5 of the full guideline: Details of consultation process.

All feedback received was reviewed by the project manager and research team. Suggested amendments and supporting evidence were reviewed by the discipline specific subgroup and consensus reached to accept or reject the amendments. Amendments were rejected following discussion between members of the relevant subgroup(s) and in instances where no superior evidence was provided or no conflict of interest form was provided. All modifications were documented and the report is available on request by contacting the NCCP at guidelines@cancercontrol.ie.

3.9.1 Patient advocacy

The views and preferences of the target population were sought by inviting patient advocacy groups (Oesophageal Cancer Fund, HSE Patient Forum, Irish Cancer Society, Cancer Care West, Marie Keating Foundation, Gary Kelly Cancer Support Centre and Purple House Support Centre) to engage in the National Stakeholder Review process (See Appendix 5 of the full guideline: Details of consultation process).

The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme. The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and their families and healthcare professionals in relation to healthy lifestyle, disease prevention and control. It aims to promote a good quality of life and prolonged survival for people who experience cancer.

3.9.2 Patient involvement

The Oesophageal Cancer Fund (OCF) is a charity specific to oesophageal cancer. The guideline was presented to a group of patient representatives and their family members at the OCF National Meeting. Attendees were invited to provide feedback in a focus group style forum on the guideline and discuss what was important to them with regards to their own experiences of the diagnosis, staging and treatment of their oesophageal cancer.

Four patients provided feedback and a list of practical considerations from a patient perspective was developed. This can be found in Section 2.1 Summary of clinical recommendations, practical considerations around patient care and summary of budget impact analysis.

3.10 External review

The draft guideline was also submitted for international expert review. The Guideline Development Group nominated three international reviewers to provide feedback on the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Stakeholder Review. The guideline was circulated for comment from the 24th of November 2017 to the 5th January 2018.

A log was recorded of all submissions and amendments from the national stakeholder and international expert review process and is available on request by contacting the NCCP at guidelines@cancercontrol.ie.

3.11 Implementation

This National Clinical Guideline should be reviewed by the multidisciplinary team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline. A Cancer Network Manager from the NCCP meets with each cancer centre on a quarterly basis for performance monitoring and service planning.

All medical staff with responsibility for the care of patients with oesophageal cancer are required to:

- Comply with this National Clinical Guideline and any related procedures or protocols.
- Adhere to their code of conduct and professional scope of practice guidelines as appropriate to their role and responsibilities.
- Maintain their competency for the management and treatment of patients with oesophageal cancer.

The Implementation Plan (See Appendix 6 of the full guideline: Economic assessment and implementation plan) details information in relation to the following areas.

- who is the lead/ group/discipline responsible for implementation
- barriers/enablers/gaps
- action/intervention/task to implement recommendation
- timeframe for full implementation
- expected outcomes
- verification.

Each area helps develop a clear outline of how each recommendation will be applied within the clinical setting and successfully implemented into practice.

The National Cancer Strategy 2017-2026 made a number of recommendations and outlined important key performance indicators (KPI) that are applicable to the recommendations made within this guideline.

A multidisciplinary team is responsible for the implementation of the guideline recommendations.

3.11.1 Dissemination and communication plan

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this guideline (HSE Clinical Programmes in Surgery/ Radiology/Palliative Care, RCSI, HSE Patient Forum, Irish Cancer Society, Cancer Care West etc.). The guideline will also be available via the NCEC and NCCP websites.

The NCCP will co-ordinate with HSE Communications to distribute, share and disseminate through the media (HSE Broadcast, Health Matters, and Twitter). The guideline will be officially launched and circulated to all relevant faculties and colleges for dissemination to their members. The implementation of the guideline will also be supported by communication, training and education.

Potential dissemination and communication strategies:

- Create a slide for inclusion in presentations by clinical leads, subgroup chairs, NCCP Director around published guidelines.
- Included link to guidelines in NCCP email signatures.
- Liaise with Oesophageal Cancer Fund, Irish Cancer Society and Faculties to ensure guidelines are represented in their patient and public information.
- Promote through NCCP website and social media.
- Direct communication from NCCP Director/CCO/Acute Operations to hospital managers raising awareness and setting out expectations/actions.
- Include discussion on implementation at launch.

A summary of tools to assist in the implementation of this National Clinical Guideline are available in Appendix 3 of the full guideline: Supporting tools.

3.12 Monitoring and audit

The NCCP engages regularly with the individual cancer centres and with Hospital Group structures. Discussion of performance data, improvement plans, and resources including manpower, service planning and development takes place at regular review meetings between the NCCP and senior management at cancer centre and hospital group level.

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care. For audit criteria see Appendix 7 of the full guideline: Monitoring and audit.

3.13 Plan to update this National Clinical Guideline

This guideline was published in August 2019 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

4 Appendices

Only appendices 8 and 9 are presented here as they are key to interpretation of the recommendations in this summary guideline.

Refer to the full guideline report for the remaining appendices:

Appendix 1: Guideline Development Group terms of reference and logic model

Appendix 2: Clinical questions in PICO format

Appendix 3: Supporting tools

Appendix 4: Systematic literature review protocol

Appendix 5: Details of consultation process

Appendix 6: Economic assessment and implementation plan

Part A: Economic evidence summary

Part B: Budget impact analysis and implementation plan

Summary of budget impact analysis

Appendix 7: Monitoring and audit

Appendix 8: Glossary of terms and abbreviations

Glossary

Definitions within the context of this document

Case control study The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups (CEBM website).

Case series A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment (CEBM website).

Cohort study The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels (CEBM website).

Validity The extent to which a variable or intervention measures what it is supposed to measure or accomplishes what it is supposed to accomplish. The internal validity of a study refers to the integrity of the experimental design. The external validity of a study refers to the appropriateness by which its results can be applied to non-study patients or populations (CEBM website).

Meta-analysis A systematic review may or may not include a meta-analysis, which is a quantitative summary of the results (CEBM website).

Randomised trial An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups (CEBM website).

Systematic review The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardised methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results (CEBM website).

Abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AJCC	American Joint Committee on Cancer
AOTI	Association of Occupational Therapists of Ireland
APC	Argon Plasma Coagulation
ASA	American Society of Anesthesiologists
BH	Beaumont Hospital
BMJ	British Medical Journal
CAP	College of American Pathologists
CEAs	Cost-Effectiveness Analysis
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CEU	Clinical Effectiveness Unit
CDR	Clinical Decision Rule
CI	Confidence Interval
CINHAL	Cumulative Index to Nursing and Allied Health Literature
CPET	Cardiopulmonary Exercise Testing
CPI	Consumer Price Index
CNS	Clinical Nurse Specialist
CPX	Cardiopulmonary Exercise
CRM	Circumferential Resection Margin
CSO	Central Statistics Office
CT	Computed Tomography
CT TAP	Computed Tomography of Thorax, Abdomen and Pelvis
CUH	Cork University Hospital
DoH	Department of Health
DoHC	Department of Health and Children
EBP	Evidence-Based Practice
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EMR	Endoscopic Mucosal Resection
ER	Endoscopic Resection
ERAS	Enhanced Recovery After Surgery
ERP	Enhanced Recovery Programme
ESD	Endoscopic Submucosal Dissection
ESMO/ACF	European Society for Medical Oncology/Anticancer Fund
EU	European Union
EUS	Endoscopic Ultrasound
FEV1	Forced Expiratory Volume in one second
FNA	Fine Needle Aspirate
FVC	Forced Vital Capacity
GDG	Guideline Development Group
GI	Gastrointestinal
HEED	Health Economics Evaluations Database
HGD	High-Grade Dysplasia
HIQA	Health Information and Quality Authority
HR	Hazard Ratio
HRQoL	Health Related Quality of Life

HSE	Health Service Executive
HTA	Health Technology Assessment
IANO	Irish Association of Nurses in Oncology
IASLT	Irish Association of Speech & Language Therapists
ICD	International Classification of Disease
ICGP	Irish College of General Practitioners
INDI	Irish Nutrition & Dietetic Institute
IMC	Intramucosal Cancer
IMT	Inspiratory Muscle Training
ISCP	Irish Society of Chartered Physiotherapists
ISMO	Irish Society of Medical Oncology
KPI	Key Performance Indicator
KPS	Karnofsky Performance Status
LGD	Low-Grade Dysplasia
LOS	Length of Stay
LVI	Lymphovascular Invasion
LYG	Life Years Gained
MDT	Multidisciplinary Team
MeSH	Medical Subject Headings
MIO	Minimally Invasive Oesophagectomy
NICE	National Institute for Health and Care Excellence
NCCN	National Comprehensive Cancer Network®(NCCN®)
NCCP	National Cancer Control Programme
NCEC	National Clinical Effectiveness Committee
NCRI	National Cancer Registry Ireland
nCRT	Neoadjuvant Chemoradiotherapy
NG	Nasogastric Tube
NHS	National Health Service
NMSC	Non-Melanoma Skin Cancer
NPSO	National Patient Safety Office
OCF	Oesophageal Cancer Fund
OGD	Oesophagogastro Duodenoscopy
OGJ	Oesophagogastric Junction
OR	Odds Ratio
PDT	Photodynamic Therapy
PFTs	Pulmonary Function Tests
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography - Computed Tomography
PICO	Population/Patient; Intervention; Comparison/Control; Outcome
PICO(T)	Population/Patient; Intervention; Comparison/Control; Outcome (Time)
PPP	Purchasing Power Parity
QALY	Quality Adjusted Life Year
QID	Quality Improvement Division
QOL	Quality of Life
Rec	Recommendation
RCPath	Royal College of Pathologists
RCSI	Royal College of Surgeons Ireland
RCT	Randomised Controlled Trial
RFA	Radiofrequency Ablation

SCC	Squamous Cell Carcinoma
SEER	Surveillance, Epidemiology, and End Results
SFH	St. Francis Hospice
SIGN	Scottish Intercollegiate Guidelines Network
SJH	St. James's Hospital
STR	Surgical Technology Related
SVUH	St. Vincent's University Hospital
TCD	Trinity College Dublin
THE	Transhiatal Oesophagectomy
TNM	Tumour, Node, Metastasis
TTE	Transthoracic Oesophagectomy
UHG	University Hospital Galway
UICC	Union for International Cancer Control
UK	United Kingdom
UL	University of Limerick
U.S	United States
WHO	World Health Organisation
WTE	Whole Time Equivalent

Appendix 9: Levels of evidence & grading systems

All data extraction tables used in the development of this national guideline are available upon request from the GDG.

Table 15: Levels of evidence for diagnostic studies (Oxford CEBM, 2009)

1a	Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
1b	Validating** cohort study with good reference standards" " "; or CDR tested within one clinical centre.
1c	Absolute SpPins (specificity) and SnNouts (sensitivity)" ".
2a	Systematic review (with homogeneity*) of Level >2 diagnostic studies.
2b	Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
3a	Systematic review (with homogeneity*) of 3b and better studies.
3b	Non-consecutive study; or without consistently applied reference standards.
4	Case-control study, poor or non-independent reference standard.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).
** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.
§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 16: Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
C	Level 4 studies; or Extrapolations from level 2 or 3 studies.
D	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.

Table 17: Levels of evidence for interventional studies (SIGN grading system 1999-2012)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table 18: Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Good practice points
Recommended best practice based on the clinical experience of the Guideline Development Group.

Practical considerations around patient care
Practical considerations around patient care are statements developed with patients on issues that were important to them with regard to their own experience of the diagnosis, staging and treatment of their cancer.

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