The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for parathyroid cancer histopathology reports

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Comments	This document replaces the 2nd edition of *Dataset for parathyroid cancer histopathology reports*, published in 2010. In accordance with the College's pre-publications policy, it was on The Royal College of Pathologists' website for consultation from 30 September to 30 October 2015. Twenty items of feedback were received. Please email publishing@rcpath.org to see the responses and comments. **Dr Lorna Williamson** **Director of Publishing and Engagement**

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other, **non-core, data items** are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholder organisations have been consulted during the preparation of the dataset:

- British Association of Endocrine and Thyroid Surgeons (www.baets.org.uk)
- British Association of Head and Neck Oncologists (www.bahno.org.uk)
- UK Endocrine Pathology Society (www.ukeps.com)

Supporting evidence and recommendations in the dataset are based on PubMed literature searches from 2010 to 2014. The supporting evidence is level B to D or meets the Good Practice Point (GPP) criteria. No major conflicts in the evidence have been identified and any minor discrepancies between evidence have been resolved by expert consensus.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Working Group on Cancer Services and placed on the College website for consultation with the membership from 30 September to 30 October 2015. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and Director of Publishing and Engagement.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Director of the Clinical Effectiveness and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

1.1 Endocrine cancer datasets

The management of patients with endocrine tumours should be the responsibility of an appropriately experienced multidisciplinary team (MDT). Because these tumours bridge various anatomical divisions, they are dealt with by a number of specialist teams and are the topics of separate cancer datasets.[1–3] Ideally, the pathologist(s) reporting them should have a special interest in endocrine pathology. Alternatively, he/she should have an interest in endocrine tumours in his/her area of systematic pathology or, if a general pathologist, should participate in a network with easy opportunity for specialist pathology review.

Although the guidelines of The Royal College of Pathologists are primarily aimed at collecting core data in the reporting of cancers, we suggest that the endocrine guidelines also provide a useful template for the reporting of benign and non-neoplastic endocrine conditions. We have therefore included some of these conditions in the histopathology reporting proforma (see Appendix D).

Target users and health benefits of this guideline

The primary target users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers and epidemiologists, and facilitates international benchmarking and research.

1.2 Parathyroid carcinoma: clinical and pathological aspects

Parathyroid carcinoma is responsible for less than 1% of cases of primary hyperparathyroidism in western countries;[4-7] and is increasing.[4,8] The majority of cases of primary hyperparathyroidism are caused by parathyroid adenomas, with most of the remainder being due to parathyroid hyperplasia. These processes may occur in supernumerary and/or ectopically located parathyroid glands. Hyperparathyroidism may arise as part of the multiple endocrine neoplasia (MEN) syndromes MEN1 and MEN2a, and very rarely MEN2b.

Parathyroid carcinoma can be a challenging histological diagnosis but its recognition is important. The best patient outcomes, and certainly the only chance of cure, follow complete surgical removal with microscopically clear margins and removal of any local lymph nodes.[4,6] This is achieved by early *en-bloc* resection, preferably at first surgery, including ipsilateral thyroid lobectomy (if the parathyroid abuts the thyroid lobe) and removal of central (level VI) lymph nodes and any adherent tissue, with clear specimen margins.[9-14] Involved surgical margins, intra-operative tumour spillage, enucleation, piecemeal removal or angioinvasion increase the risk of local recurrence.[10,15-17] The tumours may be cystic and need careful handling to avoid rupture and spillage.[16]

The natural history of parathyroid carcinomas is variable but the typical pattern of disease is that of long survival with multiple re-operations for local recurrences, and there can be a high rate of surgical complications; specialist centre care is recommended.[18] The average time to

recurrence is 2.5–5 years but recurrences may arise after a long disease-free interval;[16,17,19] lifelong follow-up is therefore advised.[4,10,20-22] Local recurrence can occur in 38% to over 50% of patients,[8,19] and distant metastases in up to 25%.[10,11,19,22] Invasion of local structures may occur.[10] Lymph node involvement is rare but may occur relatively late.[10,24] Patient deaths usually result from the metabolic complications of hypercalcaemia,[10,21,22,24,25] and medical control of hypercalcaemia is needed.[6,19,26] Chemotherapy and radiotherapy are generally ineffective but there may be a future role for targeted chemotherapeutic agents.[6,26] Adjuvant radiotherapy may reduce local recurrence rates.[6,13,23,28] Surgery is the main initial and palliative treatment, and the only chance of cure, which can be achieved in approximately 50% of patients.[10,15] Overall survival is quoted as 91% at 1 year, 74–85% at 5 years and 49–77% at 10 years.[19,25,28]

The diagnosis may be suspected pre- or intra-operatively,[13,19,30] but in practice is most often made post-operatively on paraffin section histology,[4] following which a second operation is usually needed to clear the surgical field.[4,29,30] Diagnosis may even be delayed until recurrence occurs.[4] Pre-operative suspicion may be raised if the patient is young (20–45 years), with a palpable neck mass, hyperparathyroid renal and/or skeletal disease, recurrent laryngeal nerve palsy, and/or extremely high calcium and PTH levels,[5,6,10,13,15,16,20,21,24,31,32] but these features are not always seen.[20,29] Intra-operatively, the surgeon may suspect carcinoma if the gland is large, pale and/or adherent,[5] but the surgical findings may be the same as benign parathyroid disease.[10] Non-functioning parathyroid carcinoma is rare[33] and these usually present late with mass effect.[10] Ectopically located glands may be affected.[34]

Intra-operative frozen section has limited value[6] but may suggest the diagnosis[20] and any such glands should not be used for autotransplantation.[35] Making a definitive diagnosis of parathyroid carcinoma on frozen sections alone is probably inappropriate, although raising its possibility to the surgeon may help him/her to decide to perform *en-bloc* resection at first surgery.[35]

The histology of parathyroid carcinoma has been well described elsewhere.[11,15,24,36] In some cases, the diagnosis is obvious but in others it can be very difficult, requiring further specialist opinions to help distinguish it from the more frequently seen adenoma and hyperplasia.

Typically, a parathyroid carcinoma has a thick fibrous capsule with dense fibrous septa extending into and dividing the gland.[17,21,24] The growth pattern is often in the form of diffuse sheets,[37] but trabecular or spindle cell areas, palisading or rosette-like growth may be seen.[17,21,24] The nuclei are usually quite monotonous.[24] Mitoses may be present[24] but are not specific to carcinoma, although frequent mitoses (>1 per 10 hpf) should prompt a careful search for other malignant features.[21] Abnormal mitotic figures are more suggestive of malignancy.[17,21] The most specific features are vascular invasion, perineural invasion or direct extension into adjacent soft tissues, but these can be subjective to assess.[21] Capsular invasion is also subjective.

A particular pitfall is confusion between carcinoma and degenerative changes in a hyperplastic or adenomatous parathyroid gland,[36] with degeneration causing fibrosis and pseudoinvasion of the capsule. Such degenerative changes may result from pre-operative needle sampling for cytology or parathyroid hormone measurements.[38,39] Other important differential diagnoses are parathyromatosis (multiple rests of hyperfunctioning parathyroid tissue in neck and mediastinum) and the so-called ‘atypical adenoma’ (showing some worrisome histological features associated with parathyroid carcinoma but not sufficiently for definite diagnosis).[10] Severe parathyroid hyperplasia in renal patients can show features mimicking parathyroid carcinoma (such as massive enlargement of the gland, fibrosis, nuclear monotony, mitoses, a raised Ki67 index and apparent invasion of surrounding structures), but the involvement of multiple glands and the clinical context should assist the distinction. A genuine carcinoma can, however, arise in this setting, albeit rarely. Any case in which there is uncertainty by local pathologists as to whether malignancy is present or not should be referred for a specialist endocrine pathology opinion.

Immunohistochemical markers have been shown to increase the specificity of diagnosing parathyroid carcinoma, especially if the histological features are equivocal. Some of the markers also show prognostic value.

Parafibromin is the protein product of the HRPT2 or CDC73 gene and acts as a tumour suppressor. Germline mutations are seen in hyperparathyroidism-jaw tumour (HPT-JT) syndrome and somatic mutations are seen in 68-100% sporadic parathyroid carcinomas; mutations occur rarely to never in parathyroid adenomas. The mutations are usually large-scale deletions or truncations, and lead to reduced protein expression. Wild-type immunohistochemical expression is nuclear; deletions or mutations result in loss of nuclear expression. Global or focal loss of nuclear parafibromin immunostaining shows high specificity of 82–100% for parathyroid carcinoma[7,8,25,40-44] but lower sensitivity of 61–80%.[7,40,42-44] The sensitivity can be increased by combined genetic testing for the mutation.[7,43] Interpretation of parafibromin immunohistochemistry can be difficult and labelling in the epithelial cells needs to be compared with a convincing internal positive control of the endothelial or stromal cells.[40] For parathyroid carcinomas, loss of parafibromin immunopositivity is associated with worse prognosis.[4,25,40] For 'atypical adenomas', those expressing parafibromin are said to behave as adenomas with no significant recurrence risk, whereas those with loss of parafibromin immunoreactivity have a higher risk of recurrence.[8] Parafibromin immunohistochemistry therefore has roles in the diagnosis and prognosis of parathyroid carcinoma, the triaging of patients for genetic testing for HPT-JT syndrome, and in predicting outcome for 'atypical adenomas'.[45]

PGP9.5 is coded for by the UCHL1 gene, which is upregulated in parathyroid carcinoma, often accompanying the CDC73 mutation. It can therefore be used as a companion marker with parafibromin for parathyroid carcinoma.[8] Positive cytoplasmic immunostaining for PGP9.5 has high specificity (100%) for parathyroid carcinoma but lower sensitivity (78%).[45] PGP9.5 expression also has prognostic value, being associated with recurrence.[5,8]

Galectin3 is expressed in most parathyroid carcinomas but less often in adenomas and hyperplasia, and not in normal parathyroid glands.[45]

A Ki67 labelling index of >4–5% has been suggested to distinguish carcinoma from adenoma.[21,46-48] Also, those parathyroid carcinomas with higher proliferation rates behave more aggressively.[49,50]

A combination of markers gives better specificity and sensitivity than a single marker.[42,46] A panel is therefore recommended if immunostaining is performed, e.g. the four markers parafibromin, PGP9.5, galectin3 and Ki67.[51] Any immunohistochemical markers used should be mentioned in the report.

Other markers, such as cyclin D1, APC, Rb, p27, Bcl-2a have been described and may have future diagnostic and/or prognostic value.[42,46]

It is also useful to be aware of recent developments in pre-operative imaging and parathyroid surgical technique.[36] These may lead to increasing removal of only one gland via a targeted surgical approach, with no information or sampling of the remaining glands to contribute to the histological assessment.

Occasionally, immunohistochemistry for parathormone may be required to confirm the parathyroid nature of a nodule, e.g. if located intrathyroidally.

1.3 This dataset

These guidelines describe the core data that should be recorded in the histopathology reports from specimens of parathyroid carcinoma. They should be implemented for the following reasons.

1. They will provide feedback to the surgeon on the diagnosis as well as prognostic factors such as completeness of resection.
2. They will provide accurate data for cancer registration.
3. They will potentially allow the selection of patients for future trials of adjuvant therapy.

The 2015 revision has been done to update the reference base, with most of the changes relating to the immunohistochemical assessment for diagnosis and prognosis.

This document has been devised to include the data required for a careful and thorough assessment of a parathyroid specimen. Where possible, it is evidence based. The document has been approved by the UK Endocrine Pathology Society (www.ukeps.com), the British Association of Endocrine and Thyroid Surgeons (www.baets.org.uk) and the British Association of Head and Neck Oncologists (www.bahno.org.uk). We strongly recommend its use as a dataset.

2 Clinical information required on the specimen request form

In addition to correct patient identification, the specimen request form should contain relevant clinical, biochemical and imaging data, as well as any intra-operative findings. Any local arrangements for booking intra-operative frozen sections should be followed. It should ideally be stated whether a clinically suspicious parathyroid lesion is a single large nodule or is forming multiple nodules, as multiple smaller nodules might favour a diagnosis of parathyromatosis, a benign lesion.

If surgery is performed for recurrent disease in the neck or metastatic disease, the surgeon must highlight this because histological interpretation may be altered.

3 Preparation of specimens before dissection

The specimen may be received fresh if intra-operative frozen section is required (see section 9). Otherwise, (or following sampling if frozen section is performed), routine fixation in formalin is required. The specimens are nearly always small enough to be fixed intact without needing slicing to aid fixation, and such slicing may compromise later assessment of invasion and margins.

4 Specimen handling and block dissection

The specimens should be received labelled as to site and the tissue biopsied.

Best practice in handling parathyroid specimens has been reviewed.[52] The weight (in mg if possible, or to the nearest 0.1 g) and the dimensions (in mm) should be recorded, together with description of the macroscopic appearances.

The specimens may be received fresh for intra-operative reporting. Appropriate tissue should be taken for frozen section: we suggest a block of 5–10 mm in greatest dimension, so for small specimens this may be the whole specimen, but for larger glands a block should be taken from the cross-section, including the vascular hilum if possible. In addition, imprints

may be stained for immediate cytology reporting. After frozen section reporting, the tissue, including any frozen block(s), should be fixed in formalin.

After fixation, the tissue should be embedded in its entirety for paraffin sections, regardless of whether a frozen section has been performed.

Where an *en-bloc* resection is done, the nature of the resection and the tissues included should be described, and the parathyroid tissue identified and measured. Inking the specimen surface before slicing will assist with assessing margins. The whole of the parathyroid tissue should be embedded for histology, with the blocks selected to assess specimen margins and any invasion into attached tissues. All lymph nodes received should be embedded.

5 Core data items

5.1 Clinical

- Nature of specimen
- Anatomical site

5.2 Pathological

- Diagnosis - parathyroid carcinoma
- Tumour capsule - intact, breached or cannot be *assessed [Level of evidence B – status of tumour capsule is a prognostic indicator]*
- Surgical margins – involved, clear or cannot be assessed, plus measurement *[Level of evidence B – surgical margin involvement is a prognostic indicator]*
- Adjacent tissues / structures identified in the specimen and whether these are involved by local invasion *[Level of evidence B – invasion of adjacent tissues is a prognostic indicator].*

The margin is regarded as clear if tumour cells are not seen at the surgical margin of the specimen, which may have been painted at original macroscopic handling. Adequate clearance has not been defined so the distance between the margin and the closest tumour cells should be recorded, i.e. an involved margin would have a distance of 0 mm.

6 Non-core data items

Other relevant data are non-core items and their inclusion is suggested to provide a complete report, including stating the features on which the diagnosis is based. Where other parathyroid glands are submitted, the pathologist should attempt to distinguish parathyroid hyperplasia from parathyroid adenoma although it is recognised that there is inter-observer variation in interpreting these features.[39] Any immunohistochemical staining performed, and the results, should be mentioned in the report. The prognostic value of immunostaining does not yet have a strong enough evidence base to include it as a core item.

The final written report should include the macroscopic findings, the intra-operative frozen section report, by whom and to whom this was given (with date and time), and any additional clinical information obtained from the surgeon. When thyroid tissue is submitted during surgery for parathyroid disease, it should include comment on the presence or otherwise of any thyroid pathology.

7 Diagnostic coding and staging

There is no TNM staging classification for parathyroid carcinomas.[53,54] A T staging system has been suggested based on the tumour size and involvement of surrounding tissues or organs.[55] Otherwise, staging is clinical.[28]

8 Reporting of small biopsy specimens

Small biopsy samples are rarely taken deliberately from a parathyroid tumour but the possibility of parathyroid carcinoma may need to be considered in the differential diagnosis if a neck tumour of unknown type or an extra-cervical metastatic deposit is biopsied for diagnosis.

9 Reporting of frozen sections

Intra-operative reporting is used to confirm that the tissue sampled is parathyroid.[35] It is sometimes possible to identify histological features suggestive of malignancy, although definitive diagnosis is usually made on paraffin histology. The surgeon should be asked about additional information from intra-operative findings (e.g. the appearance of other parathyroid glands) and this should be documented.

The frozen section findings should be documented, including the verbal report, the name of the reporting pathologist, the name of the surgeon receiving the report, the date and the time.

10 Specific aspects of individual tumours not covered elsewhere

Oncocytic tumours can be challenging with the differential diagnosis including tumours of parathyroid or thyroid origin, which may be benign or malignant, or metastatic carcinoma from elsewhere. Immunostaining can be helpful here; in particular it has been suggested that CK14 and Ki-67 can help to distinguish parathyroid oxyphilic adenoma from carcinoma.[48]

11 Criteria for audit of the dataset

The following are recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013, https://www.rcpath.org/resource-library-homepage/clinical-effectiveness/key-performance-indicators-kpi.html:

- Cancer resections must be reported using a template or proforma, including items listed in the English COSD, which are by definition core data items in RCPath cancer datasets. English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2016.

  Standard: 95% of reports must contain structured data.

- Histopathology cases that are reported, confirmed and authorised within 7–10 calendar days of the procedure.

  Standard: 80% of cases must be reported within seven calendar days and 90% within 10 calendar days.

The following criteria may be assessed in periodic reviews of histological reports on parathyroid cancers:

- completeness of reports as to the core data items stated above;
- turnaround times for reporting intra-operative frozen sections;
- turnaround times for reporting paraffin sections;
- inter- and intra-observer studies in the diagnosis of parathyroid carcinoma cases.

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Appendix A TNM or other classification system

There is no TNM staging classification for parathyroid carcinomas.[53,54]

Appendix B SNOMED codes

All primary parathyroid carcinomas should be coded as follows.

		SNOMED 2	SNOMED 3	SNOMED CT description	SNOMED CT
Topography	Parathyroid	T97000	TB7000	Parathyroid structure (body structure)	111002
Morphology	Adenocarcinoma	M81403	M81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007

Other relevant SNOMED codes are:

	SNOMED 2	SNOMED 3	SNOMED CT description	SNOMED CT
Normal	M-00100	M-00100	Normal tissue (finding)	30389008
Uncertain	M-09350	M-09350	Morphologic description only (finding)	85728002
Hyperplasia	M-72000	M-72000	Hyperplasia (morphologic abnormality)	76197007
Adenoma	M-81400	M-81400	Adenoma, no subtype (morphologic abnormality)	32048006

Procedure codes (P)

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes may also be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix C Reporting proforma for parathyroid carcinomas

Surname…… Forenames…… Date of birth…… Sex…..
Hospital…… Hospital no…….... NHS/CHI no…….....
Date of receipt……..……. Date of reporting……..... Report no…….....….
Pathologist……..... Surgeon…….

Nature of specimen and gross description

Parathyroid gland □

Location†: Left upper □ Right upper □
Left lower □ Right lower □
Other (specify site) .....…….

Weight: ……..…….. mg
Dimensions†: …… x …... x …… mm

***En-bloc* resection** □

Side†: Right □ Left □ Other □
Nature of specimen:……
Dimensions of specimen: …… x …... x …… mm
Dimensions of parathyroid: …… x …... x …… mm

Other □
Nature of specimen:……..

Core pathological data

Diagnosis: Parathyroid carcinoma
Tumour capsule intact: Yes □ No □ Cannot be assessed □
Surgical margins†: Involved □ Not involved □ Cannot be assessed □

Closest distance to surgical margin†: ..... mm

Other tissues identified: Thyroid □ Lymph node □ Thymus □ Other (specify)……
Other tissues involved: Thyroid □ Lymph node □ Thymus □ Other (specify)……

SNOMED † : T97000/TB7000, M…….

Signature of pathologist…… Date……..

† - Data items which are currently part of the Cancer Outcomes and Services Dataset (COSD) version 6.

Appendix D Reporting proforma for parathyroid carcinomas in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • parathyroid gland • *En-bloc* resection • Other	
Parathyroid gland location	Single selection value list: • Left upper • Right upper • Left lower • Right lower • Other	Only applicable if 'Specimen type, parathyroid gland' is selected
Parathyroid gland, other specify	Free text	Only applicable if 'Parathyroid gland, other' is selected
Weight	Weight in mg	Only applicable if 'Specimen type, parathyroid gland' is selected
Dimensions of parathyroid	Size in mm x mm x mm	
En-bloc resection laterality	Single selection value list: • right • left • other	Only applicable if 'Specimen type, *en bloc'* is selected
Nature of specimen	Free text	Only applicable if 'Specimen type, *en bloc* resection' or 'Specimen type, other' is selected
Closest distance to surgical margin	Distance in mm	Only applicable if 'Surgical margins, not involved' is selected
Other tissues identified	Multiple selection value list: • Thyroid • Lymph node • Thymus • Other	
Other tissues identified, other specify	Free text	Only applicable if 'Other tissues identified, Other' is selected
Other tissues involved	Multiple selection value list: • Thyroid • Lymph node • Thymus • Other	

Element name *(continued)*	Values	Implementation notes
Other tissues involved, other specify	Free text	Only applicable if 'Other tissues involved, other' is selected
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix E Summary table – explanation of levels of evidence

(Modified from Palmer K *et al. BMJ* 2008;337:1832.)

Level of evidence	Nature of evidence
Level A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type, or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Level B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Level C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Level D	Non-analytic studies such as case reports, case series or expert opinion Or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group

Appendix F AGREE compliance monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The health question(s) covered by the guideline is (are)specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	N/A
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	1,7,8
13 The guideline has been externally reviewed by experts prior to its publication	1
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	6,7,8
16 The different options for management of the condition or health issue are clearly presented	1
17 Key recommendations are easily identifiable	6,7,8
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword