Value of routine frozen section diagnosis of thyroid lesions

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ABSTRACT

Objectives: The value of routine frozen section examination for intraoperative diagnosis of thyroid cancer is controversial and needs to be evaluated on an institution to institution basis. This paper highlights the local experience with frozen section and analyses its role, accuracy and limitation in diagnosing thyroid cancer.

Methods: A retrospective study of 61 patients who underwent thyroidectomy with routine thyroid frozen section examination at King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia. Results were compared with the final diagnosis to evaluate its effectiveness in predicting malignancy.

Results: Frozen section diagnosis, proved to be benign in 44 (72%) specimens, malignant in 10 (16%) and the diagnosis deferred in 7 (11.5%) patients. After examination of the permanent sections of the specimens, 15 (28%) were found to be malignant including 3 (43%) out of 7 deferred cases. With an overall accuracy of >90% and a specificity of 100%, the sensitivity of frozen section diagnosis remains low. Only 60% of papillary carcinoma and 25% of follicular carcinoma were correctly diagnosed on frozen section. The low rate of diagnosis of follicular carcinoma is due to its encapsulated and minimally invasive nature.

Conclusion: The inability to diagnose follicular carcinoma intraoperatively with frozen section is the most significant factor accounting for the relatively low sensitivity of frozen section diagnosis of thyroid malignant neoplasm. In our institution, frozen section is considered a complementary investigation to emerging fine needle cytopathology in the region.

Keywords: Thyroid neoplasms, frozen section diagnosis, thyroid carcinoma, fine needle aspiration, biopsy.

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Tissue examination by frozen section (FS) was first performed by Welch in 1891 and developed for intraoperative pathology diagnosis by Wilson and MacCarty in 1905.[1] But routine use of the technique was to await the introduction of the cryostat in the early 1960's when it became an essential method for rapid tissue diagnosis.[2] Although FS has served well in the intraoperative decision making of thyroid cancer, the emergence of increasingly accurate and cheap methods of pre- and intraoperative fine needle aspiration biopsy (FNAB) has raised questions about its routine use as an intraoperative diagnostic tool.[3-5] Moreover, the refinement in imaging, combined with preoperative availability of FNA cytopathology, has enhanced the ability of surgeons to plan procedures more appropriately. Nevertheless, FS examination of the thyroid mass continues to occupy a common place with a number of institutions and surgeons in helping to determine the extent of thyroid resection. This study analyses the role, accuracy and limitations of FS as an intraoperative tool for diagnosing thyroid cancer, at King Fahd Hospital of the University (KFHU) in Al-Khobar, Kingdom of Saudi Arabia.

Methods. The pathology reports on all thyroid specimens submitted for frozen and permanent sections at KFHU, during the period January 1990 to December 1999, were retrospectively reviewed. A total of 151 thyroidectomy specimens had been

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reported out of which 61 had been examined for FS. The microscopic slides of all the specimens were read and tallied with the reports. A staff pathologist who, after a gross inspection of the specimen, had selected area(s) for FS preparation and reporting, had examined each of the specimens. In general, examination of one section was considered adequate when the question of benign versus malignant lesion was not in doubt. However, for follicular lesions, 2 to 4 sections were examined to evaluate capsular penetration or vascular invasion. The tissue was embedded in optimal cutting temperature (OCT) aqueous medium and then frozen in liquid isopentane at -50^0 for 15–20 seconds. The tissue block was cut in a cryostat, and a 6–8 mm thick section of tissue was transferred to a glass slide and immediately fixed in either 80% ethanol or formalin with alcohol. The tissue was then progressively dehydrated, this was accomplished by serial processing of the tissue in solutions of increasing concentrations of ethanol followed by final clearing in xylene. The slide was then stained with hematoxylin and eosin. Touch preparations were not a routine procedure. If the diagnosis was clearly benign or malignant, it was so reported. In the particular situation of FS diagnosis of follicular adenoma, however, the surgeon was cautioned that additional blocks of tissue might yield a different result on permanent sections. All malignant lesions, which contained both follicular, and papillary elements in any proportion were diagnosed as papillary carcinoma. The lesions with exclusive follicular growth pattern and numerous optically clear nuclei with "ground glass" appearance were diagnosed as follicular variant of papillary carcinoma. If the FS examination was inconclusive, the diagnosis was deferred and the surgeon were informed to await the results of permanent section examination. In most, but not all cases, the same pathologist who rendered the FS diagnosis made the final diagnosis. The cases in which intraoperative diagnosis was deferred were excluded from the statistical calculation of sensitivity, specificity, overall accuracy, and predictive values. Sensitivity, specificity, and accuracy were calculated as ratios according to the following formulae: Sensitivity = True-positive/sum{True-positive+False-negative}. Specificity = True-negative/sum{True-negative +False-positive}. Accuracy = sum [True-positive+True-negative]/sum (True-positive+False-positive+True-negative+False-negative).

Results. The final histologic diagnoses of all 151 thyroid patients, including 61 patients in whom FS examination was performed, are shown in Table 1. The diagnoses after FS examination in 61 (40% of all thyroid patients) specimens are listed in Table 2. The majority (72%) were benign while a definitive diagnosis of malignancy was made in 10 (16%), and

Table 1 - Permanent section diagnosis of thyroidectomy specimens.

Final diagnosis	All thyroidectomy specimens		Thyroid lesions examined by FS	
	n	%	n	%
Benign				
Nodular Goitre	88	58	31	51
Follicular adenoma	13	9	8	13
Hurthle cell adenoma	4	3	2	3
Hashimoto's thyroiditis	3	2	1	2
Grave's disease	10	7	2	3
Total	**118**	**79**	**44**	**72**
Malignant				
Papillary carcinoma	25	16.5	10	16
Follicular carcinoma	5	3	4	6
Anaplastic carcinoma	1	0.5	1	2
Medullary carcinoma	1	0.5	1	2
Lymphoma	1	0.5	1	2
Total	**33**	**21**	**17**	**28**
Total of benign and malignant	**151**	**100**	**61**	**100**

FS - frozen section; n - number

Table 2 - Frozen section and permanent section diagnoses of 61 study patients with statistical analysis for frozen section.

Frozen section diagnosis	n	Permanent pathological diagnosis Proven	
		n	%
Benign	44	40	91
Malignant	10	10	100
Deferred	7	-	*

* Likelihood that 42% malignant and 58% benign
n - number

Table 3 - Frozen section diagnosis of malignant tumor of thyroid.

Type of neoplasm	n of specimens	Malignant		Benign		Deferred	
		n	%	n	%	n	%
Papillary carcinoma	10	6	60	2	20	2	20
Follicular carcinoma	4	1	25	1	25	2	20
Undifferentiated carcinoma	1	1	100	-	-	-	-
Medullary carcinoma	1	1	100	-	-	-	-
Lymphoma	1	1	100	-	-	-	-
Total	**17**	**10**	**59**	**3**	**18**	**4**	**23**

n - number

in 7 (11.5%) the diagnosis was deferred. The permanent section examination diagnosed a malignant neoplasm in 17 (28%) of the 61 patients in this series, including 3 (43%) out of 7 in the deferred group (Table 1). There were 4 patients with false-negative FS diagnoses – 2 each of papillary and follicular carcinomas. Only 6 out of 10 (60%) patients with papillary carcinoma were diagnosed on FS examination. Out of the remaining 4, 2 were considered benign and in the other 2 the diagnosis was deferred. While there was no difficulty in making a correct FS diagnosis of undifferentiated cancer or lymphoma, the sensitivity of FS was very low for follicular carcinoma – only one out of 4 cases (25%) were diagnosed correctly (Table 3). Overall, 7 out of 17 (41%) cancers were either missed or deferred on FS examination. A low (71%) sensitivity of FS for cancer was in part (25%) due to sampling error but largely due to misinterpretation of the tissue. The overall accuracy of FS diagnosis (agreement of FS and permanent diagnosis) was 93% and its specificity 100%. The discrepancy between frozen and permanent sections diagnoses and the outcome of deferred cases is shown in Table 2. Of the 7 deferred diagnoses, 3 (43%) proved to be malignant (2 papillary and 1 follicular carcinoma) and 4 were benign on permanent section examination.

Discussion. For decades, FS has been the mainstay of intraoperative diagnosis of most malignancies. Its efficacy in the case of thyroid surgery has, however, been influenced by a number of factors: (a) limited sampling of suspicious nodules, (b) difficulty with mounting and orientation of fresh tissue, (c) suboptimal nuclear and cytologic details, (d) time constraints and (e) a degree of reluctance to commit to a definitive diagnosis of malignancy prior to the review of all material. More recently, in the environment of health economics, quality control, and managed-care health services, the institutions have been obliged to look critically at their practices and to look for cheaper and comparable alternatives as diagnostic tools. In cases of thyroid surgery, the availability of a much cheaper and reliable technique of FNAB has stimulated keen interest. A number of centers have compared (mostly retrospective studies) the role of the 2 techniques and found that their sensitivities and specificities for accurately diagnosing thyroid cancer are comparable.[6-11] There is a growing consensus also that: (a) with a definitive preoperative diagnosis of malignancy on FNAB by skilled pathologists, a routine FS for intraoperative decision making is unnecessary,[6,7,10,12,13] (b) frozen section should supplement the diagnosis only when FNAB is 'suspicious' of cancer or its result indeterminate[7,9,10,11,14] and (c) the routine use of FS is not cost-effective.[15] This being so, the use of FS diagnosis for variants of malignancy, and in more conservative institutions, will continue.

In our study, a comparison between the FNAB and FS examination results could not be made due to the limited number of cases that had both procedures carried out during the study period. We have thus confined ourselves to determine the outcome of FS practice in our hospital. As the analysis of our material indicates, our results, in terms of sensitivity, specificity and accuracy, are comparable to other institutions.[6-9,11] The procedure's relative low sensitivity is an important watershed in that only 60% of the papillary carcinomas and just 25% of follicular cancers were amenable to correct diagnosis both in our cases and that of other studies.[16,17] There appear to be 2 main reasons for the low sensitivity of FS for papillary and follicular cancers: (a) in cases of papillary tumors, the difficulty of assessing optically clean nuclei diagnostic of follicular variant of papillary tumors[18-20] – this feature being present in 2 (20%) out of 10 of our patients, (b) in cases of follicular tumors, difficulty in assessing vascular invasion or capsular penetration, or both, due to sampling error, variable thickness and irregularity of the capsule, as well as blood vessel distortion and collapse.[21-23]

The clinical significance of false negative results on FS diagnosis depends upon the surgeon's approach to the management of differentiated thyroid carcinoma. There are no definite guidelines on the subject. In centers where a surgeon may perform more than 25 thyroid operations per year, the practice of ipsilateral lobectomy and isthmectomy for solitary thyroid nodule, guided by the use of FNAB for determining the likely extent of contralateral lobe resection, is an acceptable option.[24] Similar opinions have been documented from other busy centers in view of the high specificity of FNAB and FS.[13,17] Yet others advocate a more cautious approach and a fairly liberal use of FS for diagnosis and planning of definitive surgery.[7,8] A recent report from Italy has described the use of intraoperative scrape preparations with Ultrafast Papanicolaou stain. The authors expect that with its high (98%) sensitivity compared to a low (71%) for FS for the diagnosis of thyroid lesion, it may be a 'useful adjunct' to the intraoperative management of thyroid nodules.[25] This implies that there is as yet no golden mean for the surgery of differentiated thyroid cancer.

We agree with other authors[26] that like FS, FNAB has its innate limitations and biases: its application requires specific skills in aspiration and preparation of slides as well as training and interpretive experience on the part of cytologist. The FNAB functions primarily as a screening test in which a very high sensitivity for malignancy is required at the

cost of lowered specificity. In contrast, the pathologist examining a FS is primarily disposed to avoid a false positive diagnosis and resultant excessive surgery. Hence a high specificity is desired at some loss of sensitivity. Presently in our hospital, while we remain conscious of cost-effectiveness, the 2 procedures are regarded as complementary with possible higher yield of accurate diagnosis.

References

1. Zarbo RJ, Hoffman GG, Howanitz PJ. Interinstitutional comparison of frozen- section consultation. Arch Pathol Lab Med 1991; 115: 1187-1194.
2. Ibanez ML, Russell WO, Chang JP, Speece AJ. Cold chamber frozen section for operating room diagnosis and routine surgical pathology. Lab Invest 1960; 9: 99-109.
3. Hamburger JI, Hamburger SW. Declining role of frozen section in surgical planning for thyroid nodules. Surgery 1985; 98: 307-312.
4. Keller MP, Grabbe MM, Norwood SH. Accuracy and significance fine needle aspiration and frozen section in determining the extent of thyroid resection. Surgery 1987; 101: 632-635.
5. Richard M, deMay RM. Frozen section of thyroid? Just Say NO. Am J Clin Pathol 1998; 110: 423-424.
6. Boyd LA, Earnhardt RC, Dunn JT, Frierson HF. Preoperative evaluation and predictive value of fine-needle aspiration and frozen section of thyroid nodules. J Am Coll Surg 1998; 187: 494-502.
7. Hamming GJ, Goslings BM, Songun I, Fleuren GJ, van de Velde CJ. Role of fine-needle aspiration biopsy and frozen section examination in determining the extent of thyroidectomy. World J Surg 1998; 22: 575-579.
8. Chang HY, Lin JD, Chen JF, Huang BY, Hsueh C, Jeng LB et al. Correlation of fine-needle aspiration cytology and frozen section biopsies in the diagnosis of thyroid nodules. J Clin Pathol 1997; 50: 1005-1009.
9. Sabel MS, Staren ED, Giankakis LM, Dwarakanathan S, Prinz RA. Use of fine-needle aspiration biopsy and frozen section in the management of the solitary thyroid nodule. Surgery 1997; 122: 1021-1027.
10. Davoudi MM, Yeh KA, Wei JP. Utility of fine-needle aspiration cytology and frozen section examination in the operative management of thyroid nodules. Am J Surg 1997; 63: 1084-1089.
11. Aguillar-Diosdado M, Contreras A, Gavian I, Escobar-Jimeinez L, Giron JA et al. Thyroid nodules: Role of fine-needle aspiration and intraoperative frozen section examination. Acta Cytol 1997; 41: 677-682.
12. Ersoy E, Taneri F, Tekin E, Poyraz A, Cihan A. Preoperative fine-needle aspiration cytology versus frozen section in thyroid surgery. Endocr Regul 1999; 33: 141-144.
13. Lin HS, Komisar A, Opher E, Blaugrund SM. Surgical management of thyroid masses: assessing the need for frozen section evaluation. Laryngoscope 1999; 109: 868-873.
14. Rosen Y, Rosenblatt P, Saltzman E. Intraoperative pathological diagnosis of thyroid neoplasms. Report on experience with 504 specimens. Cancer 1990; 66: 2001-2006.
15. McHenry CR, Raeburn C, Strickland T, Marty JJ. The utility of routine frozen section examination for intraoperative diagnosis of thyroid cancer. Am J Surg 1996; 172: 658-661.
16. Mulcahy MM, Cohen JI, Anderson PE, Ditamasso J, Schmidt W. Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of well-differentiated thyroid cancer. Laryngoscope 1998; 108 (4 pt 1): 494-496.
17. Chen H, Zeiger MA, Clark DP, Westra WH, Udelsman R. Papillary carcinoma of the thyroid: can operative management be based solely on fine-needle aspiration? J Am Coll Surg 1997; 184: 605-610.
18. Kraemer BB. Frozen section diagnosis and the thyroid. Semin Diag Pathol 1987; 4: 169-189.
19. Lin HS, Komisar A, Opher E, Blaugrund SM. Follicular variant of papillary carcinoma: the diagnostic limitations of preoperative fine-needle aspiration and intraoperative frozen section evaluation. Laryngoscope 2000; 110: 1431-1436.
20. Woyke S, Al-Jassar AK, Al-Jazzaf H. Macrofollicular variant of papillary thyroid carcinoma diagnosed by fine-needle aspiration biopsy: a case report. Acta Cytol 1998; 42: 1184-1188.
21. McHenry CR, Rosen IB, Walfish PG, Bedard Y. Influence of FNAB and frozen section examination on the management thyroid cancer. Am J Surg 1993; 166: 353-356.
22. Fransilla KO, Ackerman LV, Brown CL, Hedinger CE. Follicular carcinoma. Semin Diag Pathol 1985; 2: 101-122.
23. Miltenburg DM, Prost HM, Gravis EA, Arem R. The role of frozen section, gender, age and tumor size in the differentiation of follicular adenoma from carcinoma: A meta-analysis. Surgery 2000; 128: 1075-1081.
24. Chadwick DR, Harrison BJ. The role of fine-needle aspiration cytology and frozen section histology in management of differentiated thyroid cancer: the UK experience. Langenbecks Arch Surg 1998; 383: 164-166.
25. Basolo F, Baloch ZW, Baldanzi A, Miccoli P. Usefulness of Ultrafast Papanicolaou-stained scrape preparations in intraoperative management of thyroid lesions. Mod Pathol 1999; 12: 653-657.
26. Layfield LJ, Mohrmann RL, Kopald KH, Giuliano AE. Use of aspiration cytology and Frozen section examination for management of benign and malignant thyroid nodules. Cancer 1991; 68: 130-134.