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Original contribution

Pathology data set for reporting parathyroid carcinoma and atypical parathyroid neoplasm: recommendations from the International Collaboration on Cancer Reporting☆

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Summary Standardized pathologic reporting for cancers improves patient care and prognostic determination. However, access in many countries is limited. To address this issue, the International Collaboration on Cancer Reporting (ICCR), a not-for-profit organization, has the mission to develop and disseminate standardized data sets for global use. Within endocrine organs, the parathyroid gland has rarely been included in formal pathologic data sets. Utilizing an expert international panel of eleven members, an evidence-based data set was developed for parathyroid carcinoma and atypical parathyroid neoplasms. This data set consists of sixteen core (required) elements viewed as essential for documentation of these conditions. Characterizing parathyroid carcinomas and atypical neoplasms begins with correlative clinical information, the operative procedure, specimens submitted, and site of the disease. The pathologic features essential to document include parathyroid weight, size, classification, and, when a carcinoma, the tumor grade. Histologic grade of parathyroid carcinoma incorporates other core elements including necrosis, mitotic count, perineural invasion, and lymphovascular invasion. Documenting the extent of disease locally into adjacent organs, regionally, and distally is critical for staging. Pathologic staging is now included as part of the American Joint Committee on Cancer 8th edition and is included in this data set. Ancillary studies should be recorded when performed as noncore elements. Standardized pathologic data sets for endocrine organs including the parathyroid gland are now available through the ICCR website. These essential resources enhance international standardization for documenting these rare tumors for both patient care and future guidelines.

1. Introduction

The International Collaboration on Cancer Reporting (ICCR) is a not-for-profit organization sponsored by the Royal Colleges of Pathologists of Australasia and the United Kingdom, the College of American Pathologists, the Canadian Association of Pathologists in association with the Canadian Partnership Against Cancer, the European Society of Pathology, the American Society of Clinical Pathology and the Faculty of Pathology, and Royal College of Physicians of Ireland. Its goal is to produce standardized, internationally agreed upon, evidence-based data sets for cancer pathology reporting throughout the world.

Following initial discussions in 2010, an agreement to collaborate was signed with four international parties in February 2011. This quadripartite alliance of the Royal Colleges of Pathologists of Australasia and the United Kingdom, the College of American Pathologists, and the Canadian Association of Pathologists − Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer − became the ICCR. The aim of the ICCR was to reduce the global burden of cancer data set development and duplication of effort by different international institutions that commission, publish, and maintain standardized cancer-reporting data sets.

Standardized cancer-reporting data sets have been developed for national use in the UK, USA, and Australia; however, they are not internationally standardized or directly comparable. Variations in data elements, terminology, data set structure, or recommended methodology can compromise interoperability of core data for research or benchmarking in cancer management. While the classification of cancers has been internationally standardized for many years through publication of the World Health Organization (WHO) tumor classification series, international harmonization of cancer pathology reporting has never previously been undertaken.

Under the governance of the ICCR Board and Dataset Steering Committee, a worldwide network of dedicated expert pathologists is working toward the development of standardized, evidence-based data sets to support structured pathology reporting of cancer worldwide. Our goal is to improve cancer patient management across the world, to advance national and international benchmarking in cancer management and to enable standardized data supporting research and tissue banking. In addition, the creation of a single international data standard greatly facilitates eHealth integration.

2. Methods

Four endocrine tumor data sets were developed by international expert panels (Table 1). Under the leadership of Dr. Michelle Williams, and utilizing the framework established by the ICCR, an eleven-member Dataset Authoring Committee for parathyroid neoplasia, the authors herein, discussed in several teleconferences data elements for consideration based on reviewed worldwide references.

Table 1 ICCR histopathology reporting guides developed for endocrine organs structured data sets.

Parathyroid carcinoma and atypical parathyroid neoplasms
Pheochromocytoma and paraganglioma
Carcinomas of the adrenal cortex
Carcinomas of the thyroid

ICCR, International Collaboration on Cancer Reporting.

Following the draft of the proposed data set, an open-comment period was completed. The finalized data sets for the endocrine tumors were published in December of 2019 and are now freely available for public use at http://www.iccr-cancer.org/datasets. The consensus data set for the parathyroid gland is presented along with the scope by which the parathyroid data set is to be utilized.

3. Results

3.1. Scope

This data set was developed for pathologic reporting of parathyroid resection specimens when the diagnosis is parathyroid carcinoma or atypical parathyroid neoplasm (sometimes known atypical parathyroid adenoma or parathyroid neoplasm of uncertain malignant potential). No data set is utilized for parathyroid hyperplasia or parathyroid adenoma of usual type. Diagnostic biopsies of presumed parathyroid masses are not included and are generally discouraged, except in rare instances. Other disease types that may extend to involve the parathyroid (eg, sarcoma, lymphoma, and metastasis) are not covered in this data set.

3.2. Core elements

This data set is composed of 16 core elements which are defined as essential for clinical management, staging, and prognosis. Core elements have either level III-2 or above evidentiary support (based on prognostic factors in the NHMRC levels of evidence [1]) or is viewed by the committee consensus to be critical to the described disease. The summation of all core elements is considered to be the minimum reporting standard for a specific cancer. Additional noncore elements are included which should be documented when available. However, noncore data elements may not be readily available to all users of the data set and/or may fail to meet the aforementioned evidentiary criteria. A summary of the core and noncore elements for this parathyroid data set is outlined in Table 2, and each is described in further detail in the following sections:

3.3. Clinical information

Parathyroid carcinoma is a rare neoplasm representing <1% of cases of primary hyperparathyroidism [2–5]. Awareness of the clinical history is critical in the interpretation of parathyroid disease. Clinical syndromes which may be associated with parathyroid disease include multiple endocrine neoplasia syndromes and familial hyperparathyroidism of other types. In these disorders, it is more likely to find parathyroid hyperplasia or adenoma although rare cases of parathyroid carcinoma have been reported [6]. Hyperparathyroidism jaw-tumor (HPT-JT) syndrome attributable to germline mutations or large-scale deletions of the *CDC73* gene is an autosomal dominant disorder that is strongly associated with parathyroid carcinoma (lifetime risk is estimated to be as high as 15%) [7–9]. In the setting of secondary or tertiary hyperparathyroidism due to renal failure or other disorders, individual parathyroid glands may show highly atypical features that may mimic carcinoma including the presence of pseudoinvasion. Many experts are reluctant to make a diagnosis of parathyroid carcinoma in the setting of secondary/tertiary hyperparathyroidism or would use more strict criteria requiring invasion into adjacent organs (eg, thyroid, esophagus, or skeletal muscle) or vascular spaces. Therefore, knowledge of the presence of renal failure and secondary/tertiary hyperparathyroidism is important to enable proper pathological assessment. Discussion with the treating clinician (eg, endocrinologist, surgeon) for correlative clinical information as described here and under biochemical information is important for characterizing this disease. Other relevant information may include detailed family history, imaging findings of lateralization noted on ultrasound, nuclear medicine (eg, sestamibi) scan, or 4-dimensional computed tomography scans [10]. The other information response field is provided to include any history of fine-needle aspiration (FNA) of neck lesions because this procedure may lead to pathologic alterations important to consider during specimen interpretation.

3.4. Operative procedure

For clinically suspected parathyroid carcinoma, a preoperative biopsy is not recommended. Often the clinical presentation of parathyroid carcinoma overlaps with parathyroid adenoma, and the diagnosis is not made until surgical inspection and/or histologic review of the parathyroid resection specimen is made [11,12]. When carcinoma is suspected, an en bloc resection of the parathyroid gland along with the immediately adjacent or adherent structures such as the ipsilateral thyroid lobe may facilitate complete tumor resection. Advancements in preoperative imaging have reduced the need for multigland sampling, and it is not recommended in most instances when a parathyroid mass is

Table 2 Summary of core and noncore parathyroid data set elements.

Core elements (required)	Noncore elements (recommended)
Clinical information	Preoperative biochemical information
Operative procedure	Operative findings
Specimens submitted	Coexistent findings
Tumor site	Ancillary studies
Specimen weight	
Largest tumor dimension	
Histological tumor type	
Histological tumor grade	
Extent of invasion	
Lymphovascular invasion	
Perineural invasion	
Necrosis	
Mitotic count	
Lymph node status	
Histologically confirmed distant metastases	
Pathological staging	

encountered [13]. Similarly, lymph node sampling is generally not performed as the rate of regional nodal spread is low. If lymph node sampling is performed, the location of the resected lymph nodes should be specified. Resection of soft tissue of the neck, which may include skeletal muscle and nerve, most often will be encountered in the setting of recurrent disease. Other tissues to be specified if received include esophageal wall, thymus gland, or any structures not otherwise listed. In the unlikely scenario where more than one anatomically primary tumor occurs, a separate data set should be completed for each tumor.

3.5. Specimen(s) submitted

Recording each specimen submitted allows for the extent of surgery to be documented. The location of the excised parathyroid should include laterality as well as correlation with the anatomic position of superior or inferior glands. Parathyroid 'other' locations may include mediastinum or supernumerary glands for which laterality should be included if known/determined. Additional resected specimens may include the thyroid lobe either en bloc with the parathyroid or as a separate specimen. When lymph nodes are submitted, their locations should be specified (eg, level VI, right or left paratracheal, right or left lateral neck). If additional specimens are resected (eg, such as additional tissue adjacent to the recurrent laryngeal nerve, muscle, or thymic tissue), these elements are captured in the 'other' specimen field.

3.6. Tumor site

Parathyroid glands are paired endocrine structures with typically two glands on the right and two on the left. Based on patterns of embryologic development, the glands may also be located in the mediastinum associated with the thymus or partially or fully within a thyroid lobe. Tumor may involve soft tissue that is further specified (ie, adjacent to recurrent laryngeal nerve) or skeletal muscle (ie, strap muscles). Other involved structures may include adjacent organs (ie, thyroid, esophagus, or trachea). Regional tumor metastases to lymph nodes may also occur; the nodal level of involvement and laterality should be recorded (eg, right paratracheal, or right level VI, etc.) [2,14,15].

3.7. Specimen weight

A normal parathyroid gland weighs approximately 40 mg. Glandular size and weight have long been utilized to aid in defining abnormal parathyroid glands in both benign and malignant conditions. Ideally the weight is of the parathyroid gland only; however, soft tissue surrounding the gland should not be removed when an atypical parathyroid neoplasm or carcinoma is suspected. This allows for the microscopic evaluation of possible lesional extension into the adjacent tissues. On average, parathyroid carcinomas typically weigh more than 500 mg; however, there may be considerable variation in gland weight.

3.8. Tumor dimensions

Most features relating to tumor dimensions are core although there are some noncore features (Table 2). The largest dimension of the parathyroid neoplasm is recorded in millimeters (mm). The tumor dimensions may be taken from the gross examination or by microscopic examination as appropriate. Studies are conflicting as to the prognostic value of size [2,4,14].

3.9. Histological tumor type

The histological tumor types to be included for parathyroid neoplasms are those defined in the most recent edition of the WHO Classification of Tumors of Endocrine Organs (see Table 2) [16]. Parathyroid carcinoma is diagnosed by unequivocal invasion into adjacent soft tissues, muscle, or other adjacent organs (eg, thyroid); lymphovascular or perineural invasion, and/or the presence of regional or distant metastases (Fig. 1). Parathyroid carcinoma may show a fibrotic tumor capsule as well as broad fibrous bands within the substance of the tumor, although this feature is neither necessary nor sufficient for a diagnosis of carcinoma (Fig. 2). Cytologically, parathyroid carcinoma may be relatively uniform (low grade) or show high-grade features including pleomorphism, macronucleoli, high-mitotic rate, and/or coagulative necrosis (Fig. 3) [17–20].

Parathyroid neoplasms that show some histologically worrisome features but do not fulfill the more robust criteria of invasion or metastasis are classified as atypical

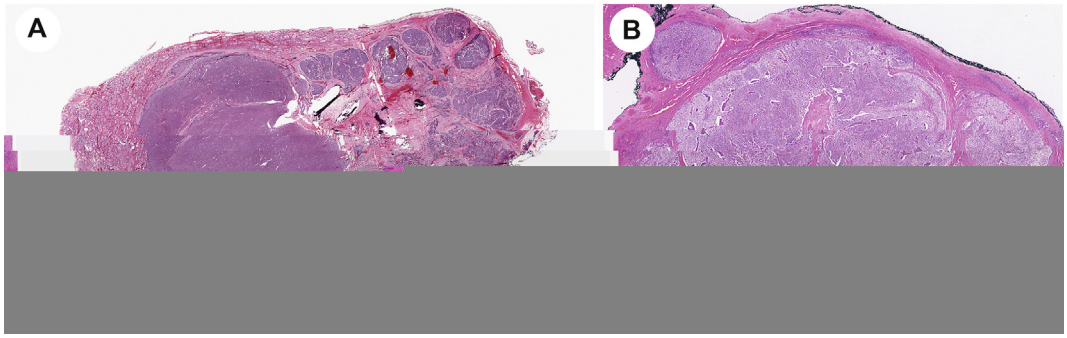

Fig. 1 Parathyroid carcinomas. (A) Low power showing tumor invading into the thyroid (left) with multinodular growth and fibrous septations. (B) Another example invading esophageal muscle.

parathyroid neoplasm (atypical parathyroid adenoma)/parathyroid neoplasm of uncertain malignant potential. These lesions lack unequivocal invasion (Fig. 4). Atypical parathyroid neoplasms generally have two or more concerning features, such as fibrous bands, mitotic figures, necrosis, trabecular growth, or adherence to surrounding tissues intraoperatively. In addition, they usually have a smaller dimension, weight, and volume than carcinomas and are less likely to have coagulative tumor necrosis [21–25]. A small percentage of atypical parathyroid neoplasms may recur locally, and this entity is now part of the pathologic staging system defined in the following [26].

3.10. Histological tumor grade

The division of parathyroid carcinoma into low grade and high grade utilizes cytologic features including pleomorphism necrosis and mitotic activity. High-grade parathyroid carcinomas are characterized by the presence of multiple concurrent histologically adverse features including sheets of cells with pleomorphic enlarged nuclei (×4 the size of background parathyroid cells) often with macronucleoli, coagulative necrosis, abnormal mitoses, and/or increased proliferation rate (Fig. 3B) [17,18,19,20]. Focal nuclear enlargement or endocrine atypia in the absence of concurrent necrosis or elevated mitotic activity may be found in benign entities and is insufficient to meet criteria for true nuclear pleomorphism.

3.11. Extent of invasion

Parathyroid carcinoma and atypical parathyroid neoplasms may be difficult to diagnose on histologic examination. The extent of tumor involvement has been proposed as one critical factor in diagnosis. Many, but not all, tumors show a fibrotic capsule with invasion (Fig. 2A and B). By definition, an atypical parathyroid neoplasm may not invade other structures (ie, cannot involve adipose tissue, muscle, or adjacent organs as these features are restricted to parathyroid carcinomas). Documentation of tumor extent may also imply severity of local disease; however, studies correlating tumor extent with prognosis are conflicting [14,19,20,27,28]. Rarely a parathyroid carcinoma may show lymphovascular involvement, a true hallmark of a carcinoma, with minimal to no localized invasive growth. As parathyroid neoplasms are very vascular, caution in making the diagnosis of carcinoma is warranted in cases where an invasive growth pattern is not encountered. Overall, the documentation of the presence and extent of local tissue involvement in parathyroid carcinomas is inconsistently presented in the literature for this rare disease. The importance of including these findings in this data set is for data collection that may aid in future stratification of these tumors for staging and outcome.

3.12. Lymphovascular invasion

Most features relating to lymphovascular invasion are core although there are some noncore features (Table 2). Lymphovascular invasion is the presence of tumor cells within a lymphatic or vascular space. Identifying this feature in the tumor capsule or in peritumoral soft tissue is one diagnostic criterion to define parathyroid carcinoma (Fig. 5). Lymphovascular invasion should not be present in an atypical parathyroid neoplasm/adenoma or parathyroid tumor of uncertain malignant potential. Vascular invasive parathyroid carcinomas have a worse prognosis than carcinomas diagnosed solely on the basis of other forms of invasive growth and appear to have a higher risk of recurrence [24]. The presence of fibrin associated with the tumor cells within an endothelial lined space supports the finding of true vascular invasion (Fig. 5A) [14,20,27–29]. As an endocrine organ, the parathyroid glands are highly vascular, and it is important not to mistake tumor next to small vessels as representing vascular space invasion. Special stains may be used for further visualization/confirmation of vascular invasion though are not essential.

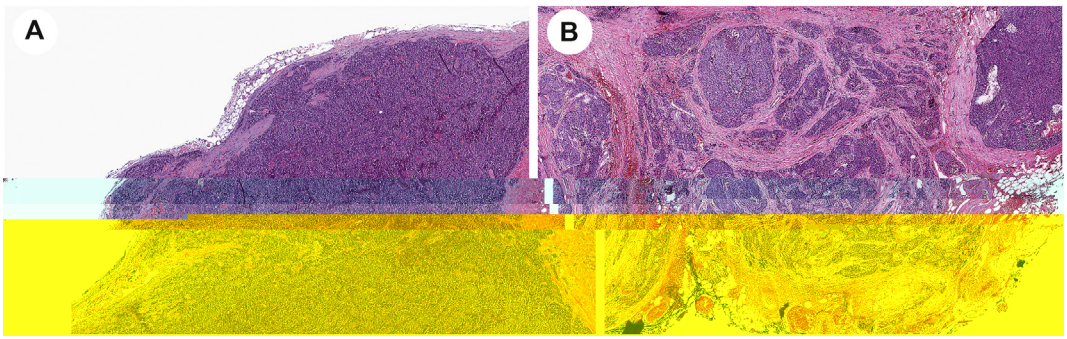

Fig. 2 Parathyroid carcinoma typically shows invasion into adjacent soft tissue. (A) The tumor may invade through a fibrous capsule with broad nests or with (B) thin cords of tumor cells often with prominent fibrosis.

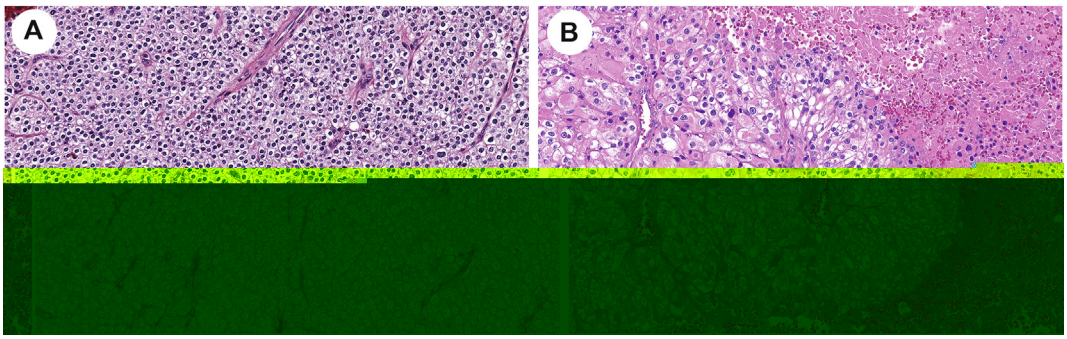

Fig. 3 Grading of parathyroid carcinoma is based on cytologic features including morphology. (A) Low-grade tumors often show relatively uniform cells versus (B) high-grade carcinomas with prominent pleomorphism and possible sheet necrosis.

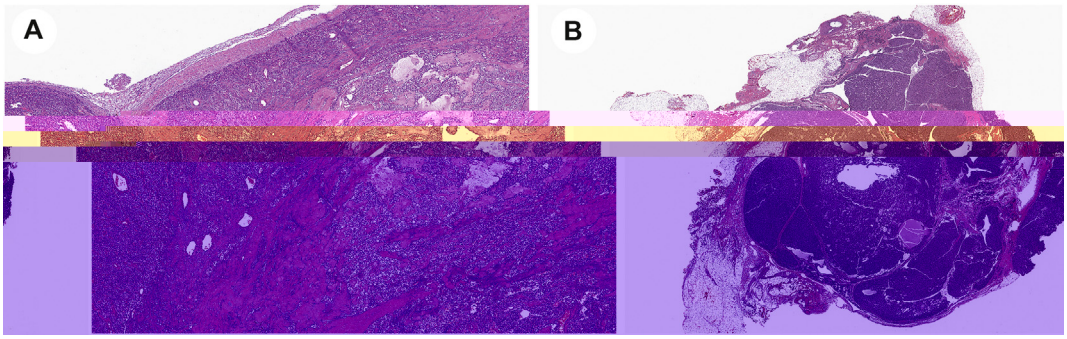

Fig. 4 Atypical parathyroid neoplasms lack invasion however show atypical features as shown here. (A) A smooth border is present; however, extensive internal fibrosis is present. (B) Multinodular nodular parathyroid proliferation without invasion also showed parafibromin loss and increased mitoses.

3.13. Perineural invasion

The close proximity of the parathyroids with the recurrent laryngeal nerve leads to potential invasion of this structure. Critical review is required of this parameter as close proximity without direct nerve involvement would be considered not involved.

3.14. Necrosis

The finding of coagulative necrosis is uncommon outside of the diagnosis of atypical parathyroid neoplasm/adenoma or parathyroid carcinoma [17]. Necrosis may also be more common in high-grade tumors (Fig. 3B). However, necrosis on its own is not a criterion for malignancy, and

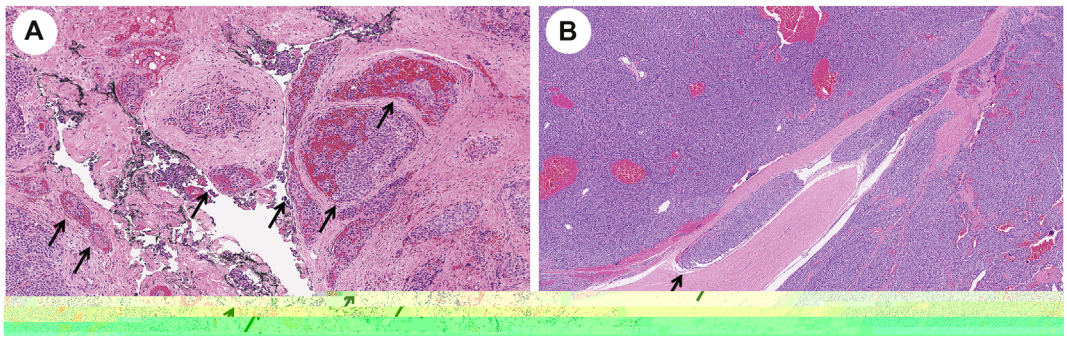

Fig. 5 Vascular invasion in parathyroid carcinomas. (A) Multiple foci of tumor are associated with fibrin and congestion within vessels (arrows). (B) A tumor focus distends a vascular space (arrow).

true coagulative necrosis is important to distinguish from nonspecific infarct-like necrosis which may be attributable to spontaneous infarction, previous episodes of rupture, and repair or preoperative FNA.

3.15. Mitotic count

The presence of mitoses is uncommon in benign parathyroid disorders and should raise concern for a parathyroid malignancy. However, absolute mitotic count does not definitively separate adenomas from carcinomas. The literature commonly refers to mitotic rates per 50 or 10 high-power fields (HPFs) without always defining the diameter of the HPFs. For this reporting protocol, mitotic count should be evaluated as the number of mitoses per 2 mm^2. It is recommended that reporting pathologists know their field diameter when calculating mitotic rates. The estimate of 10 HPFs equating to 2 mm^2 is commonly used as this reflects many microscopes in widespread use. The area of the tumor with the highest mitotic activity, ie, 'hot spot', should be preferentially counted if identified. Limited studies to date have evaluated the prognostic significance of this histologic factor [14,17,27]. The use of supplemental techniques such as Phosphorylated Histone H3 (PHH3) for identifying mitosis is not established in parathyroid neoplasms. The finding of atypical mitoses may be remarked upon in the pathology report but should not be used as the sole criterion of malignancy.

3.16. Margin status

Most features relating to margin status are core although there are some noncore features (Table 2). Parathyroid neoplasms, including adenomas, have a potential to locally recur if incompletely excised. Disruption of the gland intraoperatively, rupture, piecemeal removal, and involved surgical margins all place a patient at increased local risk of recurrence [19,24,28,29]. Such disruption of parathyroid specimens would be considered as R2 margin status when gross residual disease remains (transected margins) (Fig. 6). Often the proximity to the adjacent recurrent laryngeal nerve may lead to the tumor abutting the margin either focally or with possible circumscribed nests approximating the margin. These scenarios are consistent with an R1 microscopic surgical margin. As parathyroid masses are often received without orientation, the location of the margin involved may not be determined; however, if known, this should be specified. Currently, complete excision is the only approach that offers potential cure for parathyroid tumors.

3.17. Lymph node status

Regional lymph node metastasis from parathyroid carcinoma is uncommon with involvement mostly in the central neck (levels VI or VII) and rarely lateral neck (levels II, III, and IV) [24]. Metastases to lymph nodes have shown a potential correlation with survival; however, this has not been confirmed by large database studies [3,4,14,27,30,31]. Although the evaluation of lymph node metastasis for extranodal extension (ENE) is encouraged for other head and neck malignancies, there are currently limited data on ENE specific to parathyroid carcinoma and so it is not included in this data set.

3.18. Pathological staging

A prognostic staging system has not been formally adopted for parathyroid carcinomas. The rarity of this disease has limited standard review and comparison for meaningful stratification. However, it is recognized that standardized data collection as proposed here and outlined in the 8th edition of American Joint Committee on Cancer Staging Manual will begin the process of systematically gathering data for this rare entity [32]. It is with this goal that the parathyroid data set is established.

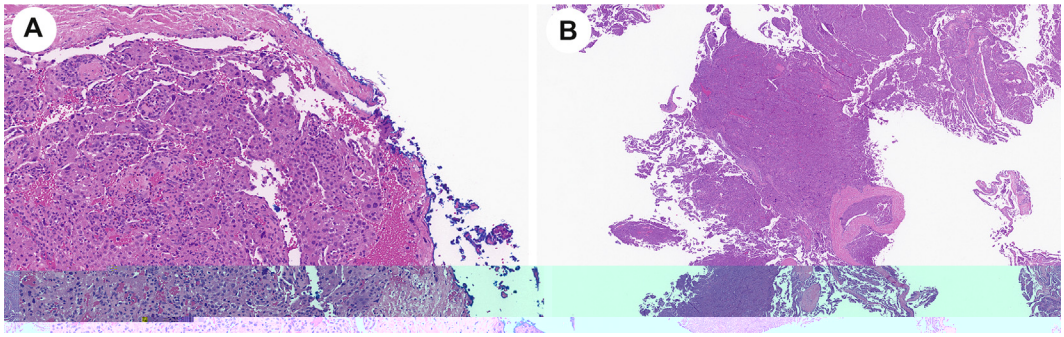

Fig. 6 Margin status should be recorded and categorized. (A) Focal/microscopic involvement of resection margin (R1 resection) versus (B) disrupted specimen with possible gross residual tumor (R2 resection).

3.19. Histologically confirmed distant metastases

The presence of histologically confirmed distant metastases is a critical component of pathological staging [32].

3.20. Noncore elements

Noncore elements are those which were unanimously agreed by the committee to be included in the data set but are not supported by level III-2 evidence. A summary of the noncore elements is outlined in Table 2, and each is described in the following:

3.21. Preoperative biochemical information

As an endocrine organ, the biochemical function observed preoperatively is correlative information of value in this disease site. A clinical concern for parathyroid carcinoma is raised when a patient presents with a palpable neck mass, very high serum calcium levels (>14 mg/dl/3.5 mmol/L), and corresponding significantly elevated parathyroid hormone (PTH) levels. It is more likely patients with extreme hypercalcemia meet the criteria for the diagnosis of parathyroid carcinoma [2,3,14,47]. It remains unclear if the preoperative levels of either calcium or PTH may have a predictive role in this disease. Documenting this associated clinical information is important and may also stratify the risk of recurrence [13]. As different institutions may use different units for measurement of calcium, the units used should be stated. In general, standard international (SI) units are preferred which is mmol/L.

3.22. Operative findings

The intraoperative findings often are clues to the possible diagnosis of parathyroid carcinoma. Specifically the observation of the parathyroid mass being adherent to nearby structures particularly in the absence of prior FNA or surgical procedures, cystic change of an adenoma, or spontaneous infarction is concerning for parathyroid malignancy. Recognition of involved structures and possible close margins are also important considerations when reviewing the intraoperative and pathologic information together.

3.23. Coexistent findings

Coexistent findings enable documentation of other histologic features identified in either the same parathyroid gland as the neoplasm or other parathyroid gland tissue submitted for evaluation. As coexisting parathyroid conditions may be encountered in other parathyroid glands submitted, it is important to detail whether the histology has normal, hypercellular (specifying if specific for hyperplasia or adenoma), or other features seen as relevant to this data set. Malignant pathology of the thyroid would utilize the corresponding thyroid data set.

3.24. Ancillary studies

Parafibromin is the protein encoded by the *CDC73* gene (previously known as *HRPT2*) [33]. Germline mutations and deletions in the *CDC73* gene occur in the autosomal dominant HPT-JT syndrome, with somatic second hits occurring in neoplasms – both carcinomas and adenomas (sometimes termed *parafibromin-deficient tumors* in this setting) [36]. Patients presenting with apparently sporadic parathyroid carcinoma may have occult HPT-JT syndrome [8,17,29,34–36]. Somatic-only double-hit mutation/inactivation of *CDC73* also occurs frequently in parathyroid carcinomas not associated with HPT-JT [36]. Immunohistochemistry for parafibromin may be used as a marker of double-hit inactivation of the *CDC73* gene in a parathyroid neoplasm. However, parafibromin immunohistochemistry is not widely available and may be technically difficult to perform and interpret [8,36]. Immunohistochemical evaluation of parafibromin shows nuclear staining in normal parathyroid cells, most benign parathyroid tumors, and normal endothelial cells. Loss of nuclear expression of parafibromin occurs in most but not all tumors associated

Fig. 7 Ancillary studies (noncore elements) include immunohistochemical expression for (A) parafibromin, the protein associated with gene *CDC73*. Note there is nuclear loss of parafibromin in the parathyroid carcinoma with retention of nuclear staining in the endothelial cells. (B) Ki-67 showed a proliferative index in hot spots of 5%.

with biallelic *CDC73* mutation/deletion [36–39]. Loss of parafibromin expression is not completely sensitive for *CDC73* mutation but may be used to triage genetic testing for HPT-JT syndrome in patients with atypical parathyroid neoplasms and parathyroid carcinoma (Fig. 7A). Parafibromin loss may be associated with a higher likelihood of recurrence in parathyroid carcinoma [8,36–38,40–42]. It has been suggested that tumors which demonstrate loss of parafibromin expression may show subtle morphological clues including sheet-like growth, eosinophilic cytoplasm, perinuclear cytoplasmic clearing, and nuclear enlargement [36].

Ki-67 proliferative index has also been reported as elevated in parathyroid neoplasms though with some overlap with hyperplasia and adenomas [20,33,39,43,44]. If performed, evaluation of Ki-67 immunohistochemical staining of the parathyroid neoplasm should be recorded as a percent of tumor cells staining in hot spots (the areas with greatest Ki-67 expression) (Fig. 7B). The method used to calculate the Ki-67 proliferative index should be specified (eg, manual count and the number of cells evaluated, or automated computer-assisted calculation including the number of cells counted).

Other markers might include Cyclin D1 and/or galectin-3 overexpression or retinoblastoma (Rb) loss of expression which has also been studied with an association in carcinomas compared with adenomas [20,45,46]. Protein Gene Product 9.5 (PGP9.5) is also overexpressed in the majority of parathyroid carcinomas and may have a complementary role to parafibromin immunohistochemical evaluation of *CDC73* mutation, albeit with lower specificity [41].

4. Conclusion

The ICCR standardized reporting of parathyroid carcinoma provides an essential resource for pathologists and clinicians for this rare entity, where limited resources exist. This data set delineates fundamental parameters for practice and evidence by which each core element was defined. As standardized reporting is adopted, the additive effect is unified data collections to understand epidemiology and further delineate pathologic correlations with outcome. Collection of noncore elements should be recorded when available as they may also evolve to provide additional value in this disease. Through widespread systematic use and adoption of the ICCR parathyroid data set and pathologic staging, a better understanding of this rare disease will emerge with standardize data for future guidelines.

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References

[1] Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence. BMC Med Res Methodol 2009;9:34.
[2] Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. Head Neck 2004;26:716–26.
[3] Harari A, Waring A, Fernandez-Ranvier G, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. J Clin Endocrinol Metab 2011;96:3679–86.
[4] Sadler C, Gow KW, Beierle EA, et al. Parathyroid carcinoma in more than 1,000 patients: a population-level analysis. Surgery 2014;156:1622–9. discussion 9-30.
[5] Shane E, Bilezikian JP. Parathyroid carcinoma: a review of 62 patients. Endocr Rev 1982;3:218–26.
[6] Agha A, Carpenter R, Bhattacharya S, Edmonson SJ, Carlsen E, Monson JP. Parathyroid carcinoma in multiple endocrine neoplasia type 1 (MEN1) syndrome: two case reports of an unrecognised entity. J Endocrinol Invest 2007;30:145–9.
[7] Carpten JD, Robbins CM, Villablanca A, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet 2002;32:676–80.
[8] Gill AJ. Understanding the genetic basis of parathyroid carcinoma. Endocr Pathol 2014;25:30–4.
[9] Weinstein LS, Simonds WF. HRPT2, a marker of parathyroid cancer. N Engl J Med 2003;349:1691–2.
[10] Christakis I, Vu T, Chuang HH, et al. The diagnostic accuracy of neck ultrasound, 4D-Computed tomographyand sestamibi imaging in parathyroid carcinoma. Eur J Radiol 2017;95:82–8.

[11] Quinn CE, Healy J, Lebastchi AH, et al. Modern experience with aggressive parathyroid tumors in a high-volume New England referral center. J Am Coll Surg 2015;220:1054–62.
[12] Ippolito G, Palazzo FF, Sebag F, De Micco C, Henry JF. Intraoperative diagnosis and treatment of parathyroid cancer and atypical parathyroid adenoma. Br J Surg 2007;94:566–70.
[13] Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99:3595–606.
[14] Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. Ann Surg Oncol 2010;17:2156–74.
[15] Chang YJ, Mittal V, Remine S, et al. Correlation between clinical and histological findings in parathyroid tumors suspicious for carcinoma. Am Surg 2006;72:419–26.
[16] Lloyd R, Osamura R, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs. 4th ed. Lyon: IARC Press; 2017.
[17] Bondeson L, Sandelin K, Grimelius L. Histopathological variables and DNA cytometry in parathyroid carcinoma. Am J Surg Pathol 1993;17:820–9.
[18] Asare EA, Sturgeon C, Winchester DJ, et al. Parathyroid carcinoma: an update on treatment outcomes and prognostic factors from the national cancer data base (NCDB). Ann Surg Oncol 2015;22:3990–5.
[19] Erovic BM, Goldstein DP, Kim D, et al. Parathyroid cancer: outcome analysis of 16 patients treated at the Princess Margaret Hospital. Head Neck 2013;35:35–9.
[20] Stojadinovic A, Hoos A, Nissan A, et al. Parathyroid neoplasms: clinical, histopathological, and tissue microarray-based molecular analysis. Hum Pathol 2003;34:54–64.
[21] McCoy KL, Seethala RR, Armstrong MJ, et al. The clinical importance of parathyroid atypia: is long-term surveillance necessary? Surgery 2015;158:929–35. discussion 35-6.
[22] Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1999;86:538–44.
[23] Shaha AR, Shah JP. Parathyroid carcinoma: a diagnostic and therapeutic challenge. Cancer 1999;86:378–80.
[24] Schulte KM, Gill AJ, Barczynski M, et al. Classification of parathyroid cancer. Ann Surg Oncol 2012;19:2620–8.
[25] Kameyama K, Takami H. Proposal for the histological classification of parathyroid carcinoma. Endocr Pathol 2005;16:49–52.
[26] Cetani F, Marcocci C, Torregrossa L, Pardi E. Atypical parathyroid adenomas: challenging lesions in the differential diagnosis of endocrine tumors. Endocr Relat Canc 2019;26. R441-r64.
[27] Silva-Figueroa AM, Hess KR, Williams MD, et al. Prognostic scoring system to risk stratify parathyroid carcinoma. J Am Coll Surg 2017;15. S1072-7515(17)30179-5.
[28] Digonnet A, Carlier A, Willemse E, et al. Parathyroid carcinoma: a review with three illustrative cases. J Cancer 2011;2:532–7.
[29] Yip L, Seethala RR, Nikiforova MN, et al. Loss of heterozygosity of selected tumor suppressor genes in parathyroid carcinoma. Surgery 2008;144:949–55. discussion 54-5.
[30] Hsu KT, Sippel RS, Chen H, Schneider DF. Is central lymph node dissection necessary for parathyroid carcinoma? Surgery 2014;156: 1336–41. discussion 41.
[31] Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. Trends in the incidence and treatment of parathyroid cancer in the United States. Cancer 2007;109:1736–41.
[32] Amin M, Edge S, Greene F, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017.
[33] Truran PP, Johnson SJ, Bliss RD, Lennard TW, Aspinall SR. Parafibromin, galectin-3, PGP9.5, Ki67, and cyclin D1: using an immunohistochemical panel to aid in the diagnosis of parathyroid cancer. World J Surg 2014;38:2845–54.
[34] Wang O, Wang C, Nie M, et al. Novel HRPT2/CDC73 gene mutations and loss of expression of parafibromin in Chinese patients with clinically sporadic parathyroid carcinomas. PloS One 2012;7:e45567.
[35] Guarnieri V, Battista C, Muscarella LA, et al. CDC73 mutations and parafibromin immunohistochemistry in parathyroid tumors: clinical correlations in a single-centre patient cohort. Cell Oncol 2012;35: 411–22.
[36] Gill AJ, Lim G, Cheung VKY, et al. Parafibromin-deficient (HPT-JT type, CDC73 mutated) parathyroid tumors demonstrate distinctive morphologic features. Am J Surg Pathol 2019;43:35–46.
[37] Kim HK, Oh YL, Kim SH, et al. Parafibromin immunohistochemical staining to differentiate parathyroid carcinoma from parathyroid adenoma. Head Neck 2012;34:201–6.
[38] Lim S, Elston MS, Gill AJ, Marsh DJ, Conaglen JV. Metastatic parathyroid carcinoma initially misdiagnosed as parathyroid adenoma: the role of parafibromin in increasing diagnostic accuracy. Intern Med J 2011;41:695–9.
[39] Fernandez-Ranvier GG, Khanafshar E, Tacha D, et al. Defining a molecular phenotype for benign and malignant parathyroid tumors. Cancer 2009;115:334–44.
[40] Gill AJ, Clarkson A, Gimm O, et al. Loss of nuclear expression of parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw tumor (HPT-JT) syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. Am J Surg Pathol 2006;30:1140–9.
[41] Howell VM, Gill A, Clarkson A, et al. Accuracy of combined protein gene product 9.5 and parafibromin markers for immunohistochemical diagnosis of parathyroid carcinoma. J Clin Endocrinol Metab 2009; 94:434–41.
[42] Kruijff S, Sidhu SB, Sywak MS, Gill AJ, Delbridge LW. Negative parafibromin staining predicts malignant behavior in atypical parathyroid adenomas. Ann Surg Oncol 2014;21:426–33.
[43] Ozolins A, Narbuts Z, Vanags A, et al. Evaluation of malignant parathyroid tumours in two European cohorts of patients with sporadic primary hyperparathyroidism. Langenbeck's Arch Surg 2016; 401:943–51.
[44] Lloyd RV, Carney JA, Ferreiro JA, et al. Immunohistochemical analysis of the cell cycle-associated antigens Ki-67 and retinoblastoma protein in parathyroid carcinomas and adenomas. Endocr Pathol 1995;6:279–87.
[45] Hemmer S, Wasenius VM, Haglund C, et al. Deletion of 11q23 and cyclin D1 overexpression are frequent aberrations in parathyroid adenomas. Am J Pathol 2001;158:1355–62.
[46] Vasef MA, Brynes RK, Sturm M, Bromley C, Robinson RA. Expression of cyclin D1 in parathyroid carcinomas, adenomas, and hyperplasias: a paraffin immunohistochemical study. Mod Pathol 1999;12:412–6.
47 Villar-del-Moral J, Jimenez-Garcia A, Salvador-Egea P, Martos-Martinez JM, Nuno-Vazquez-Garza JM, Serradilla-Martin M, Gomez-Palacios A, Moreno-Llorente P, Ortega-Serrano J, de la Quintana-Basarrate A. Prognostic factors and staging systems in parathyroid cancer: a multicenter cohort study. Surgery 2014;156(5):1132–44.