An Roinn Sláinte
Department of Health

Diagnosis and staging of patients with ovarian cancer

National Clinical Guideline No. 20

Summary August 2019

National Patient Safety Office
Oifig Náisiúnta um Shábháilteacht Othar

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

National Cancer Control Programme

Seirbhís Sláinte Níos Fearr á Forbairt | Building a Better Health Service

This National Clinical Guideline has been developed by the National Cancer Control Programme (NCCP) Guideline Development Group, within the Health Services 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 guideline is intended for all health professionals involved in the diagnosis and staging of patients with ovarian cancer and health professionals working in Genetics Services. While the Chief Executive Officer (CEO), General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this 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 ovarian 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 10: Glossary 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 Dr Josephine Barry, Consultant Radiologist, Cork University Hospital and Dr Ciarán O'Riain, Consultant Histopathlogist, St. James's Hospital. This National Clinical Guideline is supported by the National Cancer Control Programme.

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 patients, those involved in clinical practice, research and librarian services, and health economics.

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1 Background

1.1 Impact of ovarian 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 that period (NCRI, 2018b).

Ovarian cancer was ranked the fourth most common cause of cancer deaths amongst women in Ireland 2013-2015, with an average of 269 deaths annually (NCRI, 2018b). Ireland has one of the highest rates of ovarian cancer in Europe. Figures from the European Cancer Information System for 2018 estimate that in Ireland the incidence rate (European old age-standardised rate) of ovarian cancer is 16.1 per 100,000, compared with an average of 11.8 across the EU28 (European Cancer Information System, 2018).

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 to 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 (demographic projections) (NCRI, 2019).

The incidence of ovarian cancer in Ireland is projected to rise. By 2045 the cases of ovarian cancer are projected to increase by between 67% (model median estimate projection) to 80% (demographic projections) with proportionate increases in treatment rates (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, currently there are nine hospitals designated as cancer centres, seven of these centres specialise in Gynaecology Oncology — Mater Misericordiae University Hospital, St James's Hospital, St Vincent's Hospital, Cork University Hospital, University Hospital Limerick, University Hospital Galway and Waterford University Hospital. A cancer centre is characterised by the geographic concentration of all oncology disciplines with sub-specialised expertise on a tumour specific/discipline basis to provide the critical mass and support to achieve best practice in cancer care. As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

The National Cancer Control Programme (NCCP) established a National Cancer Lead Clinicians Network in 2012 for Surgical Gynaecology Oncology. The purpose of the Network is to ensure that the Cancer Centres and their associated hospitals build on robust local clinical governance arrangements in order to operate as a cohesive national clinical network for the purpose of sharing of good practice, problem solving, and clinical audit in relation to gynaecological cancer.

The NCCP engages regularly with the individual cancer centres and with Hospital Group structures. Discussion of performance data, improvement plans, 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. Discussion of multidisciplinary team location, composition and centralisation of services are also currently underway. Where resource issues are identified, these are included in the service planning process.

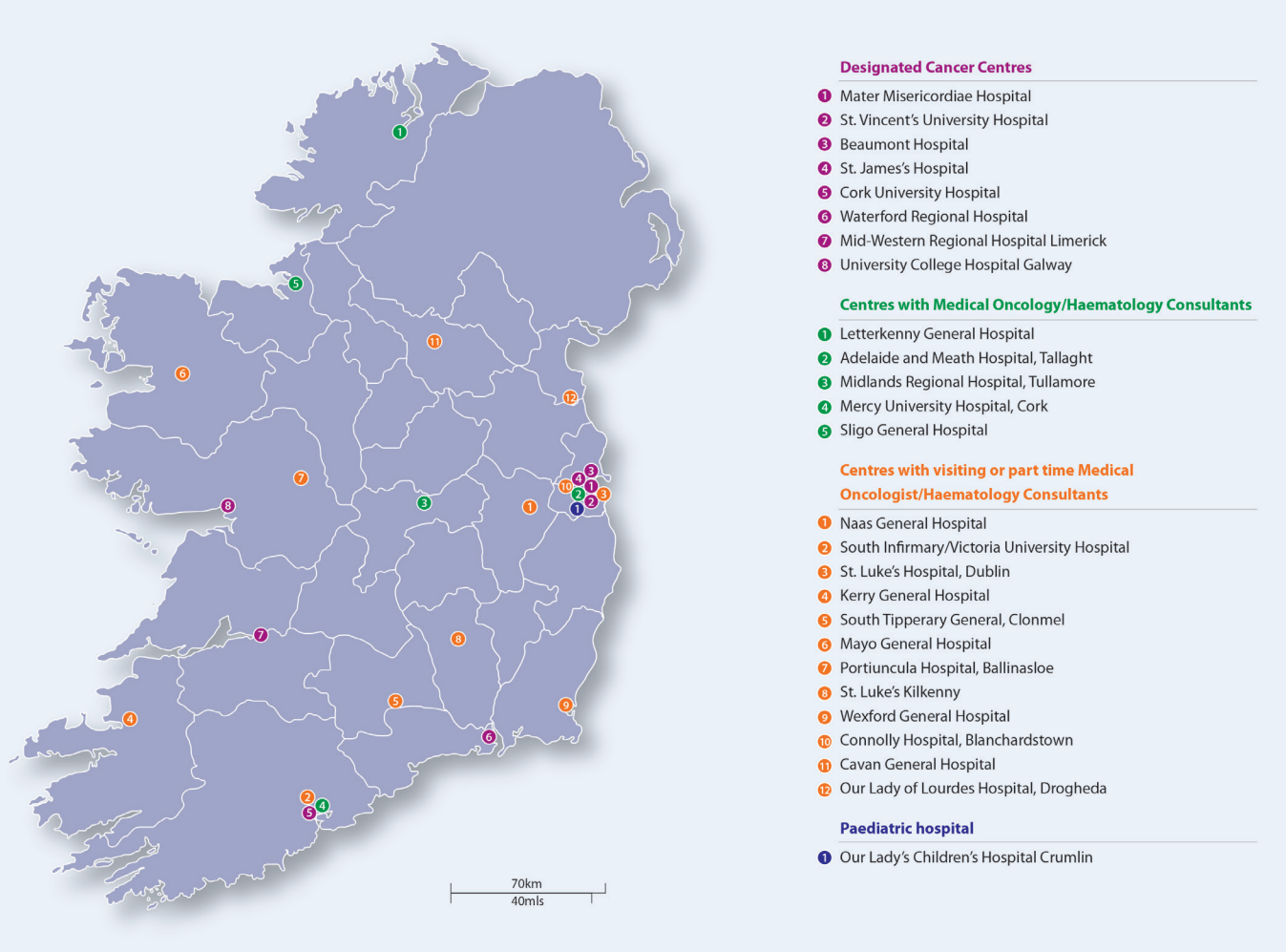

Figure 1: Publicly-funded hospitals currently providing Systemic Anti-cancer Therapy

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 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 for gynaecology 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.

1.4 Context and scope of this National Clinical Guideline

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. Audits will also be developed in accordance with the NCEC Framework for National Clinical Audit."

The National Clinical Leads Group for gynaecological oncology advise on the governance arrangements for their services within the cancer centres. In 2014, the NCCP in co-operation with the Chair for the National Clinical Leads Group for Gynaecology Oncology and the NCCP Gynaecology Leads Group proposed the prioritisation of the diagnosis and staging of patients with ovarian cancer guideline. This was due to the fact that ovarian cancer is one of the top five causes of cancer death in Irish women, accounting for 6.4% of all female cancer deaths (NCRI, 2018b).

The National Clinical Leads Group for gynaecology oncology highlighted that early diagnosis for ovarian cancer is critical for the improvement of survival rates of women. The diagnosis and staging of patients with ovarian cancer guideline was considered a priority, as the symptoms experienced by women who have ovarian cancer are vague and present challenges in relation to early diagnosis. One of the main goals of the National Cancer Strategy is to reduce cancer burden by increasing early diagnosis. It emphasises that enhancing early diagnosis will alter the landscape of cancer in Ireland by reducing mortality and improving survival and quality of life. When cancers are diagnosed at stages I and II, longer term survival is considerably better than for those patients diagnosed with stage III and IV disease (DoH, 2017).

This guideline focuses on the diagnosis and staging of patients with ovarian cancer. It does not include recommendations covering every detail of diagnosis and staging. It focuses solely on areas of clinical practice that are known to be controversial or uncertain, where there is practice variation, 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. A systematic review of cost-effectiveness (Carty et al., 2018) was also carried out as part of the scope of work in collaboration with the Health Research Board - Collaboration in Ireland for Clinical Effectiveness Reviews (HRB-CICER). A budget impact analysis including the expected service and staff costs of implementing the recommendations is available in Section 3.15 Budget impact analysis. In areas where additional resources are required these will be sought through the service planning process.

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 quality of evidence and strength of that recommendation. The quality of evidence and strength of recommendation system used is defined in Appendix 11: Level of evidence and grading systems.

A list of practical considerations around patient care were generated through collaboration with patient members of the Guideline Development Group and patient representative organisations.

Section	Recommendation	Quality of evidence	Strength of recommendation
Radiology	**2.2.1.1** In patients with suspected ovarian carcinoma a combination of transabdominal and transvaginal ultrasound should be performed and interpreted using the IOTA (International Ovarian Tumour Analysis) simple rules in conjunction with clinical assessment.	High	Strong
	2.2.2.1 In patients with an indeterminate ovarian mass MRI is the recommended imaging modality, if the MRI findings will affect patient management.	Moderate	Strong
	2.2.3.1 CT thorax, abdomen and pelvis with oral and intravenous contrast is recommended for the staging of ovarian cancer.	Low	Strong
	2.2.3.2 If the CT is indeterminate patients should be discussed at a multidisciplinary team meeting.	Low	Weak
	2.2.4.1 For patients with a high suspicion of relapse of ovarian cancer either clinically or biochemically, CT thorax, abdomen and pelvis is recommended as the first line imaging test.	High	Strong
	2.2.4.2 For patients with a high suspicion of relapse of ovarian cancer either clinically or biochemically, if the CT thorax, abdomen and pelvis does not demonstrate recurrence PET-CT should be considered, following discussion at a multidisciplinary team meeting.	High	Strong
	2.2.5 Staging algorithm for patients with suspected ovarian cancer (Figure 2).		
	2.2.6 Staging algorithm for patients with suspected recurrence of ovarian cancer (Figure 3).		

Section	Recommendation	Quality of evidence	Strength of recommendation
Pathology	**2.3.1.1** Diagnosis of tubo-ovarian cancer is recommended by histological examination of tissue sample and should allow for sub-typing by morphology and immunohistochemistry. If this is not possible, a cytological specimen may suffice. Decisions on treatment should only be undertaken after correlation with clinical, radiological, pathological and cytological findings in the multidisciplinary team setting.	Low	Strong
	2.3.2.1 Immunohistochemical panels should be appropriate to definitively sub-type tubo-ovarian carcinoma while excluding metastatic disease and non-epithelial malignancies. If complex immunohistochemistry marker testing is required this should be performed at a specialist accredited laboratory.	High	Strong

Section	Recommendation	Quality of evidence	Strength of recommendation
Genetics	**2.4.1.1** All patients with tubo-ovarian carcinoma should be offered germline mutation testing appropriate to sub-type. Specifically, testing of all high grade non-mucinous carcinoma for BRCA gene mutations is recommended.	Moderate	Strong
	2.4.1.2 All tubo-ovarian carcinoma patients with a genetic test which shows either a pathogenic variant or a variant of uncertain significance should be offered post-test counselling. If the patient has a significant cancer family history, even if BRCA1/2 testing is normal, a referral to genetic services is advised.	Low	Strong
	2.4.2.1 The tumours of all women with a diagnosis of endometrioid or clear cell carcinoma regardless of age should undergo mismatch repair (MMR) protein testing by immunohistochemistry.	Low	Weak

Practical considerations around patient care
• In patients with suspected ovarian cancer, confirmation of malignancy requires sensitive communication in an appropriate environment, with follow-up contact from appropriate clinical staff who can provide necessary psychological and practical support, in a timely manner.
• In patients with ovarian cancer, a holistic and empathetic approach for communications is required regarding disease, prognosis, and disease-related treatment choices in addition to management of intolerable symptoms and psychosocial issues.
• All patients with ovarian cancer should have access to psychological support.
• Patient information including preparation instructions should be supplied to patients with suspected ovarian cancer prior to an ultrasound examination.
• All patients with ovarian cancer should have access to a gynaecology nurse specialist.
• All patients with ovarian cancer should be made aware of expected timelines for clinical investigations.
• In patients with ovarian cancer, written information should be provided at the time of genetic testing.
• Advance care planning for women with ovarian cancer should be provided to ensure women recieve a palliative care consultation when appropriate.
• There should be integration of palliative care with gynaecology oncology for patients with ovarian cancer so that palliative interventions and end-of-life care can be considered.

Cost	2020	2021	2022	Total cost
Total operational costs for implementing recommendations	€545,161	€543,962	€543,962	€1,633,085[1](€1,542,662-€1,688,471)[2]
Total staff costs of implementing the recommendations	€3,572,498	€3,572,498	€3,572,498	€10,717,494
Total cost of implementing the guideline	€4,117,659	€4,116,460	€4,116,460	€12,350,579 (€12,260,156-€12,385,965)

1 Based on the median projected cases of ovarian cancer in 2020 (n=445) used to calculate the operational cost of implementing the guideline recommendations (NCRI, 2019).

2 Based on the minimum/maximum range of projected cases of ovarian cancer in 2020 (Nordpred model (n=426) and Demographic model (n=455)) which was used to calculate the potential minimum and maximum expected operational costs of implementing the guideline recommendations (NCRI, 2019).

2.2 Radiology

The following are responsible for implementation of the radiology 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 2.2.1

In patients with suspected ovarian carcinoma, what ultrasound features are suspicious for malignancy and require further investigation?

Evidence summary

Four meta-analyses (Meys et al., 2016, Nunes et al., 2014, Kaijser et al., 2014, Dodge et al., 2012) and a recent international cross-sectional cohort (Timmerman et al., 2016) addressed this clinical question. The Guideline Development Group found the evidence base to be of high quality and the population in the included studies were applicable to the Irish population.

The most up to date meta-analysis (Meys et al., 2016) found that the simple rules (as outlined by the International Ovarian Tumour Analysis (IOTA) group (Table 1)) in conjunction with clinical assessment (subjective assessment) performed best in patients with suspected ovarian carcinoma.

Table 1: IOTA group simple ultrasound rules

B-rules (For predicting a benign tumour)	M-rules (For predicting a malignant tumour)
• Unilocular cysts • Presence of solid components where the largest solid component <7 mm • Presence of acoustic shadowing • Smooth multilocular tumour with largest diameter <100 mm • No blood flow on colour Doppler	• Irregular solid tumour • Ascites • At least four papillary structures • Irregular multilocular solid tumour with largest diameter ≥100 mm • Prominent blood flow on colour Doppler

Table 2 below outlines the sensitivity and specificity values provided in Meys et al. (2016). The simple rules scoring system can be supplemented with the risk of malignancy index (RMI) criteria to increase specificity. The Guideline Development Group highlighted that this data applies to transvaginal ultrasound, as all current literature used to address this clinical question does not utilise transabdominal ultrasound alone.

Table 2: Pooled summary point estimates of all methods included in Meys et al. (2016)

	Sensitivity (95% CI)	Specificity (95% CI)
SA	0.93 (0.92–0.95)	0.89 (0.86–0.92)
SR+SA	0.91 (0.89–0.93)	0.91 (0.87–0.94)
SR+Mal	0.93 (0.91–0.95)	0.80 (0.77–0.82)
LR2	0.93 (0.89–0.95)	0.84 (0.78–0.89)
RMI-I	0.75 (0.72–0.79)	0.92 (0.88–0.94)
RMI-II	0.75 (0.72–0.77)	0.87 (0.85–0.89)
RMI-III	0.71 (0.67–0.75)	0.91 (0.88–0.93)

Abbreviations: CI, confidence interval; SA, subjective assessment; SR+SA, simple rules, if inconclusive classified by subjective assessment; SR+Mal, simple rules, if inconclusive classified as malignant; LR2, logistic regression model 2; RMI, risk of malignancy index.

Recommendation 2.2.1.1
In patients with suspected ovarian carcinoma a combination of transabdominal and transvaginal ultrasound should be performed and interpreted using the IOTA (International Ovarian Tumour Analysis) simple rules in conjunction with clinical assessment.

Quality of evidence: High **Strength of recommendation:** Strong

Good Practice Point
Transabdominal ultrasound and transvaginal ultrasound should be performed and interpreted by an appropriately trained sonographer/radiologist/gynaecologist.

Good Practice Point
Chaperones will be made available.

Practical considerations around patient care

- Patient information including preparation instructions should be supplied to patients with suspected ovarian cancer prior to an ultrasound examination.
- In patients with suspected ovarian cancer, confirmation of malignancy requires sensitive communication in an appropriate environment, with follow-up contact from appropriate clinical staff who can provide necessary psychological and practical support, in a timely manner.

Clinical question 2.2.2

In patients with an indeterminate ovarian mass on ultrasound, what is the utility of CT, MRI and PET-CT, for confirmation of malignancy?

Evidence summary

There is currently limited high quality evidence comparing CT, MRI and PET-CT for the diagnosis of an indeterminate ovarian mass.

MRI

The utility of MRI for the diagnosis of an indeterminate ovarian mass was addressed by a meta-analysis (Meng et al., 2016), and two systematic reviews (Anthoulakis and Nikoloudis, 2014, Medeiros et al., 2011). There was great variability in the reported sensitivities and specificities.

Meng et al. (2016) conducted a meta-analysis to assess the diagnostic accuracy of diffusion weighted imaging (DWI) in differentiating between benign and malignant ovarian neoplasms. The results showed a pooled sensitivity (0.93; 95% confidence interval (CI) 0.91-0.95), pooled specificity (0.89; 95% CI 0.86-0.91), pooled positive likelihood ratio (7.58; 95% CI 6.00-9.56) and pooled negative likelihood ratio (0.10; 95% CI 0.06-0.16).

This is supported by the European Society of Urogenital Radiology recommendations for MR imaging of the sonographically indeterminate adnexal mass published in 2017 (Forstner et al., 2017).

CT

The utility of CT for the diagnosis of indeterminate ovarian mass was addressed by a meta-analysis and a prospective study (Dodge et al., 2012, Khattak et al., 2013).

Dodge et al. (2012) conducted a meta-analysis which found the sensitivity was 87.2% (95% CI 74.2-94.1%) and specificity of 84.0% (95% CI 66.6-93.3%) for the diagnosis of ovarian cancer. Khattak et al. (2013) conducted a prospective cross-sectional study which found the sensitivity of 92%, (95% CI 0.83-0.97) and specificity 86.7% (95% CI 0.68-0.96).

CT has a lower sensitivity and specificity when compared to contrast enhanced MRI. CT has limited value in characterisation of an indeterminate mass.

PET-CT

There is currently not enough high quality evidence to address the utility of PET-CT for confirmation of malignancy.

Recommendation 2.2.2.1

In patients with an indeterminate ovarian mass MRI is the recommended imaging modality, if the MRI findings will affect patient management.

Quality of evidence: Moderate **Strength of recommendation:** Strong

Good Practice Point

The addition of contrast enhanced MRI with diffusion weighted MRI sequences will improve diagnostic accuracy.

Good Practice Point
MRI of an indeterminate mass should be interpreted by a radiologist with a specialist interest in gynaecological cancer.

Good Practice Point
Prior imaging should be available to the reporting radiologist.

Good Practice Point
Guidance on appropriate MRI sequences should be made available.

Clinical question 2.2.3

In patients with ovarian carcinoma, what is the utility of CT, MRI and PET-CT for staging ovarian cancer?

Evidence summary
There is a paucity of recent primary research to address this clinical question.

International guidelines are consistent in recommending CT abdomen and pelvis as the staging modality of choice (Scottish Intercollegiate Guideline Network (SIGN), 2018, Ledermann et al., 2013 - ESMO, National Institute for Health and Care Excellence (NICE), 2011).

The evidence regarding PET-CT for staging ovarian cancer is inconsistent. A single moderate quality study (Nam et al., 2010) favoured PET-CT over CT for the staging of ovarian cancer. However, further evidence is necessary prior to implementing the use of PET-CT in routine practice. It may have a role in a subgroup of patients following discussion by a multidisciplinary team.

There is insufficient evidence to make a recommendation on MRI as a staging tool in ovarian cancer.

Recommendation 2.2.3.1
CT thorax, abdomen and pelvis with oral and intravenous contrast is recommended for the staging of ovarian cancer.

Quality of evidence: Low **Strength of recommendation:** Strong

Recommendation 2.2.3.2
If the CT is indeterminate patients should be discussed at a multidisciplinary team meeting.

Quality of evidence: Low **Strength of recommendation:** Weak

Good Practice Point
Prior imaging should be available to the reporting radiologist.

Practical considerations around patient care

- In patients with ovarian cancer, an holistic and empathetic approach for communications is required regarding disease, prognosis, and disease-related treatment choices in addition to management of intolerable symptoms and psychosocial issues.
- All patients with ovarian cancer should have accces to a gynaecology nurse specialist.

Clinical question 2.2.4

In women who have a suspected relapse of ovarian carcinoma, what is the utility of PET-CT and CT for re-staging?

Evidence summary
There are two high quality meta-analyses to address this clinical question (Gu et al., 2009, Limei et al., 2013). The papers show that PET-CT is superior to CT for demonstrating recurrence (Table 3).

Table 3 Pooled sensitivity and specificities of PET-CT and CT in diagnosing recurrent ovarian carcinoma (Gu et al., 2009, Limei et al., 2013)

Study	Imaging modality	Pooled-sensitivity (95% CI)	Pooled-specificity (95% CI)	Area under curve
Gu et al., 2009	**PET-CT**	0.91 (0.88–0.94)	0.88 (0.81–0.93)	0.96
Limei et al., 2013	**PET-CT**	88.6% (86.6%-90.3%)	90.3% (87.6%-92.7%)	0.95
Gu et al., 2009	**CT**	0.79 (0.74–0.84)	0.84 (0.76–0.90)	0.88

For high pre-test probabilities CT and PET-CT are similar in their ability to rule in disease recurrence. However, if test negative, PET-CT is better at ruling out disease recurrence.

Therefore, if there is a high suspicion of recurrence (clinically or biochemically) CT may be a more appropriate first line test given the limited availability and cost of PET-CT.

If CT is negative, a PET-CT should be considered following discussion at an MDT.

Diffusion weighted MRI may provide an adjunct to other imaging.

Recommendation 2.2.4.1
For patients with a high suspicion of relapse of ovarian cancer either clinically or biochemically, CT thorax, abdomen and pelvis is recommended as the first line imaging test.

Quality of evidence: High **Strength of recommendation:** Strong

Recommendation 2.2.4.2
For patients with a high suspicion of relapse of ovarian cancer either clinically or biochemically, if the CT thorax, abdomen and pelvis does not demonstrate recurrence PET-CT should be considered, following discussion at a multidisciplinary team meeting.

Quality of evidence: High **Strength of recommendation:** Strong

Good Practice Point
Prior imaging should be available to the reporting radiologist.

Practical considerations around patient care

- All patients with ovarian cancer should have accces to a gynaecology nurse specialist.
- All patients with ovarian cancer should be made aware of expected timelines for clinical investigations.

2.2.5 Staging algorithm for patients with suspected ovarian cancer

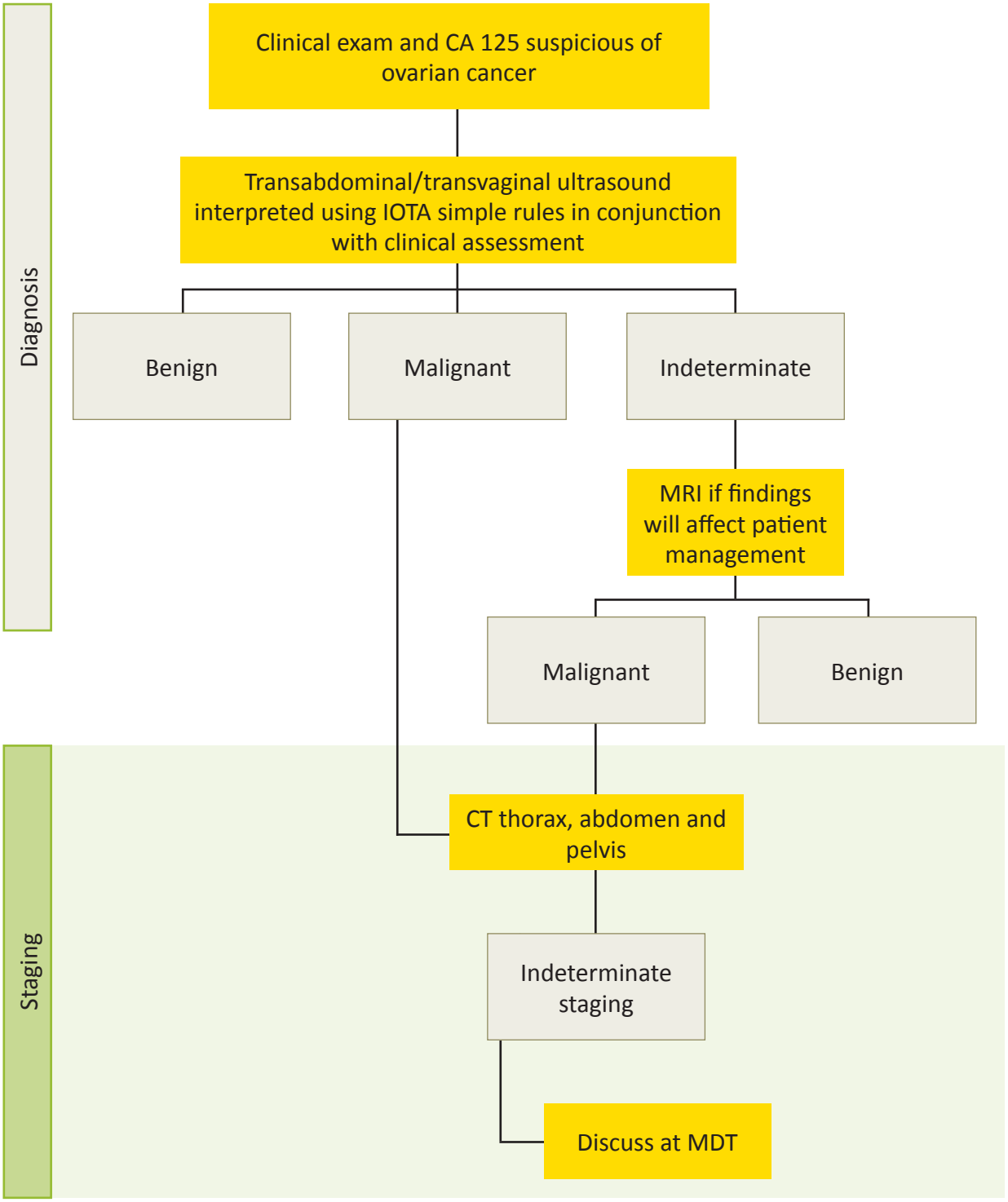

Figure 2: Staging algorithm for patients with suspected ovarian cancer recommended by the Guideline Development Group

2.2.6 Staging algorithm for patients with suspected recurrence of ovarian cancer

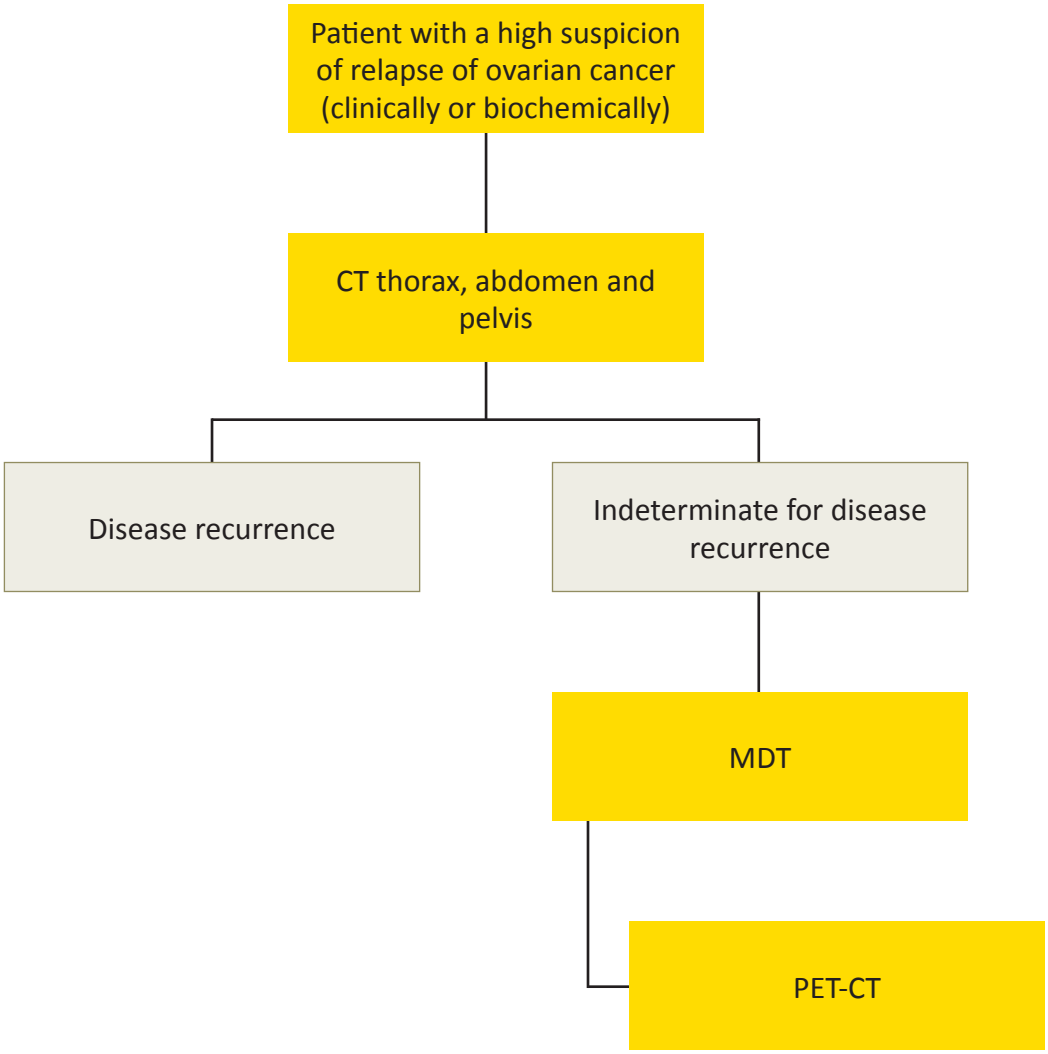

Figure 3: Staging algorithm for patients with suspected recurrence of ovarian cancer recommended by the Guideline Development Group

2.3 Pathology

Responsibility 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

In women with a suspected tubo-ovarian carcinoma, how does biopsy histology compare with fluid cytology for the definitive diagnosis and sub-typing of suspected tubo-ovarian carcinoma?

Evidence summary
Three clinical guidelines address this clinical question (NICE, 2011, Fotopoulou et al., 2017 - British Gynaecological Cancer Society, Royal College of Physicians of Ireland (RCPI), 2017).

In the absence of a strong evidence-base the Guideline Development Group refer to the following guidelines (NICE, 2011, Fotopoulou et al., 2017 - British Gynaecological Cancer Society).

Confirmation of a histological tissue diagnosis should be obtained in women with suspected advanced tubo-ovarian cancer where this can be safely achieved prior to treatment with cytotoxic chemotherapy.

If it is not possible to obtain histological tissue confirmation of suspected tubo-ovarian cancer a cytological specimen may suffice.

Decisions on treatment should only be undertaken after correlation with clinical, radiological pathological and cytological findings in the multidisciplinary team setting.

The histological specimen and/or the cytological specimen must be adequate in terms of quantity and quality to facilitate adequate diagnosis and sub-typing.

If possible a cell block should be made so that a full panel of immunohistochemistry can be more easily undertaken.

In most cases a tissue diagnosis can be obtained via a radiological procedure usually of an omental cake but rarely laparoscopy may be required if a radiological core biopsy is not possible.

All pathology laboratories making the diagnosis of tubo-ovarian carcinoma must participate and abide by the procedures of the HSE National Quality Improvement Programme, Faculty of Pathology Royal College of Physicians Ireland.

Recommendation 2.3.1.1
Diagnosis of tubo-ovarian cancer is recommended by histological examination of tissue sample and should allow for sub-typing by morphology and immunohistochemistry. If this is not possible, a cytological specimen may suffice. Decisions on treatment should only be undertaken after correlation with clinical, radiological, pathological and cytological findings in the multidisciplinary team setting.

Quality of evidence: Low **Strength of recommendation:** Strong

Good Practice Point
Patients should be discussed at a specialist centre multidisciplinary team meeting in a timely manner.

Good Practice Point
All pathology laboratories making the diagnosis of ovarian carcinoma must participate and abide by the procedures of the National Quality Improvement Programme, Faculty of Pathology, Royal College of Physicians Ireland.

Clinical question 2.3.2

In women with a suspected tubo-ovarian carcinoma, what immunohistochemistry antibody panels should be considered for diagnosis and sub-typing of tubo-ovarian carcinoma?

Evidence summary
A clinical guideline addressed this clinical question (McCluggage et al., 2015).

It is not possible to deal with each diagnostic scenario in this guideline. Assessment should be performed based on guidelines such as the International Collaboration on Cancer Reporting (ICCR) (McCluggage et al., 2015). Given that the most common and clinically relevant carcinoma is high-grade serous carcinoma, centres diagnosing ovarian cancer should have access to the following antibodies (either on site or through a linked cancer centre):

- CEA
- CA 125
- TTF1
- HNF1B
- WT1
- P53
- PAX8
- P16
- Estrogen receptor
- Progesterone receptor
- BER EP4
- Keratin 7
- Keratin 20
- CDX2
- Keratin 5 and 6
- Calretinin
- Napsin A
- CA 19.9
- GCDFP 15
- Mammaglobin
- GATA3

Not all immunohistochemical markers may be readily available in all centres. This list may change depending on the diagnostic scenario and is not exhaustive.

Recommendation 2.3.2.1
Immunohistochemical panels should be appropriate to definitively sub-type tubo-ovarian carcinoma while excluding metastatic disease and non-epithelial malignancies. If complex immunohistochemistry marker testing is required this should be performed at a specialist accredited laboratory.

Quality of evidence: High **Strength of recommendation:** Strong

Good Practice Point
Immunohistochemistry laboratories should be accredited.

Good Practice Point
All pathology laboratories making the diagnosis of ovarian carcinoma must participate and abide by the procedures of the HSE National Quality Improvement Programme, Faculty of Pathology Royal College of Physicians Ireland.

2.4 Genetics

Responsibility for the implementation of genetics 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

Which women with tubo-ovarian carcinoma should be offered genetic testing to diagnose familial cancer syndromes and/or to guide patient management?

Evidence summary
A case-control study (Alsop et al., 2012), a prospective study (Norquist et al., 2016) and two retrospective studies (Evans et al., 2017, Hoberg-Vetti et al., 2016) addressed this clinical question.

Up to 20% of women presenting with high grade serous tubal/ovarian cancer carry BRCA1/2 mutations (Alsop et al., 2012, Norquist et al., 2016). This supports universal testing of non-mucinous epithelial ovarian cancer as opposed to restricting testing to specific populations based on scoring systems such as the Manchester Scoring System (Evans et al., 2017).

Universal testing offers the opportunity to utilise preventative medicine and to tailor treatments based on genetic test results. The absence of a genetic mutation does not rule out the inherited nature of cancer in a family, further genetic assessment or screening may be necessary despite a negative test result.

Direct ordering of genetic testing and pre-test counselling by oncology staff has been found to be acceptable (Hoberg-Vetti et al., 2016). Post-test genetic counselling should be offered within four to six weeks to people with a positive test.

Recommendation 2.4.1.1
All patients with tubo-ovarian carcinoma should be offered germline mutation testing appropriate to sub-type. Specifically, testing of all high grade non-mucinous carcinoma for BRCA gene mutations is recommended.

Quality of evidence: Moderate **Strength of recommendation:** Strong

Recommendation 2.4.1.2
All tubo-ovarian carcinoma patients with a genetic test which shows either a pathogenic variant or a variant of uncertain significance should be offered post-test counselling. If the patient has a significant cancer family history, even if BRCA1/2 testing is normal, a referral to genetic services is advised.

Quality of evidence: Low **Strength of recommendation:** Strong

Good Practice Point
Patients should have access to staff with cancer genetics expertise.

Good Practice Point
Genetics liaison nurses should be appointed in cancer centres and integrated into multidisciplinary service.

Good Practice Point
There should be training for physicians and surgeons who order genetic testing.

Good Practice Point
There should be training for nurses who are involved in genetic testing.

Practical considerations around patient care

- In patients with ovarian cancer, written information should be provided at the time of genetic testing.

Clinical question 2.4.2

Which women with tubo-ovarian carcinoma should be considered for mismatch repair (MMR) protein analysis to diagnose familial cancer syndromes and/or to guide patient management?

Evidence summary
A systematic review (Murphy and Wentzensen, 2011) and two retrospective studies (Vierkoetter et al., 2014, Rambau et al., 2016) addressed this clinical question.

There is evidence from a systematic review (Murphy and Wentzensen, 2011) and two retrospective studies (Vierkoetter et al., 2014, Rambau et al., 2016) that 10-20% of patients with endometrioid or clear cell carcinoma will have mismatch repair protein abnormalities, therefore MMR protein analysis by immunohistochemistry should be performed in these patients as screening for genetic abnormalities.

Testing involves initial screening by a 4 antibody immunohistochemistry panel, looking for loss of DNA mismatch repair proteins MLH1, PMS2, MSH2 and MSH6.

As MLH1/PMS2 and MSH2/MSH6 each form linked dimer pairs with MLH1 and MSH2 being dominant respectively, loss of MLH1 will lead to PMS2 loss and loss of MSH2 will be accompanied by MSH6 loss.

In the majority of cases of immunohistochemical loss of MLH1, this loss reflects sporadic hypermethylation of the MLH1 gene rather than a genetic mutation. Hence, MLH1 loss by immunohistochemistry should prompt testing of tumour and normal tissue for MLH1 hypermethylation. In the event of MLH1 hypermethylation, this supports sporadic rather than germline loss of MLH1.

In the event of MLH1 hypermethylation being absent, referral for consideration of genetic testing for MLH1 germline mutation is appropriate.

Loss of other proteins (isolated PMS2 loss, MSH2 and MSH6 loss or isolated MSH6 loss) should lead to referral for genetic testing to consider whether such loss is due to germline mutation of the relevant genes.

The aim of this process is to identify cases of Lynch Syndrome and to allow a strategy for prevention of associated cancers including colorectal carcinoma, endometrial carcinoma and ovarian carcinoma.

Recommendation 2.4.2.1
The tumours of all women with a diagnosis of endometrioid or clear cell carcinoma regardless of age should undergo mismatch repair (MMR) protein testing by immunohistochemistry.

Quality of evidence: Low **Strength of recommendation:** Weak

3 Development of a National Clinical Guideline

3.2 Rationale for this National Clinical Guideline

The National Cancer Strategy (DoHC, 2006) recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The National Cancer Strategy 2017-2026 recommendation 37 also states: *The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards* (DoH, 2017).

The overall purpose of developing these guidelines is to improve the quality of care received by patients.

3.3 Aims and objectives

The overall objectives of the NCCP's National Clinical Guideline 'Diagnosis and staging of patients with ovarian cancer' are outlined below, along with the clinical question number that addresses that specific aim:

- To improve the quality of clinical care, improving patient outcomes by reducing morbidity and mortality (Clinical Questions 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.3.1, 2.3.2, 2.4.1, 2.4.2),
- To reduce variation in practice and improve consistency and standards of care by promoting interventions of proven benefit and discouraging ineffective ones (Clinical Questions 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.3.1, 2.3.2, 2.4.1, 2.4.2),
- To address areas of clinical care with new and emerging evidence (Clinical Questions 2.4.1).

The guideline is based on the best research evidence in conjunction with clinical expertise, patient preferences and is developed using a clear evidence-based internationally used methodology.

3.4 Financial impact of ovarian 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, in-patient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million. 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).

Ovarian cancer is one of the most costly cancers for household production losses per death. A recent productivity loss analysis carried out in an Irish context (Pearce et al., 2016) projected that by 2030, premature death will cost a value of €367,284 household production losses per ovarian cancer death.

The NCCP collaborated with HRB-CICER to conduct a systematic review of cost-effectiveness (Carty et al., 2018) which will be available on the NCCP and NCEC websites.

3.5 Guideline scope

3.5.1 Target population:

Patients that are covered by this guideline:

- Adults (over 18 years old) with newly diagnosed ovarian cancer,
- Adults that have a suspected diagnosis of ovarian cancer,
- Adults that have a suspected recurrence of ovarian cancer.

3.5.2 Target audience:

This guideline is intended for all health professionals involved in the diagnosis and staging of patients with ovarian cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this 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 ovarian cancer and their significant others. A list of medical abbreviations used throughout the guideline can be found in Appendix 10: Glossary and abbreviations.

3.6 Conflicts of Interest statement

A conflict of interest form developed by the NCEC was signed by all Guideline Development Group members and reviewers. The Guideline Development Group was managed by the Chair to promote the highest professional standard in the development of this guideline. Where a conflict arises a Guideline Development Group member absents themselves from discussion pertaining to their area of conflict.

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 and Guideline Steering Group members are provided in Appendix 3: Guideline Development Group terms of reference and logic model.

A Guideline Development Group was responsible for the development and delivery of the National Clinical Guideline and included representatives from relevant professional groups (radiology, pathology, gynaecology, genetics, medical oncology, radiation oncology and nursing) with expertise in the diagnosis and staging of patients with ovarian cancer, patients, a project manager, a methodologist, research officers, and a clinical librarian.

3.7 Source 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. Figure 4 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 or areas where there was variance in practice and formulated the list of clinical questions. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

The questions were broken down into their component parts using the PICO(T) framework:

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

The Guideline Development Group signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 8 clinical questions are listed in Appendix 4: Clinical and economic 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 (Appendix 6: 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. The literature searches and flowcharts are detailed in a supporting document available upon request. This is a live document, updates and reviews are carried out at three year intervals.

3.8.3 Step 3: Screen and appraise the evidence

Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (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 upon request.

3.8.4 Step 4: Formulation and grading of recommendations

The evidence which addressed each clinical question, both 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.

At Guideline Development Group meetings members discussed the following items which were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Consistency of the evidence
  - Generalisability/directness of the evidence
  - Imprecision of results
  - Risk of bias/publication bias
- What is the potential benefit versus harm to the patient?
- What are the patient preferences and values?
- Is the intervention implementable and applicable in the Irish context?
- Are there resource implications?

The evidence summaries and recommendations were then written. Each recommendation was assigned a quality of evidence and strength of recommendation by the Guideline Development Group using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The strength of recommendation reflects the balance of the following items:

- The quality of the evidence
- The benefit and harm to patient
- Patient preferences and values
- Cost.

The quality of evidence and strength of recommendation system used is defined in Appendix 11 Level of evidence and grading systems.

Good practice points were based on the clinical expertise of the Guideline Development Group.

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

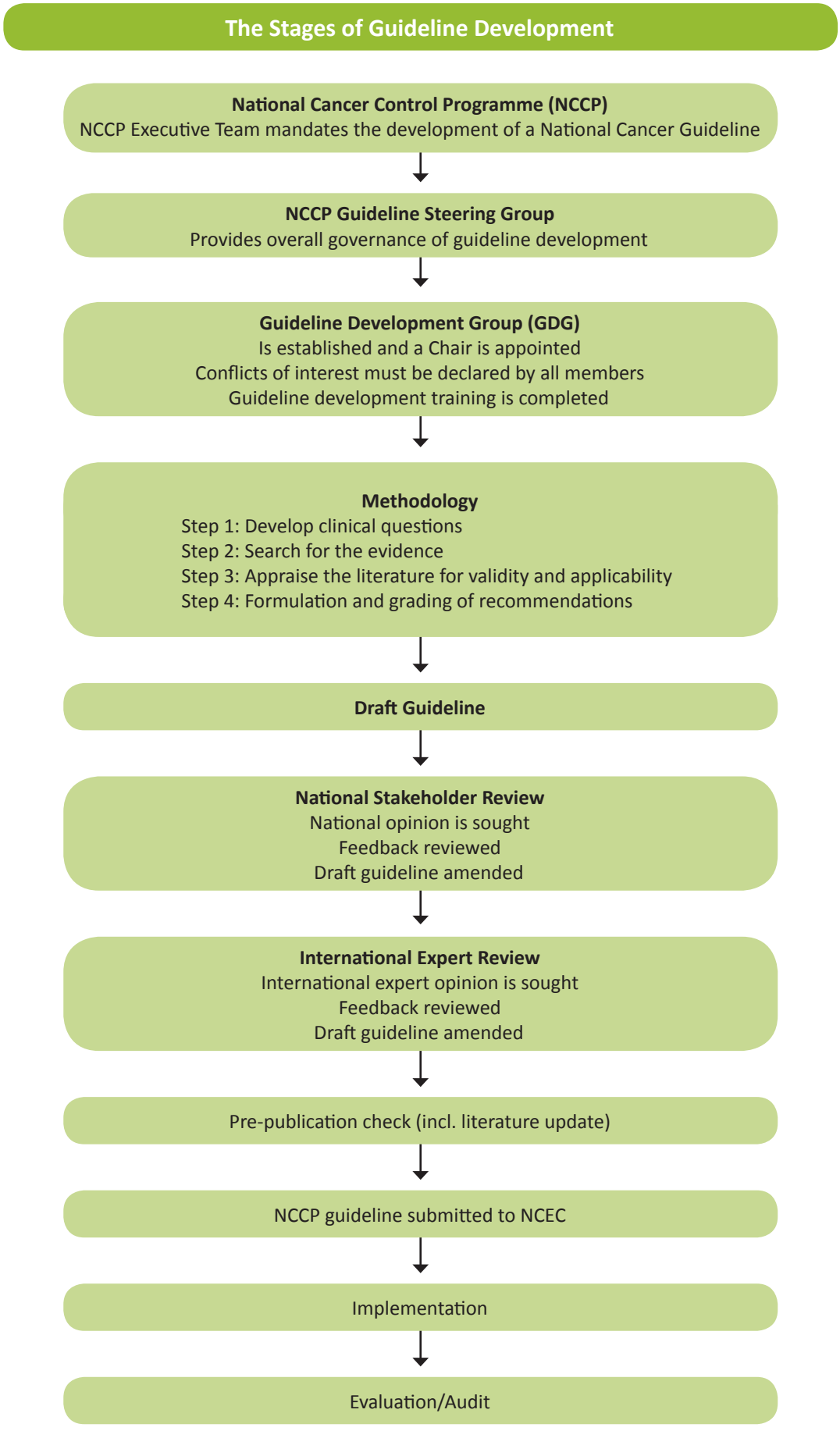

Figure 4: The stages of guideline development

3.9 Consultation process

3.9.1 Patient involvement

The NCCP worked in close co-operation with Irish Society of Gynaecology Oncology (ISGO) and the ISGO Public and Patient Group (ISGO PPI) in identifying patients who were willing to participate as members of the Guideline Development Group. The patient representatives were given training in guideline development that was designed specifically for patients by the NCCP as required by the NCEC Framework for Public Involvement (DoH, 2018). The training included the following topics;

- Objectives of the NCCP guideline
- Governance
- Guideline methodology
- Developing clinical questions
- Important outcomes for patients
- Searching for evidence
- Appraising Evidence
- Generating recommendations
- Patient preferences and values
- Patient practical issues

Prior to all Guideline Development Group meetings, pre-meetings were held with patient representatives to consider the agenda for the meeting, to review the evidence being covered, to answer questions and any issues of concern that needed to be clarified or addressed. Patients were encouraged to ask questions and to participate as full members of the Guideline Development Group.

At Guideline Development Group meetings members discussed and documented the potential benefits and harms and patients preferences and values using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. Practical considerations around patient care for specific questions were generated based on the experiences of the patients and the groups they represented. A broader list of practical considerations around patient care were then generated through collaboration with patient members of the Guideline Development Group and patient representative organisations and can be found in 2.1 Summary of clinical recommendations, practical considerations around patient care.

3.10 External review

3.10.1 National review

The draft guideline was signed off by the entire Guideline Development Group, and the NCCP Guideline Steering Group before going to National Stakeholder Review. It was placed on the NCCP website and circulated to relevant organisations and individuals for comment between 30th of March and 1st June 2018. A full list of those invited to review this guideline is available in Appendix 7: Details of consultation process.

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.

All feedback received was reviewed by the Guideline Development Group. Suggested amendments and supporting evidence were reviewed by the Guideline Development Group and consensus reached to

accept or reject the amendments. All modifications were documented and the report is available upon request.

3.10.2 International expert review

The amended draft guideline was also submitted for international expert review. The Guideline Development Group nominated Professor Glenn McCluggage, Department of Pathology, Belfast and Professor Evis Sala, Professor of Oncological Imaging at the University of Cambridge, UK, as International reviewers to provide feedback on the draft guideline. These reviewers were chosen by the Guideline Development Group 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 between the 30th of March and 27th August 2018.

A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process and is available on request.

3.11 Implementation

The implementation plan (Appendix 8: Implementation plan) was developed based on the NCEC Implementation guide (DoH, 2018). The implementation plan outlines the actions required to implement the recommendations, who has lead responsibility for delivering the action, the timeframe for completion and the expected outcomes of implementation (Appendix 8: Implementation plan).

This National Clinical Guideline including the implementation plan should be reviewed by the multidisciplinary team and senior management in the hospital which outlines the actions required to implement 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.

All medical staff with responsibility for the care of patients with ovarian 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 in the management and treatment of patients with ovarian cancer.

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available via the NCEC and NCCP websites.

A summary of tools to assist in the implementation of this National Clinical Guideline is available in Appendix 5: Supporting tools.

The following documents are also available on the NCCP website:

- NCCP Methodology Manual for guideline development
- Ovarian cancer GP Referral Guideline for symptomatic women
- Ovarian cancer GP Referral form for symptomatic women

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, 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. The implementation plan clearly lays out the actions and verification criteria to implement each recommendation in the guideline (Appendix 8: Implementation plan). Relevant Cancer Strategy KPIs and recommendations that should be considered for audit are suggested in Appendix 9: Monitoring and audit.

3.16 Plan to update this National Clinical Guideline

This guideline, published in August 2019, 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 the 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 1, 2, 5, 10 and 11 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 3 Guideline Development Group terms of reference and logic model

Appendix 4 Clinical and economic questions in PICO format

Appendix 6 Systematic literature review protocol

Appendix 7 Details of consultation process

Appendix 8 Implementation plan

Appendix 9 Monitoring and audit

Appendix 1: Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging

2014 FIGO ovarian, fallopian tube, and peritoneal cancer staging system and corresponding TNM		
I	Tumour confined to ovaries or fallopian tube(s)	T1
IA	Tumour limited to one ovary (capsule intact) or fallopian tube No tumour on ovarian or fallopian tube surface no malignant cells in the ascites or peritoneal washings	T1a
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes No tumour on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumour limited to one or both ovaries or fallopian tubes, with any of the following: IC1 Surgical spill intraoperatively IC2 Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface IC3 Malignant cells present in the ascites or peritoneal washings	T1c
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)	T2
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	T2a
IIB	Extension to other pelvic intraperitoneal tissues	T2b
III	Tumour involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T3
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	T1,T2,T3aN1
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)	
IIIA1 (i)	Metastasis ≤ 10 mm in greatest dimension (note this is tumour dimension and not lymph node dimension)	T3a/T3aN1
IIIA1 (ii)	Metastasis N 10 mm in greatest dimension	
IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a/T3aN1
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b/T3bN1
III C	Macroscopic peritoneal metastases beyond the pelvic brim N 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes (Note 1)	T3c/T3cN1
IV	Distant metastasis excluding peritoneal metastases Stage IV A: Pleural effusion with positive cytology Stage IV B: Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) (Note 2)	Any T, Any N, M1 Any T, Any N, M1
	(Note 1: includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ) (Note 2: Parenchymal metastases are Stage IV B)	

Source: (Mutch and Prat, 2014)

Notes:

1. Includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ.
2. Parenchymal metastases are Stage IV B.

Appendix 2: Classification for ovarian cancer (SIGN Guideline 135 Annex 3)

Ovarian neoplasms are a heterogeneous group of tumours classified according to morphological and clinical features. The main subgroups are:

- epithelial tumours
- sex cord–stromal tumours
- germ cell tumours
- miscellaneous and metastatic tumours.

The majority of ovarian tumours (approximately 60% of all ovarian tumours and up to 90% of all primary ovarian malignancies) are epithelial. Epithelial tumours can be further classified as follows:

- serous
- mucinous
- endometrioid
- carcinosarcoma
- clear cell
- transitional cell
- mixed epithelial
- undifferentiated carcinomas.

The most common tumours are serous lesions.

Carcinosarcomas are now considered to be carcinomas with areas of metaplastic sarcomatous differentiation.

The terms mixed mesodermal tumour and malignant mixed Mullerian tumour are no longer recommended.

A benign tumour has no abnormal cytological or proliferative features and no evidence of stromal invasion. There is no significant malignant potential.

A **borderline** (low malignant potential or atypically proliferating) tumour is a lesion which has abnormal cytological and proliferative features within its epithelium but which has no evidence of invasion into the stromal supporting tissues. Extra-ovarian disease can occur and these tumour deposits are referred to as implants. Non-invasive implants, including non-invasive desmoplastic implants, are associated with a good prognosis. Invasive implants are usually deposits of low-grade serous carcinoma and are associated with adverse outcome. Most borderline tumours present as stage I lesions and are cured by surgery. Stage by stage the overall survival of women with borderline tumours is superior to women with epithelial ovarian cancer.

A **malignant tumour** is present when there is evidence of invasion into the stromal tissues of the ovary. This is usually associated with cytological atypia and increased proliferative activity. Invasion is best defined as the presence of irregular speculated or ragged epithelial islands with individual cells extending into the stromal tissues. These stromal tissues can display reactive changes such as necrosis or an immature fibroblastic response. These cytological and proliferative changes can occur focally with the ovarian mass. An ovarian tumour must be adequately sampled for histological examination.

Primary peritoneal cancer is a tumour which shows similar morphological characteristics to ovarian cancer but which has no or minimal ovarian involvement.

GRADING OF OVARIAN CANCER

There is no single universally accepted system for grading ovarian cancers. Many studies have used different systems proposed either by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) or the World Health Organisation (WHO) or the American Gynecologic Oncology Group (GOG). A proposed grading system, based on the Nottingham system of breast cancer grading, assesses the architectural pattern of the ovarian tumour, cytological atypia and the mitotic activity with the tumour (Silverberg, 2000, Elston and Ellis, 1991). This system has not been widely accepted and is of doubtful prognostic value. Current recommendations are that serous carcinomas are graded as low and high grade; endometrioid and mucinous tumours are graded using the FIGO system for endometrioid carcinomas of the endometrium; and that clear cell carcinomas, carcinosarcomas and undifferentiated carcinomas are considered by definition grade 3 (The Royal College of Pathologists, 2010). The FIGO staging system described in Annex 2 is a surgical staging system which does not incorporate the grade of the tumour.

SEROUS CARCINOMAS

It has become apparent that there are two distinct biological types of ovarian serous carcinoma referred to by some as type 1 and type 2. However, rather confusingly, they are more commonly referred to as low-grade and high-grade despite being two different biological entities. They can be distinguished by differences in architecture, cytology, mitotic activity and pattern of necrosis. There are also significant molecular differences with high-grade serous carcinomas being associated almost universally with *TP53* mutation and low-grade serous carcinomas often containing *BRAF* or *KRAS* mutations. High-grade tumours are much more common, making up approximately 90% of serous carcinomas (The Royal College of Pathologists, 2010).

MUCINOUS CARCINOMAS

Primary mucinous carcinoma of the ovary is a rare tumour as many tumours are now recognised to represent metastatic tumours, often from the gastrointestinal tract. It is, in essence, a diagnosis by exclusion of a primary lesion elsewhere. Mucinous carcinomas are often found to have benign, borderline and malignant elements with the same tumour. This is not, however, proof of an origin at this site as metastatic mucinous tumours can exhibit a 'maturation phenomenon', producing a 'benign' or 'borderline' appearance.

IMMUNOHISTOCHEMICAL ANALYSIS

The different types of epithelial ovarian cancer can be identified by their immunohistochemical profile. A potentially useful panel of antibodies includes CK7, CK20, WT-1, Pax8, Ca125, ER, PR, p53, p16 and possibly HNF-1beta. A suitable combination of these potentially helpful antibodies can be used at the discretion of the reporting pathologist.

PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei is a clinical condition characterised by the presence of mucinous material within the peritoneal cavity. This condition may originate from either the ovary or gastrointestinal tract. In gynaecological pathology it is more often seen in association with borderline mucinous ovarian tumours. In view of the debate about the primary site of origin of these tumours the appendix should be examined. Pathological examination of the mucinous material and associated tissues should specify whether epithelial cells are present or not. The cytological characteristics of the cells should also be described.

BRCA1 AND BRCA2

Germline mutations in BRCA1, a gene on chromosome 17 and BRCA2, a gene on chromosome 13, increase susceptibility to breast and ovarian cancer.

Appendix 5: Supporting tools

Downloading this guideline
This National Clinical Guideline will be available to download on the following websites:

NCCP: https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/
NCEC: https://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/

Guide for health professionals

Resource	Available
• Ovarian cancer GP Referral Guideline for symptomatic women	https://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/gp%20ovarian%20cancer%20referral%20guideline%20and%20referral%20form.html
• Ovarian cancer GP Referral form for symptomatic women	
• National Consent Policy 2017	https://www.hse.ie/eng/about/who/qid/other-quality-improvement-programmes/consent/
• Health Service Executive Guidance for Decontamination of Semi-critical Ultrasound Probes; Semi-invasive and Non-invasive Ultrasound Probes	https://www.hse.ie/eng/about/who/qid/nationalsafetyprogrammes/decontamination/
• NCCP (2015) Prevention of clinical lymphoedema after cancer treatment: Early detection and risk reduction	https://www.hse.ie/eng/services/list/5/cancer/patient/leaflets/prevention-of-clinical-lymphoedema-after-cancer-treatment.pdf
• Algorithms available in this guideline for clinicians: Figure 2: Staging algorithm for patients with suspected ovarian cancer Figure 3: Staging algorithm for patients with suspected recurrence of ovarian cancer	

Patient information booklets/leaflets/website

- NCCP (2018) Sexual wellbeing after breast or pelvic cancer treatment: https://www.hse.ie/eng/services/list/5/cancer/patient/leaflets/sexual-wellbeing-after-breast-or-pelvic-cancer-treatment.pdf
- Cancer Genetics website https://www.cancergenetics.ie/

Service Quality

- Department of Health (2017) National Cancer Strategy 2017-2026
- NCEC (2018) Framework for Public Involvement in Clinical Effectiveness Processes
- Health Information and Quality Authority (HIQA). National Standards for Safer Better Healthcare
- Your service, your say: https://www2.hse.ie/file-library/your-service-your-say/your-service-your-say-feedback-form-english.pdf

Appendix 10: Glossary 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. (NCI Dictionary)

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

The following abbreviations are used in this document:

AGREE II	Appraisal of Guidelines for Research and Evaluation II
AJCC	American Joint Committee on Cancer
ANP	Advanced Nurse Practitioner
BGCS	British Gynaecological Cancer Society
BH	Beaumont Hospital
CAP	College of American Pathologists
CEA	Carcinoembryonic Antigen
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CI	Confidence Interval
COM-B	Capability; Opportunity; Motivation; Behaviour
CQ	Clinical Question
CSO	Central Statistics Office
CT	Computed Tomography
CUH	Cork University Hospital
DFS	Disease-Free Survival
DoH	Department of Health
DoHC	Department of Health and Children
DWI	Diffusion Weighted Imaging
EBP	Evidence-Based Practice
ECIS	European Cancer Information System
ESMO	European Society of Medical Oncology
EU	European Union
EUS	Endoscopic Ultrasound
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GDG	Guideline Development Group
GOG	American Gynecologic Oncology Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUH	Galway University Hospital
HIQA	Health Information and Quality Authority
HR	Hazard Ratio
HRB-CICER	Health Research Board - Collaboration in Ireland for Clinical Effectiveness Reviews
HSE	Health Service Executive
IANO	Irish Association for Nurses in Oncology
ICCR	International Collaboration on Cancer Reporting
ICD-O	International Classification of Diseases for Oncology
ICGP	Irish College of General Practitioners
IOTA	International Ovarian Tumour Analysis

ISMO	Irish Society for Medical Oncologists
ISGO	Irish Society for Gynaecology Oncology
ISGOPPI	Irish Society for Gynaecology Oncology Public Patient Involvement
KPI	Key Performance Indicators
MMR	Mismatch Repair
MMUH	Mater Misericordiae University Hospital
MRI	Magnetic Resonance Imaging
MSK	Memorial Sloan Kettering
MUH	Mercy University Hospital
NALA	National Adult Literacy Agency
NCCN	National Comprehensive Cancer Network
NCCP	National Cancer Control Programme
NCEC	National Clinical Effectiveness Committee
NCRI	National Cancer Registry Ireland
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PET-CT	Positron Emission Tomography-Computed Tomography
PICO	Population/Patient; Intervention; Comparison/Control; Outcome
QUB	Queens University Belfast
RCPath	The Royal College of Pathologists
RCPI	Royal College of Physicians Ireland
RCSI	Royal College of Surgeons in Ireland
RCT	Randomised Controlled Trial
RMI	Risk of Malignancy Index
SIGN	Scottish Intercollegiate Guideline Network
SJH	St. James' Hospital
SLRON	St Luke's Radiation Oncology Network
SUH	Sligo University Hospital
SVUH	St. Vincent's University Hospital
TCD	Trinity College Dublin
TUH	Tallaght University Hospital
UCD	University College Dublin
UHW	University Hospital Waterford
WHO	World Health Organisation

Appendix 11 Level of evidence and grading systems

The Guideline Development Group assigned each recommendation a quality of evidence and strength of recommendation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides an explicit system for rating the quality of evidence and whether the recommendation is strong or weak (Guyatt et al., 2008).

Quality of evidence

It is recognised that in guideline development that just assessing the level of evidence does not take into account the methodological quality of each individual study or the quality of the body of evidence as a whole (Harbour and Miller, 2001). The Guideline Development Group used the GRADE system which considers the following factors when classifying the quality of evidence; high, moderate or low (Guyatt et al., 2008):

- Study design
- Study design limitations
- Consistency of results
- Directness of the evidence
- Imprecision of results
- Reporting bias

Table 16: Quality of evidence adapted from GRADE working group 2013

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Strength of recommendation

There are two grades of recommendation: strong or weak. The strength of recommendation reflects the balance of the following items:

- The quality of the body of evidence
- The balance between benefit and harm to patient
- Patient preferences and values
- Resources/cost

Table 17: Strength of recommendation adapted from GRADE working group 2013

Strong	A strong recommendation is one for which the Guideline Development Group is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). Strong recommendations are not necessarily high priority recommendations. A strong recommendation implies that most or all individuals will be best served by the recommended course of action.
Weak	A weak recommendation is one for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values. When there are weak recommendations caregivers need to allocate more time to shared decision making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

Good practice points

Good practice points were based on the clinical expertise of the Guideline Development Group.

Practical considerations around patient care

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

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