

The role of pathology and pathologists in the detection and management of cancer

Much effort has been devoted to updating the practice of pathology in the current management of cancers, arising from increasing knowledge and availability of new technologies. In addition to a wide variety of new tools entailing molecular analysis and immunohistochemistry with ever-expanding lists of antibodies, there has also been a significant evolution in the conventional practice of histopathology. This has occurred, in parallel with the evolving changes in the practice of surgery, medicine, and other subspecialties. In this issue of the *Hong Kong Medical Journal*, two papers^{1,2} on the practice of pathology highlight such changes in routine practice in the management of cancers.

Examination of sentinel lymph nodes in breast cancer management

Leung et al¹ reported their experience with intra-operative examination of sentinel lymph nodes (SLNs) in the course of breast cancer management in a series of 300 patients. Their frozen sections yielded a correct diagnosis in 85% of the patients and a false negative rate (FNR) of 15%; the latter figure being comparable to rates ranging between 7 and 12% reported in multicentre studies.^{3,4}

Identification and assessment of SLNs in breast cancer has greatly altered the surgical management of this disease. Sentinel lymph node biopsy, with intensive histological work-up using multiple level sectioning³ and immunohistochemistry,⁵ has gained popularity to replace the routine level I and II axillary lymph node dissection for women with clinically node-negative T1 and T2 breast cancer. Concurrently, different groups, for example the American Society of Clinical Oncology have published guidelines in the use of SLNs for this purpose, though notably their use is not recommended in some special circumstances.⁴

Patients with negative SLN represent a subgroup of breast cancer patients with better prognosis with their pN0 status. Therefore, to be effective in guiding proper adjuvant therapy after removal of the primary cancer, the results of SLN biopsy must be very accurate and consistent. Accuracy depends on the tracing technique, the surgical procedure, and the extensiveness of pathological sampling of SLNs. Currently, data on the effectiveness of SLN biopsy on the long-term survival of patients with breast cancer are lacking. However, a review of the available evidence demonstrates that, when performed by experienced clinicians, it appears to be a safe and acceptably accurate method for identifying early-stage breast cancer, in patients without axillary lymph node involvement.

As for the prognostic significance of SLN, there are at least two issues: (1) negative SLN but positive non-SLNs, and (2) metastasis and micrometastasis.

A negative SLN biopsy but positive non-SLNs raises a concern about how reliable such testing is as compared to conventional methods of staging, axillary dissection, and conventional histological examination. A non-SLN, which is fully or partly replaced by metastasis, was probably once a SLN but no longer functional, because of tumour replacement. This forced lymphatic drainage via collaterals to a new lymph node, which becomes the current SLN, results in the phenomenon whereby tumour cells skip the SLN and get metastasised to other lymph nodes. Fortunately, the incidence of negative SLN but positive non-SLN is low. In one study, only one of 1087 non-SLNs was found to contain tumour in 60 patients with negative SLNs by histological and immunohistochemical examination.⁶ In a cohort study of breast cancer patients with a negative SLN biopsy, only one (1%) of all patients developed a lymphatic recurrence in the axilla after a median follow-up of 2 years.⁷ This study indicates that SLN biopsy provides accurate staging of the cancer and that patients whose biopsy is negative do not require axillary dissection.

The issue of metastasis and micrometastasis in SLNs is currently under much investigation.⁸ In the paper by Leung et al,¹ five of six patients whose SLN biopsies yielded false-negative results intra-operatively but positive final results, did not opt for second surgery. Also, in patients whose SLNs were positive in this paper, it would be useful to know how many had positive non-SLNs in the axillary dissection specimens. An analysis of multicentre results has shown non-SLN tumour involvement in 18% of SLNs with micrometastases or isolated tumour cells.³ On the other hand, the prognostic significance of SLN micrometastases (>0.2 mm and <2.0 mm) has not yet been determined.⁴ This begs the question as to whether patients with positive SLNs, particularly those with micrometastases, require completion axillary dissection. Until this is clear, current procedures directed toward detecting micrometastases or isolated tumour cells may be regarded as largely experimental in relation to the overall prognosis. Randomised clinical trials targeted at SLN-positive patients receiving axillary dissection, radiotherapy, or observation are needed to address this issue.

Which method—intra-operative consultation or formalin-fixation with paraffin embedding—for sentinel lymph nodes?

Histopathological examination of the SLN may be

performed after fixation and embedding in paraffin or intra-operatively. The choice between the two different procedures depends on individual institutions. The major advantage of intra-operative assessment is that if the biopsy is found to be positive intra-operatively, it can save a second operation, for which reason this practice is much advocated for in European countries.³ The intra-operative consultation can employ either frozen sections or touch imprints. Touch imprints have a high false-negative rate and not all pathologists are used to interpreting them, but they are much faster and tissue is not destroyed during processing.

Intra-operative frozen section assessment has its own limitations^{3,4} because it involves trimming away of substantial amounts of tissue, therefore there is always uncertainty as to whether microscopic metastasis that may be present is discarded. This shortcoming may perhaps be overcome to certain extent by flat embedding the bisected lymph node, which avoids trimming away any embedded tissue. Introduction of tissue artifacts interfering with permanent section analysis is another drawback. With intra-operative consultation, surgical time is prolonged, with increasing costs. There can also be false positives due to, for example, glandular inclusions, though fortunately these are not common. However, saving the patient from a second operation may outweigh all these disadvantages.

Intra-operative assessment of SLN is currently considered an optional procedure. The practice of intra-operative consultation using frozen section is not universal in pathology laboratories worldwide or locally. There are concerns from pathology laboratories regarding radiation risk, risk of significant damage and destruction of potentially diagnostic tissue, relatively high FNR for micrometastases, as well as manpower and resource implications. An understanding of an inevitable FNR by the surgeons and pathologists is critical, and requires an active dialogue among the multidisciplinary team of surgeons, pathologists, and nuclear medicine colleagues to optimise practice in individual institutions.

In summary, SLN biopsy is very much a multidisciplinary team effort with active involvement of surgeons, pathologists, radiologists, and nuclear medicine colleagues among others. With careful pathological examination, valuable information can be obtained from the procedure. Patients with breast cancer can then be further stratified with regard to prognosis and therapy. Intra-operative consultation for SLN can save patients a second operation. Although there are limitations to the

technique, its application as a standard practice should be considered according to the resources available in individual institutions. Delineation of the significance of micrometastases in SLN, in terms of predicting further nodal involvement, prognosis and indication of adjuvant therapy will have an impact on the extent of histological work-up that is necessary.

Fine-needle aspiration cytology in thyroid nodule

The usefulness of fine-needle aspiration cytology (FNAC) in making diagnosis for thyroid nodules is well established and exemplified again in the study by Cheung et al² in this issue. They have reported the sensitivity, specificity, positive and negative predictive values of FNAC for thyroid nodules to be 54, 100, 100, and 75%, respectively. Despite the modest size of their samples, these figures are comparable to those reported in the literature.^{9,10}

According to a recent review, the range of inadequate or unsatisfactory specimens for thyroid FNAC varies from 2 to 21% (mean of 17%),¹¹ which is consistent with the rate of 15% reported in the study by Cheung et al.² Such rates vary widely in different centres, depending on local sampling policies. The experience of clinicians or pathologists performing the FNAC—whether as part of a small group of designated specialists undertaking FNAC—the number of aspirates and slides taken per aspirate can significantly affect the yield. On the other hand, use of ultrasound guidance reduces the rate of inadequate FNAC procedures by at least two fold.¹²

In conclusion, the work described by Leung et al¹ and Cheung et al² is a valuable contribution to the ongoing attempts to provide various updated means of pathology reporting directed at cancers. The former highlights the application of intra-operative frozen section assessment of SLNs in the management of breast cancer and the latter emphasises the usefulness of FNAC in the diagnosis of thyroid cancer.

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