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Editorial

Golden rules in practice of cancer pathology

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Guidelines

Abstract
The pathologic diagnosis of cancer is an essential initial step in the management of patients, a great responsibility facing the pathologist. The present review is a critical analysis of current practice. The aim is to disclose defects, describe diagnostic strategies and outline recent changing trends in the use of diagnostic methods. The importance of recognizing syndromic cancers, interpathologist consultation and interdisciplinary cooperation is emphasized. Twenty advises and guidelines are presented which may hopefully minimize errors and assure an accurate diagnosis. Recent 5-year survival data of different cancer sites are presented with a proposed classification into four prognostic categories. Curability from cancer is not uncommon with modern therapy. It is confirmed by the demonstration of a plateau slope graph between 5 and 20 years after therapy.

"*Patients worry over the great number of diseases, pathologists worry over the difficulty to diagnose them, whereas, clinicians worry over the scarcity of effective therapy*."

The practice of oncology aims to achieve four goals, namely: correct diagnosis, effective treatment, adequate follow up and fruitful research. Interdisciplinary cooperation of staff is essential to accomplish these goals. Diagnosis must precede treatment, since it determines the line of therapy. It must be rapid and precise. This great responsibility lies on the pathologist who is expected to type the disease, as well as, to predict its biologic behavior. In most of cases, these diagnostic and prognostic challenges are successfully accomplished, but in few problematic cases, difficulties arise and errors are inevitable. The following are a group of advises and general rules that may help to avoid or minimize diagnostic pitfalls and assure a complete and accurate final pathology report.

1. Specimen identification and fixation are two essential and immediate steps. Labeling of specimen by the name of patient avoids the serious interchange of specimens. Bilateral specimens should be submitted separately with labeling of laterality. Immediate fixation is essential to preserve both morphology and biology of samples. The type of fixation varies according to the aim of investigation (Table 1).

"*Practice only does not make perfection, only perfect practice makes perfection*"

2. Full clinical data should be available to the pathologist, including: age, exact site of specimen, clinical diagnosis, type of operation, any previous biopsy or therapy. Thus, without reviewing previous biopsies, it is difficult to tell if a new mass lesion is a recurrence or a new primary. In addition, histopathologic studies after therapy are usually unreliable.

"*Pathologic reports without clinical data are both impossible and dangerous*."

3. Adequacy of a biopsy is essential for proper pathologic evaluation. For tissue needle biopsy, the WHO recommends multiple

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Table 1 Fixation of specimens.

Method	Fixative
Routine pathology	10% formalin
Electron microscopy	2.5% glutaraldehyde
Cytology	90% ethyl alcohol or air dryness
Biologic studies	Deep freezing (−20 °C to −80 °C)
Frozen section	Fresh unfixed
Tissue culture	
Karyotyping	
Flow cytometry	

cores not less than 14 mm long, a condition rarely encountered in practice. There are several causes of inadequate sample, including: scanty material (<1 mm), non-representative tissue, necrotic, crushed, cauterized or autolyzed samples. In such cases, rebiopsy of adequate material should be requested.

"*The best way to escape from a problem is to solve it*."

4. Gross data of resected cancer specimens must include the following: (a) presence of any cutaneous surgical wound denoting previous lumpectomy, (b) longest diameter (single or multiple tumors), (c) invasion of muscle layer (gut, bladder or myometrium), (d) if capsule of the organ is intact or penetrated by tumor (in thyroid, kidney and ovary), (e) number and size of regional lymph nodes and (f) longest and shortest clearance of normal tissue around the tumor in cm. Tissue for surgical margin evaluation should be taken from the shortest clearance by blocks parallel or perpendicular to the surgical margin (Fig. 1). A clearance of 1 cm is satisfactory for most cancers, but a larger distance (2–3 cm) is needed in melanoma.

5. Size of sarcomas can help to assess the expected biologic behavior. Soft tissue sarcomas usually present as deep bulky masses (>5 mm). Similarly, cartilaginous tumors >5 cm are usually malignant. It is wise not to diagnose a sarcoma <2 cm. Exception to this rule is sarcomas of the skin which may be <1 cm but behave malignant (e.g. Kaposi sarcoma, primary cutaneous lymphomas and dermatofibrosarcoma).

6. The triad foundation for diagnosis. In the nervous and skeletal systems, tumor types are numerous and show special age distribution. Imaging is the only way to gain information on their gross features. For these reasons, an accurate pathologic diagnosis is only possible after considering these three types of information, namely: the age, radiography or MRI and histology.

7. Diagnosis by probability. In the search for a diagnosis, it is wise to consider common rather than rare diseases. Thus, an axillary lymphadenopathy in a female usually represents metastasis from breast, but in males it is commonly a lymphoma or melanoma.

"*a rare presentation of a common disease is more common than a common presentation of a rare disease*."

8. The importance of consultation. A difficult case confronting a beginner pathologist will end up by misdiagnosis and mismanagement. Consultation with a senior pathologist will help to avoid this pitfall.

"*What the mind does not know, the eye can not see*"

"*Good judgment comes from experience, and experience comes from bad judgment*"

9. Diagnosis by exclusion. In difficult cases, differential diagnosis must be considered and a Sherlock Holmes detective strategy adopted. For example, in a spindle cell malignancy, fibrosarcoma is the ultimate diagnosis if neural, myogenic and sarcomatoid carcinoma are excluded (by S-100, desmin and cytokeratin negativity).

"*When you have excluded all the impossible, whatever remains must be the truth.*"

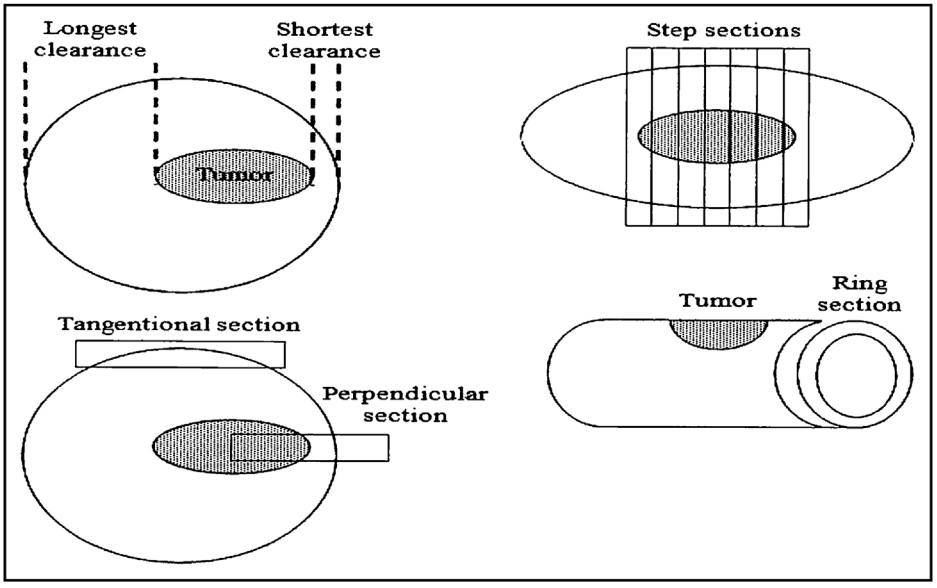

Figure 1 Tissue clearance and selection of surgical margins from excised specimens.

10. The uncertain behavior. Some tumors are difficult to predict their biologic behavior from their histologic picture (e.g. neuroendocrine tumors and gastrointestinal stromal tumors (GIST)). In such cases, prognostic markers may help (e.g. Ki-67 proliferation index, the presence of gene mutation). The following Chinese proverb applies on those who make a definite decision on the uncertain.

"*To be uncertain is to be uncomfortable, but, to be certain is to be ridiculous*."

11. The undifferentiated/unclassified tumor type. About 10% of tumors are difficult to type even with the use of immunohistochemistry. Pathologists, however, are generally ashamed to use this term. Such tumors are given names descriptive to their cytomorphology (e.g. spindle, round, epithelioid or pleomorphic cells).

12. The stem cell component. All malignant tumors have a stem cell population, but are rather difficult to visualize. There is no specific marker for stem cells (except for CD34 in hematolymphoid malignancies). Recently, some morphologic features are described to suggest stem cell component in a tumor, namely: a population of uniform mall round cells, scanty cytoplasm, marker negativity and associated fibrosis. Ki-67 nuclear labeling rate is a measure of cycling stem cells (growth fraction).

13. Limitations of frozen section. In sclerosing epithelial lesions of breast, as well as, intraductal papillary tumors, it is difficult to distinguish benign from malignant lesions by frozen section. In such cases, the definitive diagnosis should be deferred to paraffin section studies. This will also allow the use of S-100 marker to identify myoepithelial cells in the lesion, thus confirming its benign nature. The age of the patient must also be taken into consideration. Thus, in young patients (<20 years) all suspicious breast masses should be deferred to paraffin section evaluation. It is noteworthy also, that frozen section is inapplicable for bone tumors and small impalpable masses. Moreover the results of frozen section examinations for surgical margins are rather inaccurate. Currently, tissue core needle biopsy is replacing frozen section, with high sensitivity (98%) and specificity (99%). Moreover it allows informed consent of patient and is applicable in nonpalpable tumors when guided by imaging.

14. Limitations of immunophenotyping. Immunohistochemistry has its handicaps (e.g. false negativity, co-expression and aberrant expression), hence, in some cases, results of markers are ambiguous. Accordingly, whenever a disagreement exists between immunophenotyping and morphologic typing of tumors, the latter should take the upper hand and typing based on histomorphologic features. Contrary to immunophenotyping, electron microscopic studies are highly specific and helpful in the diagnosis of some difficult cases (e.g. melanoma, Langerhans histiocytosis, neuroendocrine tumors and undifferentiated cancer).

15. Molecular genetic tests (FISH and PCR technologies) are valuable for the following selected cases: (a) genotyping and classification of hematolymphoid malignancies and solid tumors, (b) detection of minimal residual disease, (c) confirm syndromic cancer by identifying germline mutations, (d) detection of oncogenes important for targeted therapy (e.g. BCR-ABL1 mutation in CML, PML-PARA fusion gene in premyelocytic leukemia, C-Kit in GIST, Her-2 in breast carcinoma, EGFR in non-small cell lung cancer and glioblastoma multiforme, VEGF as well as FLI-3 in melanoma and (e) predict prognosis (e.g. N-myc amplification in neuroblastoma).

16. Genomic tests. The recent microarray technology allows the analysis of thousands of genes from a single tumor sample. Moreover, it is also possible through next generation sequencing to analyze the entire genome. In these methods, the strategy is to identify the entire mutation spectrum of a given tumor and to develop specific drugs for its treatment (personalized medicine through pharmacogenetic approach). However, cost-benefit analysis must be considered in such cases. The high cost of this technology prohibits its routine or even research use. Other less expensive techniques may be used to accomplish the same goal.

17. Syndromic cancer, which contributes about 10% of practice, is suspected in the following clinical settings: (a) adult malignancies arising in young patients (colonic or breast carcinoma in a child), (b) bilateral or multiple cancers, whether endocrine or non-endocrine (e.g. medullary thyroid carcinoma and pheochromocytoma in MEN-2B syndrome, breast-ovary BRCA syndrome, colon-endometrium double cancers in Lynch syndrome and basal, squamous and melanoma multiple cancers in xeroderma pigmentosum). (c) Family history of the same cancer, (d) unusual presentation of cancer (e.g. breast cancer affecting males). (e) Some cutaneous manifestations are also reliable indication of syndromic cancers. It is important to recognize syndromic cancer for three main reasons, namely (a) genetic counseling of all family members with careful follow up, (b) in case of multiple tumors, the priority of management is given to the more aggressive tumor, and (c) in case of cancers resulting from defect in DNA repair or hypersensitivity to irradiation, radiotherapy is contraindicated (e.g. BRCA-related breast cancer, xeroderma pigmentosum, Lynch syndrome and ataxia telangiectasia)

18. The final pathology report. In case of radical surgical resection specimens for cancer, the report must include the following information: (a) histologic type of cancer, (b) the grade of malignancy, (c) the stage of cancer (preferably TNM if applicable, or other staging classification as FIGO, lymphoma or pediatric systems), (d) the status of regional lymph nodes (indicating the number of positive lymph nodes and total nodes examined), (e) presence of any lymphangio-invasion, (f) the status of surgical margin (negative, close or positive for malignancy) and (g) the grade of therapy effect in case of neoadjuvant chemo or radiotherapy. Three grades may be applied, namely: no effect with viable tumor cells predominating, partial effect with estimation of necrotic tumor area (%) or complete therapy effect with massive tumor necrosis, fibrosis and no viable neoplastic cells.

"*Perfection is achieved when there is nothing left to add or to take away*."

19. Survival of cancer patients. By studying historical reports from USA, a significant increase in 5 year survival of cancer patients during the 20th century (from 0.0% to over 60%). Thanks to the break through discoveries of effective therapeutic modalities, namely: radical surgery, advanced linear acceleration, combination chemotherapy, bone marrow transplantation and targeted therapy. In a recent report of SEER data a 5 year survival of 67% was reported in patients treated by recent protocols. We propose to classify survival data into four categories in descending order of survival intervals

Table 2 Five-year survival by cancer site.

Prognostic category (survival interval)	Site (survival %)	
I. Most favorable (80–100%)	Prostate (99%)	Breast (89%)
	Thyroid (98%)	Hodgkin (86%)
	Testis (96%)	CLL (82%)
	Melanoma (92%)	Endometrial (82%)
II. Favorable (50–80%)	Bladder (77%)	ALL (68%)
	Kidney (73%)	Colorectal (65%)
	NHL (70%)	CML (63%)
	Cervix (68%)	Larynx (61%)
III. Unfavorable (20–50%)	Myeloma (47%)	Stomach (29%)
	Ovary (46%)	AML (26%)
	Brain (33%)	
IV. Most unfavorable (0–20%)	Esophagus (18%)	
	Liver (7%)	
	Pancreas (7%)	

SEER data, USA (2015) [1].
Abbreviations: CLL: chronic lymphocytic leukemia. NHL: non-Hodgkin lymphoma; ALL: acute lymphatic leukemia; CML: chronic myeloid leukemia; AML: acute myeloid leukemia.

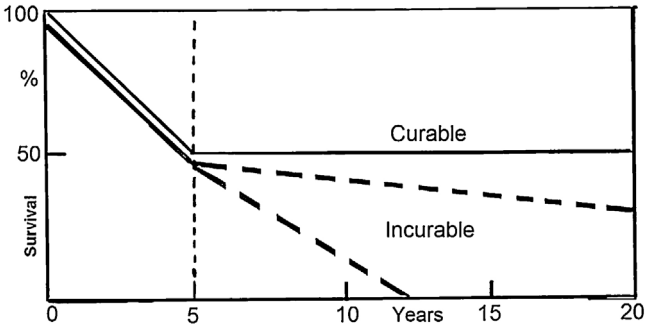

Figure 2 Long-term Edward Taft slopegraphs for cancer patients. Curable cases has a plateau curve (solid line), whereas, incurable patients show a declining curve (dashed lines).

(Table 2). In addition, 5 types of cancer have zero percent 5 year survival due to the present lack of effective treatment, survival time is only 4–20 months. This fatal group include: glioblastoma, small cell lung cancer, anaplastic thyroid carcinoma, brain lymphoma (NHL) and acute adult T-cell leukemia/lymphoma. It is noteworthy, however, that survival statistics are just a rough estimate of groups of patient but never precise in an individual patient.

> *"Patient and their families may forgive a wrong diagnosis, but not a wrong prognosis"*

20. Curability of cancer. There are three unhappy outcomes after cancer therapy, namely: locoregional recurrence, distant metastasis and iatrogenic new primary. These events usually develop over a period of 20 years after therapy. A patient is considered cured if he survives 20 years after treatment and did not develop any of these mishaps. Thus it is possible to evaluate curability by long-term survival analysis and studying the slopegraphs during the period of 5–20 years [2]. Patient with plateau shaped curve are considered cured (Fig. 2). A classic example of potentially curable cancer is Burkitt lymphoma.

Author's contribution

M.N. Elbolkainy is a sole author.

Conflict of interests

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Further reading

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