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# Examination of parathyroid gland specimens

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The pathological examination of parathyroid glands is an essential component of the evaluation of hyperparathyroidism. Traditionally, this has involved intraoperative frozen sections during bilateral surgical exploration of the neck, to confirm removal of parathyroid tissue. With recent developments in imaging, some diseased glands can be localised preoperatively, enabling removal by minimally invasive, targeted surgery, with or without additional non-histological intraoperative procedures to confirm the removal of all hyperfunctioning parathyroid tissue. This article reviews these developments and describes the ideal approach to reporting parathyroid specimens.

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**M**any pathologists are familiar with the intraoperative confirmation of tissue type during the surgical treatment of hyperparathyroidism. This article details the best practice for reporting such specimens, and then reviews recent developments in the surgical approach to hyperparathyroidism.

### CLINICAL SCENARIO AND PATHOLOGICAL BASIS

Parathyroid gland specimens are surgically removed and sent for histological examination in cases of hyperparathyroidism. The types and causes of hyperparathyroidism are listed below:

(1) Primary hyperparathyroidism occurs when excess parathyroid hormone is produced autonomously, usually causing hypercalcaemia. This is the most common reason for surgical removal of parathyroid glands. Most (80–85%) cases result from parathyroid adenoma of a single gland, with the remainder (around 15%) mainly resulting from primary chief cell hyperplasia of multiple glands, although up to 1–4% of cases are caused by parathyroid carcinoma.[1] [2] Lithium treatment can produce spurious calcium and parathormone concentration results, but patients on lithium are also more likely than usual to develop parathyroid hyperplasia.

(2) Secondary hyperparathyroidism is an adaptive increase in the production of parathyroid hormone in response to a known clinical stimulus, usually via hypocalcaemia and hyperphosphataemia. The most common cause is chronic renal failure. Other causes are vitamin D deficiency, calcium deficiency, malabsorption, and low serum magnesium. The parathyroid glands show hyperplastic changes resembling those of primary chief cell hyperplasia. These are not treated surgically unless parathyroid hormone secretion has become autonomous.

(3) Tertiary hyperparathyroidism is apparently autonomous parathyroid hyperfunction on a background of known secondary hyperparathyroidism. Most cases result from diffuse or nodular chief cell hyperplasia affecting multiple glands, but about 5% of patients have adenomas; carcinoma may occur on rare occasions.[2]

Some cases, usually hyperplasia, may develop within the context of familial hyperparathyroidism, usually multiple endocrine neoplasia (MEN) syndromes.[3] About 20% of patients with primary chief cell hyperplasia will have MEN, usually MEN1. The likelihood of developing parathyroid hyperplasia or neoplasia varies between the MEN syndromes: approximately 90% in MEN1, 30–40% in MEN2a, and 4% in MEN2b.

> "Adenomas are treated by excision, which should be curative if complete"

Parathyroid hyperplasia can be treated by subtotal parathyroidectomy—that is, the complete removal of three glands and partial removal of the fourth, leaving the remnant either in situ or implanted into the soft tissue of the forearm. An alternative strategy is total parathyroidectomy with replacement treatment (calcium and 1α calcidol). Recurrence can occur, especially if there was inadequate initial exploration and/or ectopic glands. Approximately 5% of individuals can have supernumerary glands, usually totalling five or six, with these lying between the upper pole of the thyroid and the mediastinum. Therefore, cervical thymectomy is also necessary, especially in the context of renal failure or MEN1. Recurrence of hyperplasia is more likely in chronic renal failure, in which the stimulation to hyperplasia may not be curable.

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**Abbreviations:** IOQPTH, intraoperative quick assay of intact parathyroid hormone; MEN, multiple endocrine neoplasia; MIP, minimally invasive parathyroidectomy

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Adenomas are treated by excision, which should be curative if complete. Cases of ''recurrence'' may represent incomplete initial excision of an adenoma or misclassification of nodular hyperplasia with multiple asymmetrical gland involvement.

Parathyroid carcinoma should have primary surgical treatment for clearance of the field, which usually entails ipsilateral thyroid lobectomy and lymph node dissection.[1 2 4–6]

## THE ROLE OF THE PATHOLOGIST

The aim is to produce an accurate histological diagnosis that will inform the clinicians about the probable natural history of the process and the need for further interventions.

Traditionally, the pathologist has provided an intraoperative frozen section assessment of the specimen(s), but this approach is gradually being superseded by other developments in imaging, biochemical, and surgical techniques. The role of a frozen section is primarily to confirm the presence of parathyroid tissue, but an indication of the underlying pathology can frequently be made. Intraoperative cytology using imprint preparations can also be used as a rapid method for identification of the tissue type sampled, and can be a helpful method alongside frozen sections (fig 1A).[7–9]

## MACROSCOPIC HANDLING OF A PARATHYROID SPECIMEN

Notice should be given in advance to the pathologist as to whether or not an intraoperative result is required. If a frozen section is needed, the specimen must be received fresh immediately after surgical removal. Alternatively, the specimen can be placed into formalin for fixation and later examination.

The specimens should be received already labelled as to the site and likely tissue biopsied. The weight (in mg) and the dimensions (in mm) should be recorded, together with a description of the macroscopic appearances. If appropriate, excess fat can be dissected off the parathyroid gland before weighing. (A single gland weight above 60 mg is abnormal. The total parathyroid gland weight is 120 mg and 140 mg in men and women, respectively.)

For frozen section, an appropriately sized sample should be taken: for small specimens this may be the whole specimen, but for larger glands a block should be taken from the transverse cross section, including the vascular pole if possible. After frozen section reporting, all tissue should be fixed in formalin for paraffin wax embedding and sectioning. If no frozen section is required, the fixed specimen should be transversely sliced and processed in its entirety for sectioning.
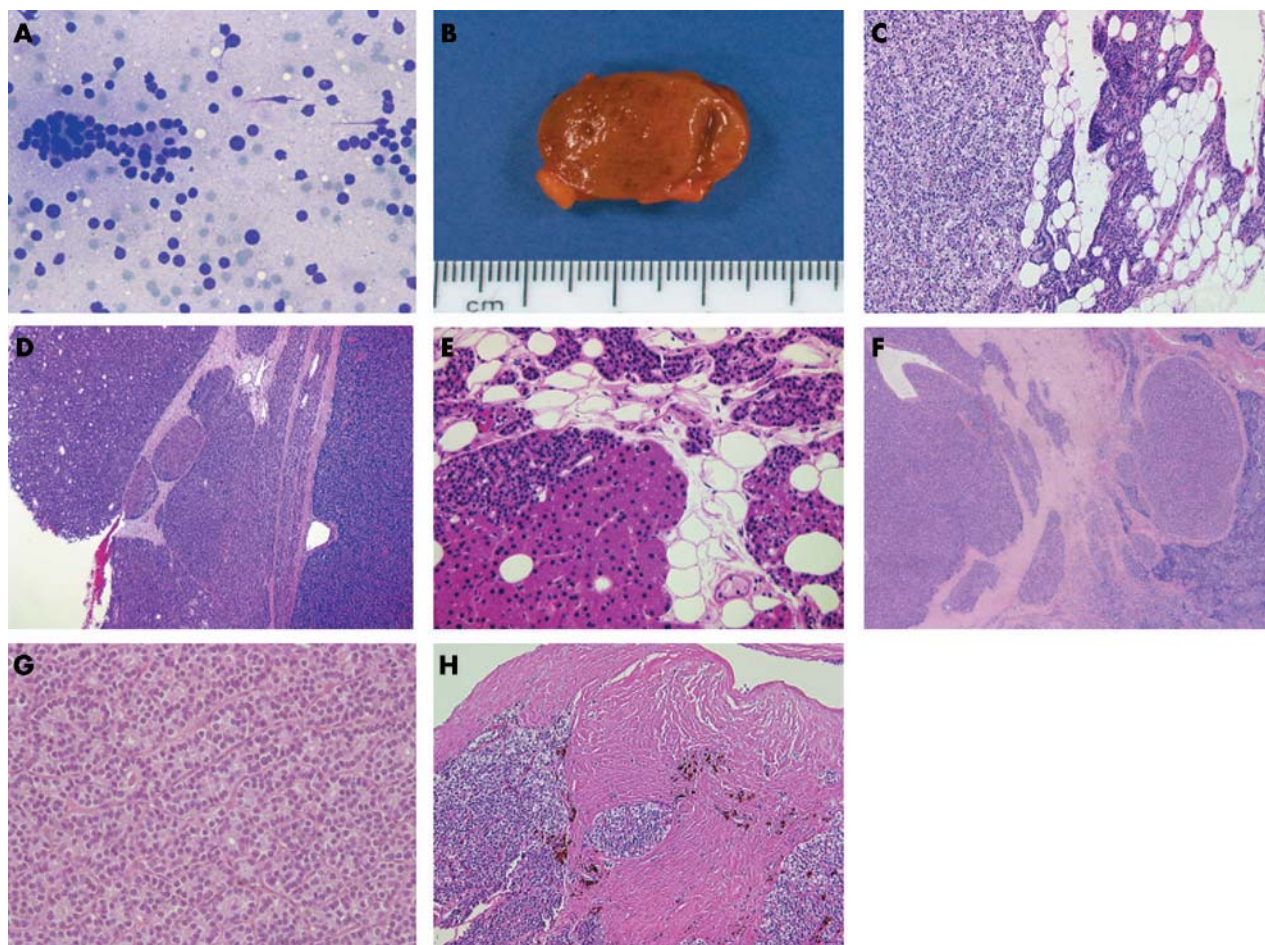


**Figure 1** (A) Parathyroid imprint cytology showing the typical evenly stained round nuclei (May-Grünwald-Giemsa stain). (B) A typical parathyroid adenoma with a tan cut surface and a thin rim of fat. (C) A thinly encapsulated parathyroid adenoma (left) with adjacent background parathyroid tissue (haematoxylin and eosin (H&E) stain). (D) Nodular parathyroid hyperplasia showing multiple non-encapsulated nodules (H&E stain). (E) Nodular parathyroid hyperplasia showing a combination of chief and oxyphil cells (H&E stain). (F) A parathyroid carcinoma showing invasion through its capsule and into the adjacent thyroid tissue (H&E stain). (G) A parathyroid carcinoma showing the striking nuclear monomorphism often seen in these lesions (H&E stain). (H) Dense fibrosis and haemosiderin accumulation accompanying cystic and degenerative changes in parathyroid hyperplasia.

## MICROSCOPIC EXAMINATION AND REPORTING
### Identification of parathyroid tissue on frozen section

The tissues most likely to be sampled during a search for parathyroid glands are parathyroid, thyroid, lymph nodes, and thymus. The distinction is usually straightforward, but can occasionally be problematic, especially when parathyroid acini show enlargement and luminal material, thereby resembling thyroid follicles containing colloid. Distinction is facilitated by high quality frozen sections and recognition of more typical areas of either parathyroid or thyroid parenchyma, with parathyroid usually showing smaller acini and vacuolated or clear epithelial cell cytoplasm.

### The distinction of parathyroid hyperplasia from adenoma

This differential diagnosis is thoroughly discussed in standard endocrine pathology texts,[3 10] and is usefully summarised in table form in one.[3]

In brief, parathyroid adenoma is a single gland disease, with enlargement of that gland by a single nodule surrounded by a delicate fibrous capsule (fig 1B). The nodule is usually composed of a single cell type, most commonly chief cells, although there may also be intermediate cells and oncocytic change. Nuclear pleomorphism is not uncommon and should not be interpreted as a sign of malignancy. There is little if any intracellular or extracellular fat, except in the uncommon lipoadenoma. Outside the capsule there may be a thin rim of residual normal or atrophic parathyroid tissue; this is usually seen at the vascular pole of the gland (fig 1C). In this area, there may be slight encroachment of fibrous tissue into the parathyroid tissue; this is a normal phenomenon and does not indicate invasive activity.

The remaining parathyroid glands should be of normal size and histology, or may appear suppressed with reduction in the parenchymal component. Assessment of the amount of fat in a parathyroid gland may help to determine the degree of suppression or hyperplasia. However, it is important to recognise that there is normal variation in the amount of fat in parathyroid glands. Older or more obese individuals will show more fat as a normal feature, and the distribution of fat varies even within an individual gland,[11] and between glands in the same person. The fat cells cluster, and a single section may suggest a proportion of fat that is higher or lower than is present as a whole in the parathyroid gland.

> "Parathyroid adenoma is a single gland disease, with enlargement of that gland by a single nodule surrounded by a delicate fibrous capsule"

In contrast, chief cell hyperplasia involves multiple parathyroid glands, although this may be strikingly asymmetrical. The glands are enlarged, either diffusely or with multiple nodules that are not fully encapsulated (fig 1D). The cell type varies, as does the amount of intraglandular fat (fig 1E).

It is usually possible to distinguish an adenoma from hyperplasia, especially with biopsy of more than one gland, although it is recognised that there is interobserver error in interpreting the features.[12] Some overlap of features may be seen, which hinders the distinction, especially if only one gland is sampled. Some adenomas may show a degree of multinodularity in a solitary gland that is identical to that seen in nodular hyperplasia. Conversely, in some multinodular hyperplastic glands there may be less fat within larger nodules than in the rest of the gland, thereby mimicking an adenoma. It is becoming less common for surgeons to biopsy apparently normal background parathyroid glands, so the final pathological diagnosis may have to include a caveat such as "the appearances are consistent with an adenoma providing the other glands are normal".

In general, it is not possible to make a confident distinction between primary and secondary parathyroid hyperplasia on histological features alone.

### The rare problem of parathyroid carcinoma

The surgeon and pathologist must both be alert to features that suggest parathyroid carcinoma. This may be suspected preoperatively, but the classic clinical picture is not always seen.[2] Intraoperatively, the surgeon may note difficulty in dissection of the gland as a result of the formation of a thick fibrous capsule around the gland, with adhesion to and/or overt infiltration of adjacent tissues including thyroid. This is in contrast to an adenoma, which has a smooth thin capsule, making dissection easy. Histological features suggestive of a carcinoma include a thick fibrous capsule, fibrous septa, a trabecular or rossette-like cellular architecture, and frequent mitoses, especially if abnormal.[2 13–18] Capsular, vascular, or perineural invasion are useful diagnostic features, but are seen in only a few cases (fig 1F). The nuclei are often bland and monotonous (fig 1G). If a parathyroid hyperplasia or adenoma has undergone previous haemorrhage and/or degeneration, this can induce a potentially misleading dense irregular fibrotic capsule, possibly with "pseudoinvasion", but this is usually accompanied by haemosiderin deposition, which is absent in carcinomas (fig 1H). Cytology touch preparations from carcinomas show increased cellularity and often strikingly monomorphic nuclei.

Assessment of the proliferative fraction with the MIB1 antibody (which recognises the Ki-67 antigen) has been reported to be helpful because, in contrast to adenomas, carcinomas tend to show a proliferative rate greater than 5–6%.[19 20] However, there is overlap between labelling indices in the different lesions, which limits its diagnostic value,[21] and we have found that the labelling index does not always correlate with the histological features. A higher proliferative fraction is said to predict more aggressive behaviour of carcinomas.[19 22] Local recurrence and distant metastasis are more likely if the primary tumour capsule was breached at initial surgery.[15 17] Therefore, the pathologist should assess the completeness of excision of the primary lesion.

The best prognosis is achieved with early recognition of the diagnosis and complete resection at the time of initial surgery, to include the ipsilateral thyroid lobe and adjacent soft tissue. Lymph node dissection is also required, at least the central compartment, but also a lateral dissection if there is clinical or radiological evidence of enlarged nodes. If the diagnosis is only made postoperatively, then an early second procedure may be the only practical alternative to achieve surgical clearance.[1 2 4–6] Postoperatively, parathyroid hormone concentrations can be used as a marker for the recurrence of parathyroid carcinoma.

The term "atypical adenoma" has been used for cases with worrying histological features, such as a thick capsule or traversing fibrous septa, but without definitive evidence of malignancy.[3]

### The intraoperative frozen section report

The frozen section report should be relayed as quickly as possible to the surgeon. The report on each specimen should state which tissue type has been sampled—usually parathyroid, thyroid, lymph node, or thymus. For parathyroid tissue, the report should include whether or not the gland is enlarged. If more than one gland has been sampled, it may be possible to comment on whether an enlarged gland is hyperplastic or contains an adenoma.[13]

The frozen section findings should be documented, including the verbal report given, the name of the reporting pathologist, and the name of the surgeon receiving the report. Additional information may be provided by the surgeon from intraoperative findings (for example, the appearance of the

other parathyroid glands, ease of dissection) and this should also be documented.

### The final written report
The final written report should include:

- the macroscopic findings;
- information on the intraoperative frozen section report, if used;
- any additional clinical or intraoperative information obtained from the surgeon;
- and finally a written description of the histological features, with an attempt to distinguish parathyroid hyperplasia from parathyroid adenoma, and to make the diagnosis of carcinoma when appropriate.

## WILL THE PARATHYROID FROZEN SECTION SOON BE LEFT OUT IN THE COLD?
The traditional surgical approach for parathyroidectomy is bilateral exploration of the neck via a collar incision, to examine all four glands and remove any diseased glands, with intraoperative confirmation of the tissue by frozen section.[13 23 24]

Based on the fact that most primary hyperparathyroidism is caused by single gland disease, it is argued that a more limited surgical examination of the neck is possible. Unilateral exploration to remove the adenoma and visualise and/or biopsy the other ipsilateral gland has been advocated. Further advances in the accuracy of preoperative localisation techniques now allow targeted minimally invasive parathyroidectomy (MIP), in which a single abnormal gland is identified and excised with no attempt to visualise the remaining glands. Various MIP techniques are available. These include a ''mini open'' approach through a 2–3 cm unilateral incision, videoscopically assisted surgery, and an entirely endoscopic technique.[25 26]

> ''Advances in the accuracy of preoperative localisation techniques now allow targeted minimally invasive parathyroidectomy''

The standard preoperative imaging for primary hyperparathyroidism is technetium-99m sestamibi scanning, which can accurately predict the success of MIP[27] or facilitate a traditional four gland examination.[28] Sestamibi scanning has a high positive predictive value, but is more accurate for single gland rather than multigland disease.[29–32] High resolution ultrasound scanning alone is less accurate than sestamibi scanning, but used in combination the accuracy of detection improves,[33–35] especially for single gland disease.[29]

There is a false negative rate of up to 22% with sestamibi scans in primary hyperparathyroidism; this is more likely with small adenomas, multigland disease, superior glands, or normal preoperative calcium concentrations.[30 36] Other scanning modalities in use include subtraction scintigraphy,[36–38] positron emission tomography scanning,[39] computed axial tomography-sestamibi image fusion,[40] and pinhole single photon emission computed tomography to complement planar scintigraphy views.[36]

Intraoperative cytology and/or conventional frozen sections merely confirm tissue type rather than functional status. Additional techniques are now available for intraoperative confirmation of removal of all hyperfunctioning parathyroid tissue. Intraoperative quick assay of intact parathyroid hormone (IOQPTH) is performed before and after excision of any parathyroid.[41] A fall in the parathyroid hormone concentration of at least 50% (for example, from pre-excision to 10 minutes after excision) predicts the removal of abnormal parathyroid tissue and therefore cure.[32 42] The IOQPTH assay is most accurate in primary hyperparathyroidism, especially single gland disease, but can also be used in secondary and tertiary hyperparathyroidism, thereby eliminating the need for intraoperative frozen sections,[42] and in reoperative parathyroidectomy.[43] When combined with preoperative localisation and MIP, IOQPTH gives cure rates similar to conventional bilateral neck exploration.[32 34 44 45]

False positive drops in IOQPTH values can occur, suggesting adequate removal of hyperfunctioning parathyroid tissue when this has not in fact been achieved. For example, this may occur when simultaneous thyroid surgery is performed; additional intraoperative confirmation of adequate parathyroid removal may then be required.[46] Intraoperative measurement of serum calcium concentrations has recently been proposed as an easier and cheaper alternative to IOQPTH.[47]

Radioguided parathyroidectomy is used in only a few centres. It involves the injection of technetium-99m sestamibi 1.5–2 hours before surgery, followed by the intraoperative use of a γ probe to guide dissection and confirm the removal of all hyperfunctioning parathyroid tissue.[29 48–51] Radioguidance can also be useful in reoperative parathyroidectomy.[52]

MIP has many potential benefits for both the patient and the medical services, including shorter operative time and shorter hospital stay, the procedure even being performed on a day case basis. Improved cosmesis and lower postoperative morbidity are also potential benefits.[27 31 37 45 49] These benefits have to be balanced against the additional costs of preoperative localisation, with or without additional intraoperative procedures, such as IOQPTH assay or radioguidance. Overall, the costs are said to be broadly similar to, or possibly lower than, the traditional bilateral approach with intraoperative frozen sections.[31 44]

> ''Minimally invasive parathyroidectomy has many potential benefits for both the patient and the medical services, including shorter operative time and shorter hospital stay, the procedure even being performed on a day case basis''

However, MIP will not be possible for a large proportion of patients (up to 50%) in whom there is discordant imaging and/or coexistent thyroid disease.

## CONCLUSION
Intraoperative frozen sections are a useful method of confirming tissue type during the traditional bilateral four gland surgical exploration for hyperparathyroidism. This approach remains relevant in many cases, especially multigland disease, and the guidance above should be followed for handling the pathology specimens.

Increasingly, there is a trend towards minimally invasive parathyroidectomy guided by preoperative imaging, possibly facilitated by intraoperative techniques other than frozen sections. This approach is most likely to be used for single gland disease, and there will be no visualisation or sampling of the remaining glands. Pathologists need to be aware of these developments.

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