SCIENTIFIC ARTICLE

Role of routine frozen sections for parathyroid exploration in a resource poor setting

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Key words: Parathyroid; frozen section diagnosisl parathyroid hormone

Abstract

Removal of parathyroid is recommended for patients suffering from hypercalcemia due to excess parathyroid hormone levels. There are several causes for a hyperfunctioning parathyroid gland out of which parathyroid adenoma is the most common pathological entity. There is great variation in the number and location of parathyroid glands. Hence, intra-operative confirmation of parathyroid tissue makes it easier for the surgeon to be confident of the outcome of the procedure and assure the patient of a permanent cure.

A descriptive cross sectional study was done in a cohort of 26 patients who presented with elevated total serum calcium and parathyroid hormone concentrations. Intra-operative frozen section diagnoses were correlated with routine histological studies and post-operative parathyroid hormone concentration. The majority of patients were diagnosed as having parathyroid adenoma (88.46%). Three out of 26 patients (11.53%) had parathyroid hyperplasia involving more than one gland. Sensitivity and specificity of intra-operative frozen section diagnosis was 100%. There was a statistically significant association ($p<0.05$) with post-operative parathyroid hormone concentration was performed from the same laboratory and the intraoperative diagnosis. The concordance between the intraoperative findings and routine histological diagnoses was highly satisfactory.

In the light of the discussion on parathyroid surgery it is apparent that frozen sections play a pivotal role in resource poor settings, when facilities for novel intra-operative imaging studies such as sestamibi scan and single-photon emission computed tomography are limited. The participants of the study have been followed up during last 5 years with no evidence of residual disease or recurrence up to date.

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Received: 06-03-2019 Accepted: 24-04-2019

http://orcid.org/0000-0002-0451-0257

DOI: http://doi.org/10.4038/sljs.v37i1.8599

Introduction

Parathyroid glands were discovered for the first time in 1852 by Richard Owen in Indian rhinoceros (1). In 1880 a Swedish medical student at the Uppsala University noted its existence in humans, dogs, cats, horses and rabbits (2, 3). Removal of parathyroid dates back to 1928 and Isaac Y Olch, a medical doctor had been acknowledged for performing parathyroid surgery for the first time in human beings (4).

Parathyroid glands are usually located on the posterior aspect of the right and left lobes of thyroid, but separated from it by a delicate connective tissue capsule. Parathyroid glands are known to be derivatives of 3rd and 4th branchial pouches of the primitive foregut during embryogenesis (5). There are two pairs of parathyroid glands; superior and inferior. The vast majority has four glands although there is variation in the number (6). There is great inconsistency in the location of parathyroids in relation to the thyroid gland, thus causing difficulties in identification during parathyroid surgery for patients with effects of hypercalcemia.

Parathyroids are small, yellow-brown, ovoid shaped structures with a flattened body, weighing approximately 35 to 45mg (7). The constituent cells of parathyroid parenchyma are of three types; chief cells, oxyphil cells and clear cells. The major function of the gland is to secrete parathyroid hormone (PTH) that regulates serum calcium level (8).

During surgery, parathyroids can be easily mistaken for lymph nodes, thyroid nodules and fat globules in the near vicinity, thus resulting in misdiagnosis and a repeat operative procedure. In a minority of patient's parathyroid tissue can be ectopic, located in an unusual site such as the mediastinum (9). Role of the pathologist is to agree or disagree as to the presence of parathyroid tissue, during the surgical procedure. Intraoperative confirmation of parathyroid tissue by frozen section diagnosis makes it easier for the surgeon to be confident of the accuracy of the operative procedure and to assure the patient of a permanent cure in most of the instances (10). Although parathyroid adenoma stands out as the most common cause of parathyroid surgery there are few less common pathological entities such as parathyroid hyperplasia and carcinoma that would also require surgical intervention (11).

Most of the patients with parathyroid lesions present with symptoms related to a hyperfunctioning gland known as primary hyperparathyroidism (12). Clinical presentations include nephrolithiasis, nephrocalcinosis, metastatic calcification, generalized osteitis fibrosa cystica, neuropsychiatric disturbances and hypertension. Secondary hyperparathyroidism occurs due to excessive parath hormone levels resulting from a disease elsewhere. Hypocalcaemia results in compensatory stimulation of the gland in secondary hyperparathyroidism. Tertiary hyperparathyroidism is a complication of secondary hyperparathyroidism where the gland remains to be hyperactivity independent of the etiological factor. Both secondary and tertiary hyperparathyroidism are less common than primary hyperparathyroidism (13).

Medical errors in surgery is responsible for the majority of preventable in-hospital adverse events (2-4). The factors causing human errors can be classified as excessive workload, inadequate knowledge, ability or experience, inadequate supervision or instruction, stressful environment and mental fatigue or boredom (5). There is growing evidence to suggest that non-technical skills are required to overcome these human errors in a surgical team (6-10). Non-technical skills can be divided mainly into two categories; interpersonal skills and cognitive skills (7). Out of the interpersonal skills, communication plays a key role in bridging the gap in human error and continuum of patient care during surgical interventions (5, 7, 11, 12).

Inter-professional integration is essential in the field of surgery. Therefore, communication does not necessarily mean an exchange of vital patient information among consultants such as anaesthetists, radiologists and surgeons, but also sharing basic information with theatre staff, ward nurses and other relevant parties to work as a team. Mishaps in communication occur at different points in the surgical care. This is broadly divided into inaccuracies that occur in preoperative assessment and optimization phase, pre procedure/procedural phase, post-operative phase and daily ward care (13). These miscommunications among team members could lead to devastating outcomes resulting in high morbidity and mortality (14). In 2009, the World Health Organization (WHO) emphasized the importance of effective communication and exchange of critical information for the safe conduct of the surgeries (5).

Several systematic reviews and studies conducted in intra-hospital patient handover (15-19), information transfer among healthcare workers (13, 20, 21) and effectiveness of surgical checklists (22, 23) concluded that communication errors are a shared the issue throughout the world. However, presently there are no reviews evaluating communication.

Objectives

- Correlation of frozen section diagnosis with routine histological findings.
- Assess the diversity of parathyroid lesions.
- Comparison of pre-operative and post-operative parathyroid hormone levels with the histological diagnosis.
- Determine the role of frozen sections in parathyroid surgery.

Methodology

A descriptive cross sectional study was conducted, which included the parathyroid specimens during the period of January 2014 to December 2018. Laboratory procedures were done at the histopathology section of Lanka Hospital, Colombo 05, in which the basic facilities required for intraoperative frozen section diagnosis were readily available. Study sample included included 26 patients in whom the pre-operative total serum calcium concentration (normal range – 2.2 to 2.7 mmol / L) was more than 3 mmol / L and parathyroid hormone levels (normal range – 10-65 pg/ml) were elevated and in the range of 90 to 170 pg/ml. Pre-operative radiological findings have been suggestive of pathological lesions involving one or more of the parathyroid.

Following parathyroid surgery fresh specimens wrapped in gauze were immediately transported to the laboratory in screw capped bottles. Samples were handled and reported by the principal investigator. After recording the macroscopic core data items which included the size, weight and colour of the specimen, tissue sections were prepared and placed on a metal "chuck" and frozen to reach the cutting temperature which is -20 degrees Celsius. Once the tissue was frozen thin sections (1-2 μm) were cut with the freezing microtome and stained with haematoxylin & eosin. The entire procedure took around 15 to 20 minutes thus allowing a rapid tissue diagnosis during the intraoperative period.

Following frozen section diagnosis, tissue on the chuck and any remaining tissue were submitted for routine histological procedure, for re-confirmation of the intraoperative diagnosis by two independent consultant pathologists. All laboratory procedures were of the highest standard as per the accreditation guidelines (All laboratory procedures have been accredited by the College of American Pathologists).

Results

In the cohort of patients with hyperfunctioning parathyroids the most common intraoperative diagnosis was parathytoid adenoma (n=22; 88.46%). Parathyroid hyperplasia was seen in 3(11.53%) cases and there were no cases of parathyroid malignancies (Figure. 1).

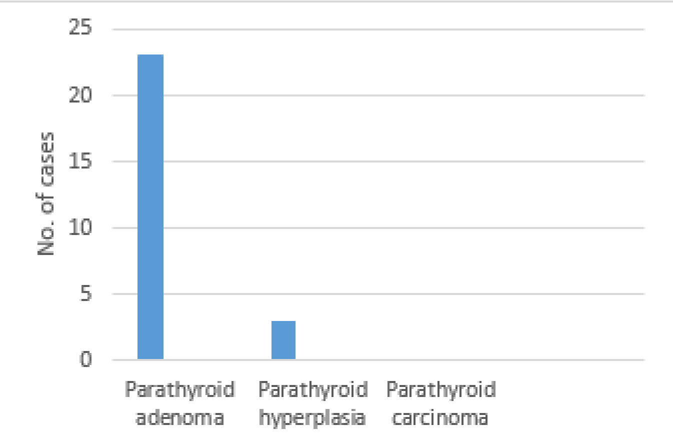

Figure 1. Intra-operative frozen section diagnosis

Symptoms

Majority of the patients presented with symptoms of renal calculi. Other presenting complaints were abdominal pain, weakness and bone pain. In 15.46% the diagnosis was an incidental finding. One patient was diagnosed as having a parathyroid adenoma during the diagnostic work up for recurrent abortion (Figure .2).

Identification of parathyroid tissue by the naked eye appearance (gross examination) had a sensitivity and specificity of each 98%. The concordance of results for gross examination, between the surgeon and the pathologist was > 95% (table 1).

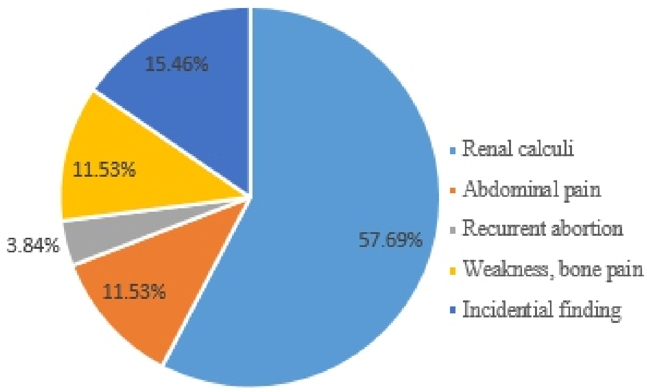

Figure 2. Symptoms

Table 1. Gross examination findings of surgical (parathyroid) specimens

	Sensitivity	Specificity	Concordance (between surgeon & pathologist)
Gross examination & identification	98%	98%	>95%

Table 2. Sensitivity & specificity of intra-operative frozen section procedure

	Sensitivity	Specificity
Parathyroid abnormalities	100%	100%
Non- parathyroid tissue (small lymph nodes, fat globules & thyroid nodules in the vicinity)	100%	100%

Intra-operative frozen section diagnosis for parathyroid abnormalities had a sensitivity of 100% and specificity of 100% (table 2).

Table 3. Correlation with parathyroid hormone levels (Pre and post- operative values)

	Pre-operative level	Post- operative level
Parathyroid adenoma n=23	90-170 pg/ml	<80 pg/ml (statistically significant association with the intra-operative frozen section diagnosis, p<0.05)
Parathyroid hyperplasia n=3	90-150 pg/ml	<80 pg/ml (statistically significant association with the intra-operative frozen section diagnosis, p<0.05)

Pre-operative parathyroid hormone levels were recorded and compared with the post-operative values. Post- operative parathyroid hormone level of <80 pg/ml showed a statistically significant association with the intra-operative diagnosis (table 3).

Table 4. Concordance of results (between intraoperative frozen section diagnosis and routine histology)

	Concordance	Disconcordance
Parathyroid lesions n=26	100% (statistically significant with a p value < 0.05)	<1% (statistically insignificant)

Concordance of results between the intra-operative frozen section diagnosis and subsequent histology review was 100% with a p value < 0.05 (table 4)

Discussion

In the cohort of 26 patients with hyper functioning parathyroid glands the vast majority was diagnosed as having parathyroid adenoma (88.46%). There were no cases of parathyroid carcinoma and 11.53% of the study population had parathyroid hyperplasia (figure:1). The most common clinical presentation was renal calculi (57.69%). In 15.46 % of the cases the diagnosis of parathyroid adenoma was an incidental finding (figure: 2). One patient was found to have a parathyroid adenoma during the diagnostic work up for recurrent abortion.

In all of these patients the pre-operative parathyroid hormone level was above the normal range (10-65 pg/ml). Pre -operative imaging studies have been performed in all of these patients and the results were suggestive of pathological lesions in parathyroid glands.

Parathyroid specimens of all of the above patients were subjected to intra-operative frozen section diagnosis and the findings were conveyed to the surgical team within a period of 20 minutes from the time of reception of the specimen at the laboratory. Identification of parathyroid tissue by frozen section method is highly reliable and poses no difficulty as there are characteristic histological features (table 1& 2).

In contrast to follicular structures present with thyroid tissue, parathyroids consist of adipose tissue (25-40%) and densely

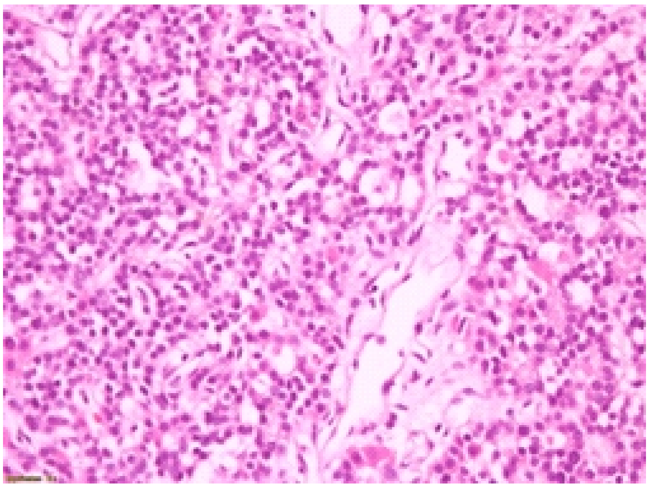

Figure 3. Parathyroid adenoma composed of small, round chief cells -arrow (H&E stain x 40)

packed parenchymal cells which are of two types (14). The predominant cell type is uniform, small and round chief cells having regular nuclei. Chief cells show different patterns of growth and are usually arranged in nests, clusters and sheets (figure 3). Microfollicular and trabecular patterns may also be seen. Chief cells may be admixed with a variable number of oxyphil cells having a moderate amount of eosinophilic cytoplasm (14). Twenty-three out of 26 cases had a single gland involvement and the intra-operative findings were consistent with a diagnosis of parathyroid adenoma. The frozen section findings that helped to arrive at a diagnosis of parathyroid adenoma were the presence of an encapsulated (figure 4), cellular nodule and the identification of compressed but otherwise normal parathyroid tissue at the periphery of the lesion. There was a mild variation in nuclear size. Mitotic figures were indistinct and there was no evidence of necrosis. Complete encapsulation with no evidence of capsular or vascular invasion greatly supported a benign

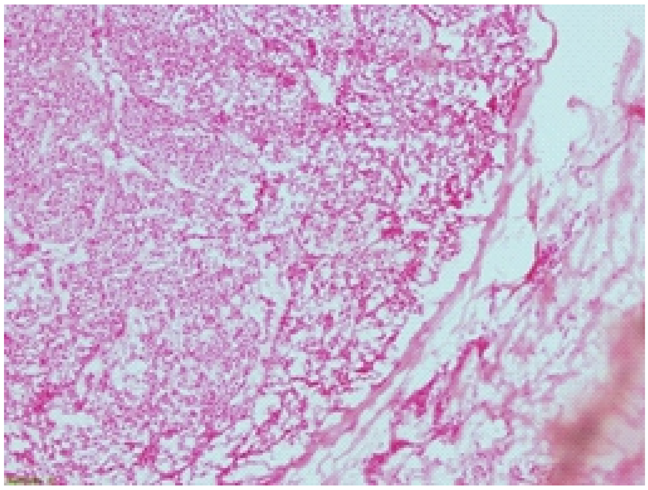

Figure 4. Parathyroid adenoma surrounded by a thin capsule -arrow (frozen section, H&E stain x 10 magnification)

diagnosis. In view of the small size of the lesions (usually less than 25 mm in maximum diameter) an entire cross section could be examined before concluding the intra-operative results.

In the cohort of cases there were 3 patients with parathyroid hyperplasia. Parathyroid hyperplasia usually involves all four glands in an equal manner but there could be variations with regard to the number of diseased glands. One out of 3 patients with hyperplasia showed the involvement of all 4 glands. In the other 2 patients, only 3 glands from each had features of hyperplasia. Although the cellular and architectural patterns were similar to parathyroid adenoma the absence of a capsule was a useful feature that helped to distinguish hyperplasia from adenoma. There were no cases of parathyroid carcinoma in the cohort of 26 patients.

Mistakenly submitted small lymph nodes, fat globules and bulging thyroid nodules with a naked eye appearance similar to parathyroid tissue were correctly reported as "non-parathyroid" by the frozen section procedure and the findings were immediately conveyed to the surgical team. This enabled to re- send, further samples before closing up the neck incision.

Approximately 15 minutes after successful parathyroid removal, blood samples were taken for parathyroid hormone assay (15). Lowering of parathyroid hormone concentration from the pre-operative value supported the accuracy of frozen section diagnosis (table 3). There was a statistically significant association ($p < 0.05$) with the intra-operative diagnosis and post-operative parathyroid hormone levels. Concordance between intra-operative frozen section diagnosis and routine histological results was 100% (table 4).

A study done by Westra WHDD et al, (10) has shown similar results with a high intraoperative diagnostic accuracy of 99.2%. Scientific paper published by Anton RC et al, further strengthened the value of frozen section evaluation with a low false-positive rate (16). Farquin WC et al, has also emphasized the important role of intraoperative frozen section diagnosis in the context of parathyroid surgery (17). Dewan AK et al, has concluded that a decision to omit frozen sections need to be carefully balanced against the possible risk of misidentifying the actual lesion (18).

Conclusion

Success of parathyroid exploration lies with accurate localization of the glands. There is great diversity in the location of parathyroid tissue as well as problems in relation to intraoperative identification in view of the small size of the glands. The diagnostic accuracy of the frozen section method can be highly satisfactory in the hands of experienced personnel from both medical and technical sides.

In contrast to developed countries which have readily available sophisticated techniques such as sestamibi scan, single- photon emission computed tomography, centres with limited facilities consider intraoperative frozen section diagnosis as a valuable tool for identification of the glands.

Undoubtedly the cost effectiveness of this procedure in terms of human resource, infrastructure and equipment along with high accuracy will continue to have a positive impact on parathyroid surgery in a resource poor setting. Sensitivity & specificity of frozen section diagnosis and concordance of results between frozen section and subsequent histological review can be as high as 100%. In the current study there were no false negative or false positive results. There was a statistically significant association ($p<0.05$) with the post-operative parathyroid hormone concentration and the intra-operative diagnosis, thus reinforcing the valuable contribution of frozen sections for routine parathyroid surgery.

All of these patients have been followed up during last 5 years, with serum calcium and parathyroid hormone levels and it is noteworthy to mention that there is complete cure with no evidence of residual disease or recurrence. Decision to move away from routine intraoperative frozen sections in the context of parathyroid surgery may carry a risk of misdiagnosis and possibility of a repeat surgical intervention.

All authors disclose no conflict of interest. The study was conducted in accordance with the ethical standards of the relevant institutional or national ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

References

1. Cave AJE. (1953). "Richard Owen and the discovery of the parathyroid glands". In E. Ashworth Underwood. Science, Medicine and History. Essays on the Evolution of Scientific Thought and Medical Practice. 2. Oxford University Press. pp. 217–222. Retrieved 2009-07-20. https://en.wikipedia.org/wiki/Parathyroid_gland
2. Eknoyan G. "A history of the parathyroid glands". American Journal of Kidney Diseases. 1995;26 (5): 801–7. doi:10.1016/0272-6386(95)90447-6.
3. "On a New Gland in Man and Several Mammals (Glandulæ Parathyreoideæ)". Journal of the American Medical Association. 1938;111 (2): 197. doi:10.1001/ jama.1938. 02790280087037.
4. DuBose Joseph, Ragsdale Timothy, Morvant Jason. ""Bodies so tiny": The history of parathyroid surgery". Current Surgery.2005; 62 (1): 91–95. doi:10.1016/j.cursur.2004.07.012
5. Zajac Jeffrey D, Danks Janine A. "The development of the parathyroid gland: from fish to human". Current Opinion in Nephrology and Hypertension.2008; 17 (4): 353–356. doi:10.1097/MNH.0b013e328304651c
6. Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P. "Location, number and morphology of parathyroid glands: results from a large anatomical series". Anat Sci Int. 2012; 87(3): 160–4. doi:10.1007/s12565-012-0142-1.
7. Johnson S J. "Best Practice No 183: Examination of parathyroid gland specimens". Journal of Clinical Pathology. 2005.58 (4): 338–342. doi:10.1136/jcp.2002.002550. 1770637.
8. Felsenfeld AJ, Rodríguez M, Aguilera-Tejero E . "Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism". Clinical Journal of the American Society of Nephrology.2007; 2 (6): 1283–305. doi:10.2215/CJN.01520407.
9. Dsouza Caren, Gopalakrishnan, Bhagavan K R, Rakesh K. (2012). "Ectopic parathyroid adenoma". Thyroid Research and Practice. 2012; 9(2): 68–70. doi:10.403/0973- 0354.96061.
10. Westra WHDD, Pritchett , Udelsman R. Intraoperative confirmation of parathyroid tissue during parathyroid exploration: a retrospective evaluation of the frozen section. Am J Surg Pathol. 1998; 22:538–544. (Crossref) (Google Scholar) https://scholar.google.com/scholar?
11. Mizamtsidi M, Nastos C, Mastorakos G, Dina R, Vassiliou I, Gazouli M, Palazzo F. Diagnosis, management, histology and genetics of sporadic primary hyperparathyroidism:old knowledge with new tricks. Endocr Connect. 2018;7(2):R56-R68. doi: 10.1530/EC-17-0283.
12. Bilezikian JP, Cusano NE, Khan AA, Liu JM, Marcocci C, Bandeira F. Primary hyperparathyroidism. Nat Rev Dis Primers. 2016;19(2):16033. doi: 10.1038/nrdp.2016.33

13. Al-Thani H, El-Matbouly M, Al-Sulaiti M, Asim M, Majzoub A, Tabeb A, El-Menyar A. Management and outcomes of hyperparathyroidism: a case series from a single institution over two decades. Ther Clin Risk Manag. 2018;14:1337-1345. doi: 10.2147/TCRM.S160896.

14. "Parathyroid adenoma: Diagnosis & treatment". Cleveland Clinic. June 11, 2012. ttps://my.clevelandclinic.org/disorders/parathyroid_disease/

15. Sharma J, Milas M, Berber E, et al. Value of intraoperative parathyroid hormone monitoring. Ann Surg Oncol. 2008;15(2):493–8. doi: 10.1245/s10434-007-9683-2.

16.Anton RC1, Wheeler TM. Frozen section of thyroid and parathyroid specimens. Arch Pathol Lab Med. 2005;129 (12): 1575-84. doi:10.1043/1543-2165(2005)129(1575:FSOTAP)2.0.CO;2

17 Faquin WC, Roth SI. Frozen section of thyroid & Parathyroid Specimens. Arch Pathol Lab Med.2006;130(9):1260. doi:10.1043/1543-2165(2006)130(1260a:FSOTAP)2.0.CO;2

18.Dewan AK, Kapadia SB, Hollenbeak CS, Stack BC Jr. Is routine frozen section necessary for parathyroid surgery? Otolaryngol Head Neck Surg.2005;133(6):857-62. doi:10.1016/j.otohns.2005.05.001

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