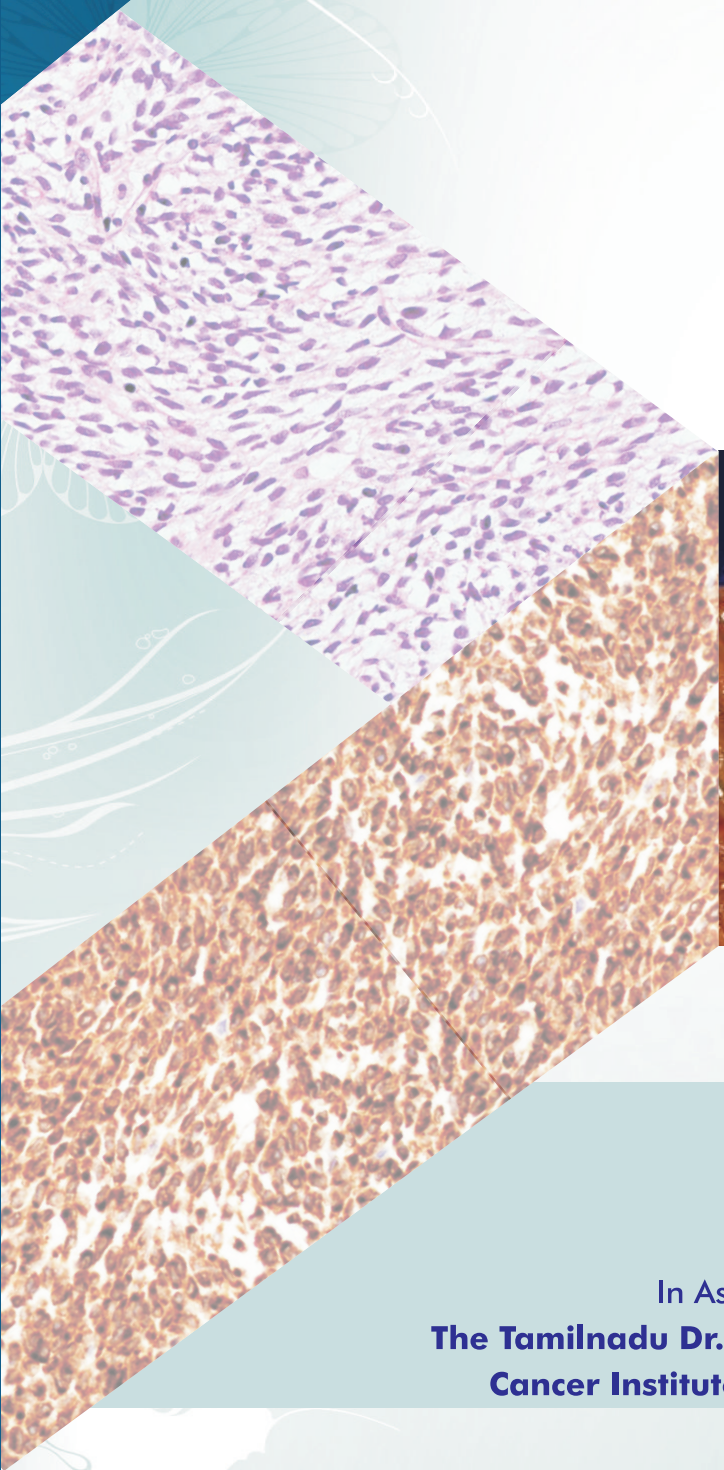
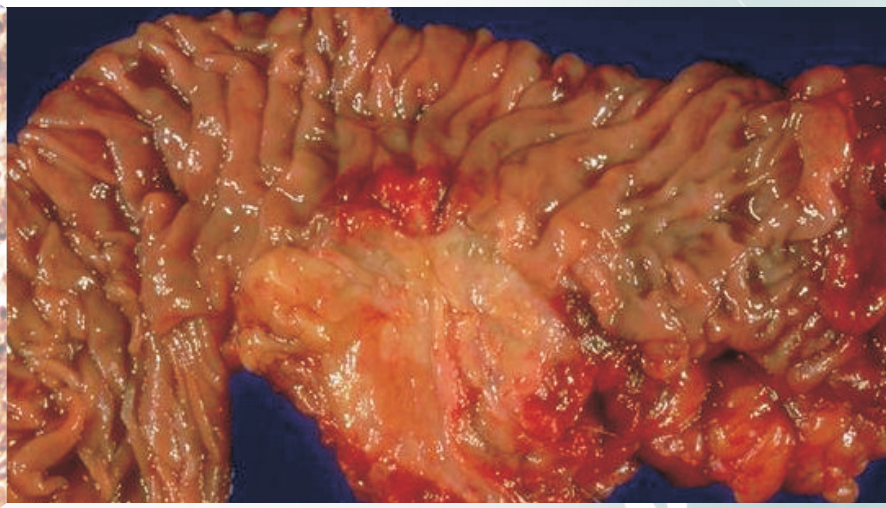
Annual Conference of
Tamilnadu and Pondicherry Chapter
Indian Association of Pathologists and Microbiologists

July 12 & 13, 2019, Chennai

TAPCON 2019





Souvenir

In Association with

The Tamilnadu Dr. MGR Medical University &

Cancer Institute (WIA), Adyar, Chennai.

TAPCON 2019 Organizing Committee

IAPM National President Message

Dr. Pradeep Vaideeswar
(President, IAPM - 2019)
Department of Pathology (Cardiovascular & Thoracic Division)
Seth GS Medical College, Parel, Mumbai 400 012
(09833509435, shreeprajai@yahoo.co.in)

4th July 2019

The Organizing Committee

TAPCON 2019

Please accept my best wishes for the forthcoming conference of the TNPCIAPM, TAPCON scheduled to be held on 12th &13th July 2019. I am sure that the updates and diagnostic problems of pathology of the gastro-intestinal tract, hepato-biliary system, uro-genital system and soft tissue will be unraveled by eminent faculty from both clinical and pathology branches, which will benefit the postgraduates. There are also additional sessions, which will help those who are inclined towards teaching, medical writing or laboratory work

Dr. Pradeep Vaideeswar
(President, IAPM - 2019)
Department of Pathology (Cardiovascular & Thoracic Division)
Seth GS Medical College, Parel, Mumbai 400 012
(09833509435, shreeprajai@yahoo.co.in)

TNPC IAPM State President Message

Dr. P. Arunalatha

Organising Chairman, TAPCON 2019
Professor & HOD of Pathology
Govt. Stanley Medical College, Chennai

Respected seniors, my dear colleagues and the juniors,

First and foremost Dr.Padmavathi and myself would like to whole heartedly thank you all for your overwhelming support and confidence in our teamwork in uplifting our TN & Pondy chapter of IAPM into the national arena. Following the footsteps of doyens in pathology like Prof. Dr.Sarasabharathi and Prof.Dr.Panchanadam Madanagopal which was an era of supremacy at the national level, now we as a team will work in unison to march forward to take TNPCIAPM chapter to greater heights.

Pathology is a profession with 2 eyes, one the teaching aspect and the other the laboratory service. So our idea would be to percolate knowledge to the technicians, MBBS and post graduate students to serve the society the right way. Presently with automation in laboratories, NABH & NABL setting standards in quality assurance and management, there is a beeline of CME's to foster our brains. So let the TAPCON 2019 be one such start up to kindle the younger pathologists through the advancement in pathology, and targeted therapy.

Hope this TAPCON 2019 July 12, 13 be a small step that would bring a big leap ahead. Looking forward to all your wishes and blessings for a great success towards this academic fiesta.

Thanking you all

With warm regards

Dr. P. Arunalatha

Organising Chairman, TAPCON 2019
Professor & HOD of Pathology
Govt. Stanley Medical College, Chennai

TNPC IAPM State Secretary Message

Dr. R. Padmavathi

Organizing Secretary
TAPCON 2019
Professor of Pathology, Madras Medical College, Chennai

We welcome you all for this prestigious conference TAPCON 2019 from July 12th 2019 to July 13, 2019 being held in Chennai **-"Bustling Hub of Pathology Professionals"…**

We're making a great start for this event at this time of the year as all of us seem to experience the dawn of a new era of most advances in the field of HISTOPATHOLOGY & LABORATORY MEDICINE and I'm sure this marquee event witnessing experts and visionaries would provide greater insight into the wide range of topics chosen from the fields of Histopathology, Laboratory medicine and Medical education. Have your eyes and ears wide open to listen from these experts across the nation and get benefitted!

The conference committee has done an exceptional job over the past 6 months in putting together a befitting program schedule covering wide range of topics in the field of Diagnostic Pathology and I'm sure this would provide an overall enriching experience to the participants.

We're thankful to every member of the TAPCON organizing committee, HODs, Professors and Consultant Pathologists for their advice and support. Our thanks to the sponsors and other supporting organizations. Our special thanks to our great set of volunteers for their relentless support for making this event in all its grandeur.

With all the great support and efforts aligned, we're sure that this year's TAPCON 2019 will set a new standard for future conferences over the years to come!

We look forward to seeing you and having you as part of our initiative of TNPCIAPM in future events too...

With warm regards

Dr. R. Padmavathi

Organizing Secretary
TAPCON 2019
Professor of Pathology,
Madras Medical College, Chennai

TAPCON 2019 Organizing Co-Chairperson Message

Dr. M.P. Kanchana, MD

Professor of Pathology
Madras Medical College,
Chennai.

It gives me immense pleasure to welcome all the distinguished speakers, Chairpersons and delegates to the two day academic feast TAPCON 2019 held in Chennai, the city of rich heritage and culture. This meet provides an excellent platform for students to acquire knowledge, sharpen their skills and for professionals to share their knowledge and experience. Presenting scientific papers and posters at an academic event is an opportunity that most young postgraduates look forward to. To encourage young researchers and postgraduates I am sponsoring three cash awards Rs.10000, Rs.5000 and Rs. 2500 for best three papers and Rs. 2000 each for three best posters. Expecting an enthusiastic participation from all young researchers. My best wishes and warm regards.

Dr. M.P. Kanchana, MD

Professor of Pathology
Madras Medical College,
Chennai.

TAPCON 2019 Organizing Co-Chairperson Message

Dr. Sudha Venkatesh

Organising Co Chairperson
TAPCON 2019
Professor of Pathology, Madras Medical College, Chennai

It has been a delight to be a part of the TAPCON 2019 Organising Committee. What started as an informal conversation amongst a few pathologists has shaped into this conference after almost a year's discussions, planning and action. The efforts of the senior pathologists and junior colleagues have been instrumental in bringing the Tamilnadu and Pondy Chapter of IAPM back into the limelight. It has been a wonderful experience collaborating and working with the entire team who have put in their best efforts to make this event a grand success. I am sure that the delegates will not only benefit from the academic deliberations in the Conference and technical expertise from the Pre-Conference Workshop but will also take back fond memories.

Dr. Sudha Venkatesh

Organising Co-Chairperson
TAPCON 2019
Professor of Pathology,
Madras Medical College, Chennai

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Prof. Dr. Sarasa Bharati

MD.,PhD.,FICP.,FCCP.,FIAMS.,FEMSI.,FICA.,FMMC.,FNSI.,
Director Laboratory Services & Advisor Academics

I am very happy to be able to write this note for the IAPM –Madras & Pondicherry chapter souvenir, to be brought out this year, at the annual conference. Indeed, I do feel like a proud mother having watched the birth, growth and development of her child who has grown up, fully qualified and now fit, able and raring to go and be counted among the peers in the international arena. It has taken a long time since early February 1976 when we started this chapter, the first in India (all others did so the next year only) to reach where we are at present. I am sure the future will see dynamic progress in the many various aspects of pathology, perhaps starting from in depth investigation to find a non carcinogenic replacement for formalin, extending on to the most complex immunological mechanisms and the manipulation of stem cells leading to the molecular genetics and epigenetic factors predisposing to or leading to disease.

I am privileged to extend my hearty good wishes to all members and others working in the many fields of Pathology striving to help the physician to improve the quality of life for the humanity at large.

I also wish continued success in all the scientific endeavours of the members of the Madras and Pondicherry chapter of the IAPM in all the years to come.

Prof. Dr. Sarasa Bharati
Director Laboratory Services & Advisor Academics
Frontier Lifeline Hospital, Chennai

Message

Dr. D. V. Gomathi

Retd Prof and Head, Department of Pathology, Kilpauk Medical College, Chennai

I am delighted to share my thoughts for the souvenir to be released at this year's Annual IAPM Conference - Tamil Nadu and Pondicherry Chapter.

Going down the memory lane, I must say that it has been an impressive journey for the IAPM, Tamil Nadu Pondicherry Chapter. Since its inception, it has grown in stature and in its contribution to the field of Pathology. It has provided an excellent platform for pathologists to have constructive discussions and a valuable sharing of experiences thereby enabling them to keep abreast of the latest developments in the field.

The IAPM which was envisaged to be a congregation of academic pathologists, clinical pathologists, researchers and students of Pathology will greatly benefit from the souvenir and the various events of the 2019 conference too as they have done in the past.

I wish to share here a couple of unforgettable workshops which we held during my tenure as the Convenor of IAPM (Tamil Nadu-Pondicherry Chapter). I was ably assisted in my role as a Convenor by Dr. Hemalatha Ganapathy. We witnessed a very enthusiastic participation by the community of Pathologists in the Tamil Nadu Pondicherry Chapter during our bimonthly meetings.

One of those workshops at that time entitled

"Early Diagnosis of Leprosy for Pathologists" was conducted by Prof. Dr. C. K. Job, a pathologist of International reputation. He had also distributed a manual showing the clinical picture and histologic features to assist the General Pathologists to get a clear understanding of the skin lesions of Leprosy, especially the kind that they commonly encountered in their practice. Another memorable workshop was on the "Museum Technique". It was conducted by the Late Prof. Dr. Nagalothimath, Former President of IAPM. It was an extremely useful and interesting workshop in which even the Forensic Pathologists participated.

Coming back to the present and looking at the content of the 2019 Annual Conference invite of IAPM, I am greatly pleased to note that it has been very well planned by the organisers encompassing all branches of Pathology. With participants from other cities also getting together this year at this Chapter, and with its inclusion of the topics pertaining to state-of-the-art techniques and current technology aiding the field of Pathology, we can look forward to more exciting and pathbreaking studies which would greatly benefit mankind.

I am certain that this conference and the souvenir will leave lasting memories and herald a more productive future for Pathologists. I wish the Annual IAPM conference all success. My Best Wishes also to the very efficient team of organisers.

Dr. D. V. Gomathi

Retd. Prof. and Head, Department of Pathology,
Kilpauk Medical College, Chennai

Message

Prof. Snehalatha
Retd Director
Institute of Pathology and Electron microscopy, Madras Medical College, Chennai

I am very happy to know that TNPCIAPM is conducting it's annual conference (TAPCON 2019) in July 2019 at Chennai. I commend the organizers on their efforts in arranging the national conference. I wish the meeting all success.

Prof. Snehalatha
Retd Director
Institute of Pathology and Electron Microscopy
Madras Medical College, Chennai

Message

Dr. Ezhilvizhi Alavandar. MD. PhD.,
Retd. Professor and HOD
Kilpauk Medical College, Chennai

Warm Greetings To Tapcon – 2019

It's a great pleasure to note the rejuvenation of our TN state Chapter activities.

Like "Little Drops Of Water Make A mighty Ocean" , collective participation of all Pathologists will result in a great Chapter.

I would be pleased to offer my support to the chapter as and when required.

I offer my congratulations to the office bearers for their effort in the revival of the Chapter activities.

As per Aristotle quote, "*Excellence is an art won by training and habituation*."

Dr. Ezhilvizhi Alavandar. MD. PhD.,
Retd. Professor and HOD
Kilpauk Medical College, Chennai

Message

Prof. Dr. Hemalatha Ganapathy, M.D.,

Retd. Dean
Coimbatore Medical College

I wish the organisers of TNPC IAPM, " TAPCON 2019 " a great success in their endeavour

It is admirable that it covers a wide range of topics incorporating recent advances and practical aspects of Pathology.

I am sure it will be an intellectual feast for students, faculty and practising pathologists.

Henry Ford has said "*Anyone who stops learning is old, whether at twenty or eighty*" -

Let us be young always !

Prof. Dr. Hemalatha Ganapathy, M.D.,

Retd. Dean
Coimbatore Medical College

Message

Dr. P. Karkuzhali. M.D

Former President of TN & Pondy Chapter of IAPM (2009 – 2011)

I am profoundly pleased to know that the office bearers of Tamilnadu & Pondicherry Chapter of IAPM are organising TAPCON – a national level state conference for two days on 12th & 13th July at Chennai, along with a preconference workshop on 11th July.

The Indian Association of Pathologists & Microbiologists (IAPM) was founded in 1949 and the State chapter of Tamilnadu was created in 1974. Like the parent organisation, which retained Microbiology within their realm of Pathology, the Tamilnadu state chapter included and retains the neighbouring union territory in its fold. Indeed, it is only natural, as a diamond requires a gold setting to be of ornamental value. Since its inception, several doyens in Pathology Profession have contributed immensely and endlessly to the scientific advancement of the practice of Pathology in this state and now the flaming torch is being carried head high by the current president, Prof. Dr. Arunalatha, and Secretary, Prof.Dr. Padmavathi, of the TN & P Chapter. I laud and appreciate their effort and hard work in reviving the national conference of TAPCON and I am positive that the scientific programmes will be a regular fixture in future under their able leadership and guidance.

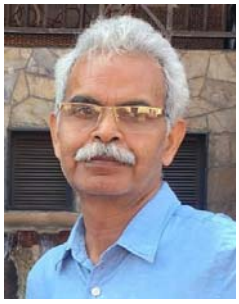
This conference has been well planned, covering all aspects of Pathology and I do sincerely wish a grand success for this event.

Regards and best wishes

Dr. P. Karkuzhali. M.D

Former President of TN & Pondy Chapter of IAPM (2009 – 2011)

Message



Dr. Surendra Kumar Verma
Senior Professor, Dept. of Pathology
JIPMER, Puducherry.

I am happy to learn that the Annual Tamil Nadu and Pondicherry Chapter of Indian Association of Pathologists and Microbiologists (TAPCON) of 2019 is being organised under the able leadership and guidance of Dr. Arunalatha, Prof. and HOD of Pathology at Stanley Medical College, Chennai and Dr. R. Padmavathy, Prof. of Pathology, Madras Medical College, Chennai. I understand that the speakers are of repute from various institutions across the country. The scientific deliberations will surely benefit postgraduates and practicing Pathologists. This is also an opportunity for networking and academic exchange.

Medical field, particularly diagnostics, has made tremendous technological strides and such academic meets are necessary to keep abreast with these advancements.

I wish the organisers and their team, speakers and delegates a fruitful and successful academic meet.

With Best Wishes

Dr. Surendra Kumar Verma
Senior Professor, Dept. of Pathology
JIPMER, Puducherry.
Former President
TN & Pondy Chapter of IAPM

Tribute to Professor Dr. Panchanadam Madanagopalan Former Director MMC and Cofounder of Tamil Nadu and Pondicherry Chapter of IAPM

Dr. Panchanadam Madanagopalan

Dr.Panchanadam Madanagopalan fondly called as "Panch ma'am" is highly respected and a doyen in the field of pathology. She was not only a teacher and mentor to many pathologists but also a friend, philosopher and guide to all. She was courteous, gentle and humble But at the same time strong and stoic at times of distress. Her determination was coupled with a friendly approach and willingness to listen to people junior to her, set her as a class apart.

She started the M.D pathology course at Kilpauk medical college. She conducted the IAPM national conference in 1990 at Chennai in a time when computers, mobile and social networking were unheard of. Panch ma'am as the organising secretary worked along with major general C.S.V who was the chairperson/president. This great event covered all aspects of pathology and was meticulously planned and executed. A unique administrator beyond comparison, madam created two medals to students of pathology in the T.N DR.MGR medical university. She also helped financially national IAPM during construction of a building at Cuttack.

She ensured that in the years that followed the T.N and Pondicherry chapter of IAPM gained visibility nationwide. She also served the central body as vice-president for a term. Periodical quarterly meetings were conducted in and outside Chennai and an annual meeting every year. She also conducted distance education programmes which consisted of interesting slides being circulated to members for their contribution to difficult diagnosis. Her special fields of interest were in Gastro Intestinal and liver pathology

She was a visionary and a person par excellence and we take this unique opportunity to salute her. We conclude with madam's oft quoted saying

"*Knowledge is proud that it knows so much, but wisdom is humble that it knows no more*"

Dr. Chitra Srinivasan
Dr. Ezhilvizhi Alavandar
Dr. K N. Alli
Dr. K. Rama

TAPCON 2019 Organizing Committee

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Organizing Secretary
Dr.R.Padmavathi

Organizing Co chairperson
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Dr.K.Shantaraman

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Dr.A.Dhanalakshmi.

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Dr.K.Indhumathy
Dr.Uma Srinivasan

Quiz
Dr Arasi Rajesh
Dr.K.Swaminathan
Dr.Leena Dennis Joseph
Dr.BH.Srinivas

Contents

Grossing Techniques of Colorectal Specimens

Dr. S. Shirley

M.D (Pathology), DNB, MNAMS, PhD (Molecular Oncology)
Professor and Head
Dept. of Oncopathology, Cancer Institute (WIA), Adyar, Chennai

Introduction

Pathology reports play an important role in the care of colorectal cancer patients since accurate staging, prognostic information and treatment decisions are based on the results of pathological examination and reports. The standards for pathological examination of rectal carcinoma specimens have evolved over years. Dukes in 1930s established the fundamental principle of tumour staging as a predictor of patient outcome (T,N). This forms the basis for prognostication in most patients suffering from cancer. The most widely accepted standard for reporting colorectal carcinomas is the tumor size, node status and metastasis (i.e) the TNM classification scheme.

Pathology report in rectal cancer

Pathology report in rectal cancer confirms the diagnosis, provides information on prognosis, enables planning treatment of individual patients (lymph node involvement, perforation, serosal involvement, incomplete resection or extensive local spread) and confirms that radical surgery was necessary. In addition, it determines the effects of pre-operative therapy, allows audit of diagnostic and surgical procedures in relation to clinical outcomes, facilitates improvements in the quality of rectal cancer surgery, helps to collect accurate data for cancer registration and epidemiology and do high quality research.

Clinical information

Clinical information about the nature of resection and the site of the tumour, histological type of tumour, pre-operative stage of the tumour, preoperative therapy, plane of operation attempted, type of abdominoperineal excision and type of local excision have to be documented in the specimen request form.

Specimen handling

Specimens have to be sent fresh and intact immediately to the pathology department after surgical resection. As soon as the specimens are received in the laboratory they have to be inspected externally to locate the tumour and look for the presence of any macroscopically obvious perforation. For anterior resection (AR) and abdominoperineal excision (APE) the plane of resection should be evaluated and photographs of the intact specimens taken in order to support the evaluation. Hence, it is important to photograph and grade the plane of surgical excision and record the quality and type of abdominoperineal excisions.

Plane of surgical resection

Plane of surgical excision predicts margin positivity, local recurrence and survival. In total mesenteric excision (TME) specimens done for rectal cancers it can be mesorectal, intramesorectal or muscularis propria. Grading of mesorectum is as follows:

- Grade 1 – incomplete surgery, little mesorectum, muscularis propria exposed
- Grade 2 – partially complete surgery with incomplete removal of mesorectum
- Grade 3 – complete surgery with complete mesorectal excision

An optimal surgery is a Grade 3, complete, with good bulk of mesorectum, smooth surface, good clearance anteriorly and no defects in mesorectum. Excision in the mesorectal plane has the best outcome, while that extending into the muscularis propria has the worst. The plane of resection can also be used as a marker of the quality of surgery and continual feedback leading to improved quality of surgery and clinical outcomes.

The plane of surgical resection in the levator/sphincter area around the anal canal namely extralevator, sphincteric or intrasphincteric should to be assessed separately in APE specimens only in addition to evaluation of the mesorectal plane of excision. Grading of APE is done similar to TME.

- Grade 1 – incomplete, into muscle/perforation
- Grade 2 – partially complete, apple core muscular wall with no surrounding tissue
- Grade 3 is complete – with substantial surrounding tissue with levators

Similar to rectal cancer, complete mesocolic excision (CME) with central vascular ligation has been popularized for the treatment of colonic tumours in recent years although grading the quality of mesocolic excision is not generally performed.

Specimen fixation

The circumferential resection margin (CRM) around the tumour is inked to enable the subsequent identification of margin involvement. This margin represents the 'bare' area in the connective tissue that is not covered by a serosal surface (non-peritonealised). Low rectal tumours will be completely surrounded by a circumferential non-peritonealised margin. Upper rectal tumours have a non-peritonealised margin posteriorly and laterally and a peritonealised (serosal) surface anteriorly which should not be inked.

After inking the CRM, the specimen has to be opened anteriorly. A segment extending to 1–2 cm above and below the tumour is left intact to avoid confusion over whether the serosal surface or CRM is involved and to facilitate comparison with pre-operative imaging. Place loose, formalin-soaked gauze into the unopened segment of the specimen. Fix for at least 48 hours (preferably 72–96 hours). This is the Quirke technique that is followed in many laboratories which not only preserves the anatomy of the specimen but also facilitates correlation with radiology findings and enables evaluation of completeness of TME by providing cross- sectional slices. However, this technique requires longer fixation times.

In colon cancer resection specimens, the radial margin refers to the soft tissue margin created by surgical resection and not to the serosal surface. The radial margin can be of two types, depending on anatomical location. The ascending and descending colon are covered by peritoneum on the anterior surface, leaving the posterior retroperitoneal aspect (non-peritonealised area) as the radial margin. In the transverse and sigmoid colon and often the caecum, the peritoneum usually completely envelopes these segments thus leaving the vascular ties to be considered as radial margin. A clearance of <1mm defines a positive CRM.

Specimen grossing

After fixation, the specimen is cut through unopened rectum at 2 mm intervals, maintaining their order and orientation(anterior, posterior, right lateral or left lateral with photo

documentation) recording the extent of tumour, the closest distance of tumour to the CRM and any grossly positive nodes (measure the distance of these to the CRM).

Gross description should include the type of operation and nature of specimen, site of tumour, maximum tumour diameter, longitudinal resection margins – proximal/distal, tumour perforation, relation of the tumour to the peritoneal reflection, plane of surgical excision (in AR and APE specimens) and distance of the tumour from the dentate line (APE specimens).

Blocks recommended to be submitted are:3 blocks of tumour in relation to the closest CRM, 2 blocks of tumour in relation to the lumen, 2 blocks of tumour with serosa (where appropriate), all lymph nodes, polyps (if seen), proximal and distal resection margins (ensuring that distal resection margin includes both mucosa and mesorectum).

All of the lymph nodes that have been retrieved from the specimen should be examined histologically. It is important to examine the highest node – for proper Duke's staging. Median number of lymph nodes to be evaluated in rectal carcinoma specimens is 12 lymph nodes. Fat-clearing agents and intra-arterial methylene blue injection of the fresh specimen enables better yield in resection specimens following pre-operative therapy.

Microscopic description

Microscopic description should include histological tumour type, histological differentiation, maximum extent of tumour (pT stage) and maximum distance of extramural spread, resection margins (longitudinal and circumferential margins), lymph node status (number present, number involved, highest lymph node status), vascular invasion, grade of tumour regression following pre-operative (neoadjuvant) therapy, histologically confirmed distant metastatic disease and background abnormalities.

Tumour Regression Grade:

Response to pre-operative therapy can be done by using Dworak Tumour Regression Grade (TRG) system where

- TRG 0 – no regression
- TRG 1 – dominant tumor mass with obvious fibrosis and/or vasculopathy
- TRG 2 – dominant fibrotic changes with few tumor cells or groups (easy to find)
- TRG 3 – very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucus substance
- TRG 4 – no tumor cells, only fibrotic mass (total regression)

It is important to standardize assessment of complete response. If no residual tumour is identified, additional blocks from 3 levels have to be submitted and if still no tumour is identified it indicates complete response.

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Grossing (Surgical Cut-Up) of Radical Prostatectomy Specimen

Dr. Sheba S K Jacob, DNB DCP

Senior Consultant Pathologist
Apollo Main Hospitals, Chennai

Grossing is an art. It requires the knowledge of what needs to be sampled for diagnosis and prognostication and is very crucial for management of the patient. Before grossing it is important to understand the nature and the type of surgery performed on the patient. Robotic radical prostatectomy is performed these days in many centres for prostatic adenocarcinoma.

Prostatectomy (Greek προστάτης *prostátēs*, "prostate" and ἐκτομή*ektomē*, "excision") refers to the surgical removal of all or part of the prostate gland. Although the first prostatectomy was done more than a century ago, laparoscopic prostatectomy was started only in 1991 and this was fine tuned by the introduction of the robotic radical prostatectomy in the current millennium. This led to a drastic change in the approach to prostate cancer where once surgical treatment was a nightmare.

The adult prostate measures about 4 cm transversely at the base, 2 cm antero-posteriorly, and 3 cm vertically. It weighs around 8 gm. It is perforated by the urethra and the ejaculatory ducts. The urethra usually lies along the junction of its anterior and mid third. The ejaculatory ducts pass obliquely downward and forward through the posterior part of the prostate, and open into the prostatic portion of the urethra at the verumontanum.

The base is directed upward, and is applied to the inferior surface of the bladder. The apex is directed downward, and is in contact with the superior fascia of the urogenital diaphragm.

Radical prostatectomy (removal of prostate with seminal vesicles and vas deferens) is usually done for treatment of malignancy after diagnosis by transrectal ultrasound guided (TRUS) biopsy or transurethral resection of prostate (TURP).

Some institutions assess margins by frozen sections, so the prostate is sent in a fresh state without fixation. Fresh or fresh-frozen tissue samples are sometimes preferred for molecular profiling and biobanking.

The tissue is fixed adequately in 10% neutral buffered formalin before grossing. All surgical clips, sutures and catheters are removed prior to fixation. The three dimensions and weight (after removal of the seminal vesicles and vas deferens) are documented. Some studies have shown that men with smaller prostates had high grade cancers, more advanced disease and were at greater risk of progression after radical prostatectomy.

The prostate is painted with ink. Two or more colours may be used to identify the sides. The seminal vesicles are separated from the prostate at the base and submitted. Then the prostate is serially sectioned at 3-4mm intervals from the apex to the base and laid down serially. The apex and the base are further cut into sections parallel to the urethra and submitted entirely. The rest of the sections are submitted entirely if possible. If not atleast the foci with tumour close to the margin and

areas of possible extraprostatic extension (posterior aspect) are submitted. Then the lymph nodes if any are identified, numbered, measured and sampled.

Synoptic style of reporting based on evidence-based checklist, effectively communicates complex cancer-related data, such as radical prostatectomy specimen findings. This kind of organized information is useful not only for individual cases for treatment and prognostication but can also be used for teaching, research, quality monitoring, and system planning. The prostate carcinoma is staged using the (pTNM, AJCC 8th Edition)

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Find Your Voice (Box)-Grossing Techniques of Laryngectomy Specimens

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Grossing is the cornerstone of surgical pathology. Surgical pathology report is an important medical document and gross description is an integral part of surgical pathology report and it is the only document by which gross features can be evaluated once gross specimen is discarded. Gross descriptions are thus a permanent record of all pertinent information regarding a specimen and should be precise, concise and factual. Ability to accurately examine, describe and handle gross specimens is one of the important skills of a surgical pathologist. Based on keen observation and detailed dissection, the pathologist should be able to submit precise sections for microscopy, which will yield important diagnostic and prognostic information which is critical in treatment of patients. Even the most skilled microscopic examination will not be able to compensate for any shortcomings in grossing.

The general principles to be followed in grossing:

- Specimen identification
- Clinical details
- Basic knowledge of the anatomy of the structure to be grossed.
- Orientation of specimen
- Identification of all anatomical landmarks
- Measurement, weight
- Margins
- Identify pathological process/tumor
    - Site
    - Size
    - Structures involved
    - Status of resection margins
    - Lymph nodes in specimen

The pathologist should also have an awareness of the staging of tumor for the anatomical site that they are grossing. This helps to submit all relevant areas from a specimen and avoid missing important areas in the grossing which will influence patient management. In complicated radical surgery specimens, in case there is difficulty in identification of important landmarks it is always helpful to call in the operating surgeon, rather than compromising on your grossing.

Anatomy of Larynx

Larynx is a complex hollow structure. Larynx has nine cartilages, three single and three paired. The single cartilages are the epiglottis, thyroid and cricoid cartilages. The paired ones are

arytenoids, cuneiform and corniculate cartilages. Larynx is subdivided into supraglottis, glottis and sub glottis. The clinical significance of this division is that the lymphatic drainage and hence spread and behavior of tumor from these sub sites is different. The glottis is virtually devoid of lymphatics. However supraglottis has a rich lymphatic supply.

Supraglottis connects larynx to base of tongue. Supraglottis extends from epiglottis up to ventricle. Ventricle is the space/pocket between true and false vocal cords. Supraglottis includes

Epiglottis (suprahyoid and infrahyoid epiglottis)

Aryepiglottic folds containing cuneiform and corniculate cartilages

Arytenoids

False cords (vestibular fold)

Glottis extends from a horizontal plane passing through the lateral margin of the ventricle, at its junction with the superior surface of true vocal cord, to an imaginary horizontal plane 10 mm inferiorly from the lateral margin of the ventricle. It comprises of

True cord (vocal fold)

Anterior and posterior commissures

Subglottis is the lowermost portion of the larynx and extends from lower border of glottis to lower end of cricoid cartilage

Clinical Significance of anatomical subdivision of larynx

Majority of laryngeal cancers are glottic or supraglottic. Subglottic and transglottic cancers are rare. Knowing the location of tumor is of clinical significance because symptoms and nature of spread of tumors and hence surgical management depend on the site of tumor. Supraglottis is rich in lymphatic network which crosses the midline resulting in supraglottic tumors spreading to lymph nodes. Hence supraglottic tumors require bilateral neck dissection. However glottic tumors spread locally with infiltration into adjacent structures. Glottic region is almost devoid of lymphatic and hence spread to lymph nodes is not usual in initial phase. Subglottic tumors also like the glottic tumors spread to adjacent structures first and later only to lymph nodes.

Anatomical features that influence spread of laryngeal cancer

Fenestrations: Fenestrations in epiglottis for vessels, nerves and glands allow spread of laryngeal cancer to lingual side and vice versa.

Anterior Commissure Tendon (Broyles ligament): is a band of fibrous tissue 1 mm in width and 10 mm in length that extends from the vocal ligaments to the midline of the inner surface of the upper thyroid cartilage .Unlike true cord it contains lymphatic and blood vessels, and is devoid of perichondrium at the attachment to the thyroid cartilage, thereby acting as a path for tumor spread from glottis into the adjacent soft tissue or the prelaryngeal (Delphian) lymph node.

Pre-epiglottic space: It is a triangular space bordered by epiglottis posteriorly, thyrohyoid membrane and thyroid cartilage anteriorly and hyoepiglottic ligament superiorly. It contains mostly adipose tissue, but also some elastic fibers, collagen fibers and lymphatic ducts. It is involved in T3

tumors of supraglottic region. Suprahyoid epiglottic tumors are however above the level of this space and spread to base of tongue.

Paraglottic space: It is a potential space deep to ventricle, which extends to pre-epiglottic space superomedially and is bordered by thyroid lamina laterally and pyriform sinus mucosa posteriorly. This space is most commonly involved in advanced glottic cancer. Involvement of this space results in supra and subglottic spread of tumors resulting in transglottic tumors

Treatment of laryngeal cancer

Treatment of laryngeal cancer depends on stage of disease. Early stage cancers are T1, T2 tumors with N0, M0 status. The vocal cords in early stage disease will have normal/impaired mobility but are not fixed. Disease is limited to one subsite in T1 or can involve adjacent subsite in T2.There is no invasion of pre-epiglottic or paraglottic space. There is no involvement of thyroid cartilage. Advanced stage cancers are T3, T4 tumors with nodal or distant metastasis. There is involvement of pre-epiglottic /paraglottic space. There is erosion (T3) or through and through involvement of thyroid cartilage (T4).Also in T4, adjacent structures like thyroid, anterior strap muscles, and deep muscles of tongue can be involved. Radiotherapy or Trans oral laser surgery (TOLS) or partial laryngectomy is done for T1N0, T2N0 cancers of glottic and supraglottic region. Partial laryngectomy can also be done for selected cases of T3 cancers. Near total and total laryngectomies are done for advanced diseases (T3, T4).

Grossing of laryngectomy specimen

A. Orient the specimen

B. Examine the external surface-hyoid bone, thyroid cartilage, strap muscle, thyroid tissue. Look for any tracheostomy stoma and if present, examine the skin of the stoma site .Inspect the external surface thoroughly for any evidence of extra laryngeal spread of tumor.

C. Open the specimen by cutting longitudally in the posterior aspect through cricoid cartilage.

D. Fix the specimen after placing cut end of cotton swab to prop it open. If not propped open, after fixation it will be difficult to open and gross the specimen and properly visualize the inside.

E. Identify location of tumor-glottis, supraglottis, subglottis, pyriform fossa. The laterality and two dimensional measurement of tumor should be recorded and whether the growth is crossing midline or showing transglottic extension. After serial section, the third dimension of tumor is recorded and whether or not there is involvement of thyroid cartilage. Examine pyriform sinuses and pre-epiglottic space

F. Distance of tumor from margins- anterosuperior, right and left lateral, postero-inferior mucosal margins, anterior soft tissue margin and tracheal margin

H. Sections to be submitted

Tumor full thickness including thyroid cartilage after separating into supraglottic, glottic and subglottic area. In case of calcification of cartilage, sections may need decalcification.

Margins: Mucosal margins, tracheal margin, anterior soft tissue margin.

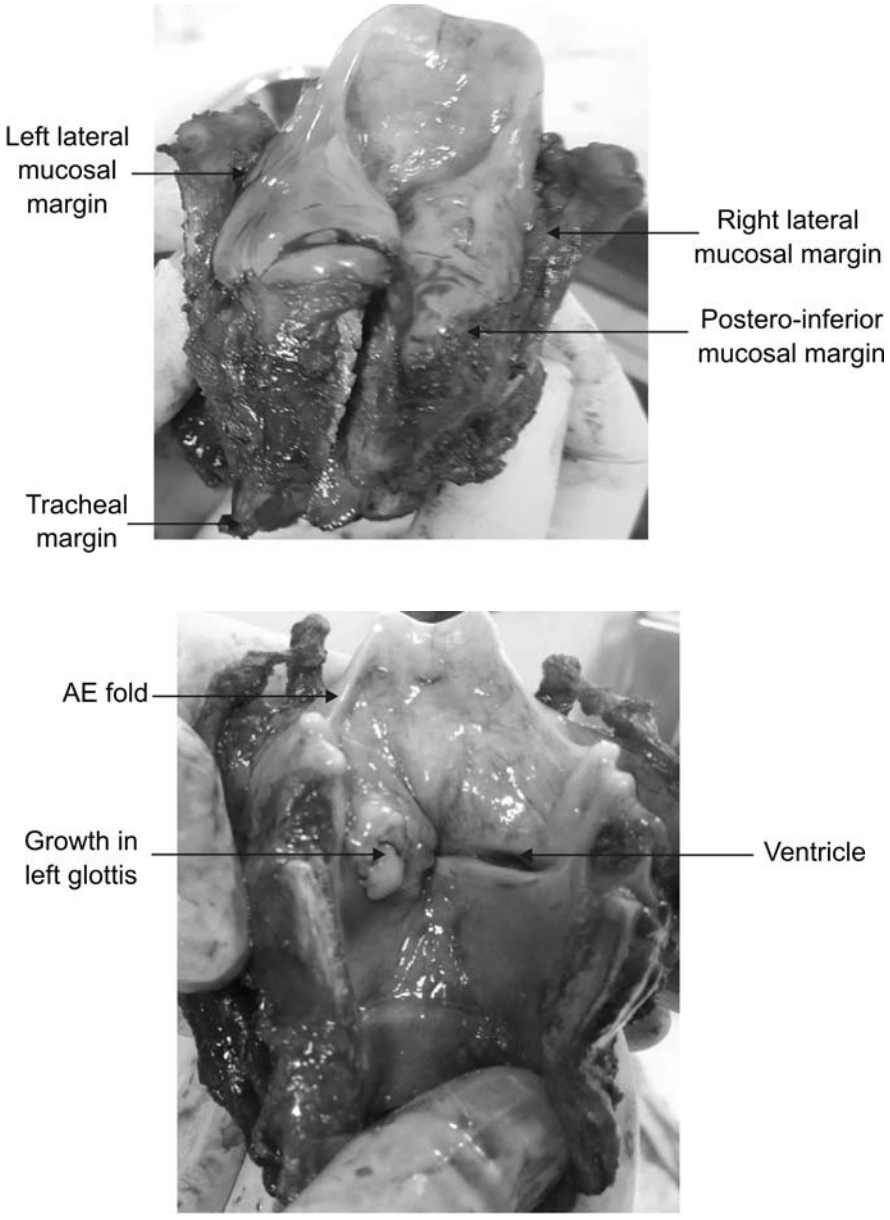
Pyriform fossa

Tracheostomy site

posite glottis, supraglottis and subglottis

Pre-epiglottic space fat

Thyroid



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Grossing of Whipple Resection Specimen

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Pancreaticoduodenectomy (PD) specimen is one of the most complex resection specimens encountered by pathologists. This surgery is performed most often for oncological reasons, such as (pre)cancerous lesions of the pancreas, ampulla, duodenum, and common bile duct. Improvements in surgical techniques and perioperative care have markedly reduced the mortality rates associated with PD. Moreover, the advancements in imaging have made the pancreatic lesions more easily detectable. Hence, unlike in the past, PD specimens are not rare nowadays. The anatomic complexity of the specimen, lack of uniform criteria regarding the margins and surfaces, and variety of dissection methods contribute to the complexity in grossing.

Components

The essential components of Pancreaticoduodenectomy are Pancreatic head, duodenum and common bile duct.

- Classic Whipple: Pancreatic head, duodenum, common bile duct, pylorus and segment of the antrum. Gall bladder and cystic duct are also removed routinely.
- Pylorus-preserving PD**:** The stomach is not included.
- Total PD**:** The body and tail of pancreas are also removed.

Orientation of the specimen

Anatomy

- The head of the pancreas is cradled by C-loop of duodenum.
- Stomach/duodenum form the proximal end and duodenum/ jejunum form the distal end of the specimen.
- Common hepatic duct and cystic duct join to form the common bile duct (CBD).
- Superior mesenteric vein (SMV) together with superior mesenteric artery (SMA) on its left ascends along the anterior surface of uncinate process, hook underneath pancreatic neck and continue posteriorly.
- SMV indents pancreatic surface and form a smooth curvilinear tract.

During surgery

- Pancreatic neck is transected from the body of pancreas at the region of major vessels. The site of transection is directly anterior to the superior mesenteric/portal vein.
- Pancreatic head is dissected from retroperitoneal soft tissue.
- In the posterior-inferior aspect of uncinate process, the pancreatic tissue is dissected out of the retroperitoneal soft tissues. The surgeon sharply dissects the uncinate process from SMA thus producing a rough triangular area on uncinate process. This constitutes the uncinate (retroperitoneal) margin.
- Surgeon retracts SMV off the groove, exposing a curvilinear smooth glistening tract.

- CBD is cut at the level of distal third to half before it enters pancreas.

Margins and surfaces

Manually dissected areas are regarded as margins and those which come off readily and are serosa covered are considered as free surfaces.

1. 1.Anterior pancreatic surface- Peritoneum covered, irregular bulge, typically contains abundant adipose tissue and is convex in appearance.
2. 2.Posterior pancreatic surface-Formed when the pancreas is peeled off the aortocaval groove and is flat and smooth.
3. Pancreatic neck margin/ pancreatic duct margin/distal pancreatic margin- Transected margin created when pancreatic head is divided from pancreatic body and is ovoid, flat with fine granularities of the dense pancreatic tissue.
4. SMV surface- Reflects the tract of the SMV and is a curvilinear groove with smooth and glistening surface.
5. Uncinate margin/ retroperitoneal margin/ SMA margin- Posteroinferior aspect of uncinate process, created by the sharp dissection and is elongated, irregular with lumpy bumpy appearance.
6. 6.CBD margin: If this margin reveals a double duct (goggle appearance), it means the cystic duct has also been included in the specimen. Depending on the type of the operation, not only a segment of cystic duct but the whole gallbladder may be attached to the CBD in which case technically the cut margin would be the hepatic duct margin. A lymph node that is large and often blood-rich is often present adjacent to the CBD.

Opening and sectioning

Open the stomach along the greater curvature of the stomach, continue along the anterior wall of pylorus and open the duodenum through antipancreatic edge.

Examine ampulla from duodenal aspect. Documentation of the findings in the duodenal surface of the ampulla is crucial for ampullary carcinomas and their recent site-specific categorization into 4 categories.

Sections from margins - CBD margin, cystic duct margin, pancreatic neck margin (shaved and submitted en face), uncinate margin (ink the uncinate margin, cut as a 3- to 5-mm-thick slice, and then bread-loaf and submit entirely as a perpendicular margin) , proximal stomach/ duodenal margin, distal duodenal/jejunal margin.

Orange peeling method for lymph node dissection- To ensure proper identification of all lymph nodes, the soft tissue surrounding the pancreatic head is shaved off , which also serve as shaved samples of the so-called “peripancreatic soft tissue” that defines pT3 in the current American Joint Committee on Cancer TNM. Shave off all the free surfaces of the pancreatic head and separate them into 7 arbitrary regions: Peri-CBD, anterior pancreatic, anterior pancreaticoduodenal, superior pancreatic, inferior pancreatic, posterior pancreatic, posterior pancreaticoduodenal.

Sectioning of pancreatic head-

1.Bivalving of pancreas

Probing of CBD and pancreatic duct followed by bivalving of pancreatic head along the plane that goes through both the ducts and ampulla. After bi-sectioning, the two halves can be serially sliced in three different planes: either by axial slicing, multi-valving (serial slicing along each half of the pancreas), or bread loafing (parallel to the neck of the pancreas).

Advantages

- Bi-sectioning of the pancreatic head is the most revealing approach for determination of the primary site and extend of the tumor and for the evaluation of the compartments of the ampulla.
- This method allows the assessment of distribution of tumors in relation to the ducts. Bi-sectioning allows much more accurate documentation of cystic tumors and their relationship to the ducts. After successful bi-sectioning, the main pancreatic duct can be completely evaluated, inked if appropriate and a distinction can be made between the CBD, main pancreatic duct, and side branches, facilitating diagnosis of main and/or side branch IPMN.

Disadvantages

- Difficult to perform.
- Assessment of circumferential margins difficult.

2.Axial sectioning method

Specimen is serially sliced perpendicular to the long axis of the duodenum over its entire craniocaudal length.

Advantages

- Easy to perform.
- The circumferential margins can be assessed easily.
- Good for documentation of the peri-Oddi spread of the intra-ampullary tumors.

Disadvantages

- The optimal plane of the section for capturing the ampullary region cannot be ascertained beforehand. The ampullary region frequently happens to fall between sections, hindering accurate assessment of tumor origin. Determining the precise tumor origin may be especially relevant for ampullary tumors.
- In case of an intraductal papillary mucinous neoplasm (IPMN), axial slicing does not allow to distinguish between lesions originating from the main pancreatic duct or side branches.

Tumour-Description and sections: Identify the epicentre of the tumor. Note its size, appearance, extent, relation to anatomic sites and distance from the resection margins and surfaces. Sections should include tumor with ampulla, with CBD, with duodenum and with pancreatic head.

Conclusion

PD specimens are fairly complex. Proper orientation, dissection, and sampling are crucial for the accurate diagnosis, classification, and staging of tumors.

The important steps in grossing – 1.Orient the specimen, 2. Identify various components, margins and surfaces, 3. Take measurements, 4.Examine the external surfaces and paint the surfaces, 5. Open the stomach and duodenum, 6.Record the findings in the ampullary region and duodenum, 7. Take sections from margins, 8.Section the pancreatic head (bivalving or axial section), 9. Identify the tumor, describe cut section of the tumor, its relation to adjacent structures and margins,10. Describe adjacent structures, 11.Dissect the lymph nodes, 12. Take sections from the tumor, surfaces, adjacent duodenum, pancreas, CBD and gall bladder.

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Neoplasms of Small and Large Intestine

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Part-1 Lymphomas of Intestines

Classification and immunophenotyping of GI Lymphomas

Like all earlier classifications, the WHO classification recognizes the fundamental distinction between Hodgkin lymphomas and Non-Hodgkin lymphomas (NHL) with basic differences in the biology of these diseases. Hodgkin lymphoma in extranodal sites, including GIT, is exceedingly rare. Non-Hodgkin Lymphomas comprise several entities broadly classified as B-cell or T-cell processes, with each group being further sub-classified as precursor cell or mature cell lymphomas. Many lymphoid neoplasms can present either as a mass lesion (lymphoma) or as circulating cells (leukemia) in different patients or in the same patient over the course of the disease. In the context of primary GIT disease, a mass lesion ("lymphoma") will be expected. B-cell lymphomas constitute the vast majority of lymphomas in the Western hemisphere (>80%) and at a lower frequency in the far East (about 60%), with Indian incidence being intermediate. B-cell lymphomas generally respond better to current chemotherapy than T-cell lymphomas and have a better prognosis. The precursor B-cell or T-cell lymphoblastic lymphomas, Burkitt lymphoma, and large B-cell lymphomas are aggressive and highly proliferative while those with small cells are usually indolent. There are, however, important exceptions such as mantle cell lymphoma (MCL) and T-cell lymphomas, in which the behavior does not correlate with the cell size. In addition to characteristic cell morphology, many lymphomas also demonstrate fairly typical architectural features which are useful in diagnosis. Specific cytogenetic abnormalities are seen in many lymphomas and appear to influence their behavior to a great extent.

I. B-Cell Lymphomas

A. Low grade B-cell lymphoma of MALT type.
B. High grade B-cell lymphoma of MALT type (Diffuse Large B Cell lymphoma).
C. Mantle cell lymphoma
D. AIDS-Related lymphomas.
E. Burkitt Lymphoma
F. Post-transplant lymphoproliferative disorders (PTLDs).
G. Intestinal Follicular Lymphoma
H. Other B Cell Lymphomas

II. T-Cell Lymphomas

A. Enteropathy-associated T-cell lymphoma (EATL).
B. Adult Tcell Leulemia/lymphoma
C. Extranodal Natural Killer/T cell lymphoma

Diagnostic trouble spots in gastrointestinal lymphomas

1. Distinguishing between reactive lymphoid hyperplasia and small cell lymphomas.
2. Distinguishing between low grade MALT lymphoma and other small cell lymphomas.
3. Mistaking intermediate or large lymphoid cells for small cells due to poor fixation.
4. Mistaking large cell lymphomas with other large cell malignancies: Large cell lymphoma of the gastrointestinal may resemble poorly differentiated carcinomas, melanomas, and other non-lymphoid neoplasms in the gut to the extent that it may be considered prudent to perform at least a limited panel of paraffin section immunoperoxidase stains (such as cytokeratin, LCA, and S-100) to properly categorize poorly differentiated large cell malignancies unless there is unequivocal histologic evidence of differentiation (such as gland formation in adenocarcinoma). Combining AE1/AE3 and CAM 5.2 keratins produces a cocktail which will react with virtually all epithelial tumors, and combining CD45RB (leukocyte common antigen, or LCA) with a the pan-B cell marker CD20 and pan-T cell marker CD43 can similarly produce a cocktail capable of detecting even anaplastic lymphomas which may loose LCA expression. Keep in mind that CD43 is also a sensitive marker for myeloid differentiation, and consideration should be given to the possibility of an extramedullary myeloid tumor (granulocytic sarcoma) before diagnosing a T-cell lymphoma on the basis of CD43 expression alone. For poorly differentiated tumors with a "null cell" phenotype in initial screening with a panel such as keratin/LCA/S-100, consider anaplastic lymphoma (confirm with specific B and T cell markers), plasmacytoma/myeloma (confirm with plasma cell markers such as CD38 and CD56 as well as the B-cell marker CD79a, which stains most plasma cells), and extramedullary myeloid tumor (confirm with myeloperoxidase or CAE). Note that disaggregated gastric foveolar cells in gastric MALTomas may resemble infiltrating signet ring cells of a gastric adenocarcinoma, but can generally be distinguished by their lack of significant cytologic atypia, their occurrence only in areas of dense lymphoid infiltrate, their localization to the superficial lamina propria, and other diagnostic features of MALT lymphoma present elsewhere in the specimen. Immunohistochemistry must always be seen as an adjunct to diagnosis, however, and never as a substitute for adequate clinical history, good specimen fixation, and good routine H&E stains.

Part-2 Gastrointestinal Stromal Tumours of Intestines

Pathologic features of GIST

Most GISTs are well-circumscribed lesions arising within the wall of the intestine. They typically exhibit a tan-white, fleshy cut-surface with foci of cystic degeneration, hemorrhage, or necrosis. Large tumors may show ulceration of the overlying mucosa. Microscopically, most GISTs demonstrate 3 main histologic subtypes: spindle cell type (most common), epithelioid type, and mixed spindle and epithelioid type. In general, GISTs are characterized by a uniform, monotonous appearance with minimal cytologic atypia or mitotic activity. Nuclear pleomorphism is occasionally evident in a GIST and, when present, is often admixed with the more conventional cytologic features. Spindle cell GISTs account for nearly 70% of cases and are composed of cells arranged in

short fascicles and whorls. The stroma may exhibit areas of myxoid change or, rarely, osseous metaplasia. The individual cells reveal ill-defined cell borders with ovoid nuclei, fine nuclear chromatin, and inconspicuous nucleoli. The cytoplasm has a pale, eosinophilic, and fibrillary quality. Many gastric spindle cell GISTs show extensive paranuclear vacuolization, originally thought to be a diagnostic feature of smooth muscle tumors. The degree of paranuclear vacuolization, however, is much more pronounced in GISTs than it is in smooth muscle tumors. Occasionally, nuclear palisading, similar to Antoni A areas of aschwannoma, are encountered Other schwannoma-like features, such as microcystic degeneration and stromal lymphocytes, may also be seen. Tumors arising in the small bowel are often associated with a peculiar stromal change composed of brightly eosinophilic, hyaline, or fibrillary structures known as *skenoid fibers*.Epithelioid GISTs account for approximately 20% of cases and are characterized by rounded cells arranged in nests or sheets, with variably eosinophilic to clear cytoplasm and vesicular nuclei. Approximately 10% of GISTs show a combination of both epithelioid and spindle cells.Rare examples of GISTs that show abrupt transformation from conventional KIT-positive tumor cells to KIT-negative cells with marked anaplasia have been documented by Antonescu et al. These tumors have been termed *dedifferentiated GISTs*. Of the 4 patients documented by Antonescu, 3 (75%) did not have either a *KIT* or *PDGFRA* mutation in either the conventional or dedifferentiated component, whereas 1 (25%) had a *KIT* exon 11 deletion in both components. Gene copy number abnormalities, either because of loss of heterozygosity or low-level *KIT* amplification, were the most common alterations found in the dedifferentiated component.

Immunohistochemistry of GIST

Strong and diffuse immunoreactivity for KIT (CD117) is seen in about 95% of cases. The high sensitivity and specificity of KIT is a useful marker in differentiating GIST from other mesenchymal tumors of the gastrointestinal tract. Most tumors demonstrate a cytoplasmic staining pattern. In some tumors, a coexisting, dotlike, or Golgi staining pattern can also be seen. Less commonly, a membranous staining pattern is observed. Because KIT positivity has significant therapeutic implications, it is critical to titrate each new batch of KIT antibody with appropriate positive and negative controls. Fortunately, mast cells in the adjacent nonneoplastic tissue serve as an excellent internal control for evaluating the quality of the KIT staining. Another common marker that is not as sensitive or specific for GIST is CD34. It is expressed in nearly 80% of gastric GISTs, 50% of small intestinal GISTs, and in 95% of GISTs arising in the esophagus and rectum.Immunoreactivity for smooth muscle actin is found in nearly 30% to 40% of GISTs. Caution is advised when interpreting smooth muscle markers (smooth muscle actin and desmin) because entrapped smooth muscle cells from adjacent muscularispropria or muscularis mucosae may be misinterpreted as positive staining within the tumor. This phenomenon usually occurs toward the periphery of the tumor. Variable and weak immunopositivity is also seen with other markers, such as h-caldesmon, S100, desmin, and cytokeratins 8 and 18. Of note, focal desmin staining is more common in epithelioid GISTs arising in the stomach.

Part-3 Neuroendocrine Tumours

In 2010, the WHO launched a new classification system for NENs of the digestive tract, which categorizes them as follows: NET G1, NET G2, NEC (large- or small-cell type), and MANEC. NET

can be equated with carcinoid. "G3-NET" has been used as the category for NEC but is not advised, since NETs are by definition well-differentiated. This current WHO classification classifies NENs based only on the Ki-67 index and the evaluation of mitoses in histological material. This classification system is based on the grading system formerly proposed by the European Neuroendocrine Tumor Society (ENETS). According to the current WHO and ENETS grading systems, G1-NET is designated by a mitotic count of <2 per 2 mm^2 (10 high power fields [HPF], 40× magnification) and/or ≤2% Ki-67 index; G2-NET by a mitotic count of 2–20 per 2 mm^2 and/or 3–20% Ki-67 index; G3-NET by mitotic count of >20 per 2 mm^2 and/or >20% Ki-67 index. The survival analysis for foregut NENs (gastric, duodenal, or pancreatic), according to the ENETS-WHO 2010 grading system, showed that survival for patients who had G3 tumors was significantly poorer than that for patients who had G1 and G2 tumors (G1 vs. G3 and G2 vs. G3, $P < 0.01$). La Rosa et al. proposed a new global histologic grading system that combined the histologic patterns, based on the WHO 2000 classification, and the ENETS-WHO 2010 proliferative grading system. This global grading system improved tumor prognostic stratification ($P < 0.001$; global grade 1 vs. global grade 2, $P = 0.007$; global grade 1 vs. global grade 3, $P < 0.001$; global grade 2 vs. global grade 3, $P = 0.001$). The WHO classification requires scanning of at least 50 fields (at 40× magnification) in the areas with the highest mitotic density for the evaluation of the mitotic index in 10 HPF, while ENETS requires at least 40 fields. According to the ENETS grading system, 10 HPF corresponds to 2 mm^2 . However, the size of the HPF differs according to the field number of the eyepiece of each microscope. In breast carcinoma, the adjustment criteria for mitotic count according to the field number of each microscope eyepiece have been proposed. To our knowledge, adjustment criteria for mitotic count according to eyepiece field number for NENs have not been proposed. Accurate grading of NENs might require the development of adjustment criteria for determining mitotic count. The Ki-67 index is calculated as the percentage of Ki-67–positive tumor cells in the areas of the highest density of Ki-67–positive cells, otherwise known as "hot spots." To evaluate the Ki-67 index, the WHO classification requires 500–2000 tumor cells, while ENETS requires 2000 tumor cells. Careful selection of hot spots is crucial for accurate evaluation of the Ki-67 index. In some cases, Ki-67 staining on different and multiple slices could be useful for accurate Ki-67 index evaluation.

The new changes brought out in 2017

Table 1. WHO classifications 2010 and 2017.

WHO Classification 2010			**WHO Classification 2017**		
Well Differentiated NET's	**Ki67 index**	**Mitotic index**	**Well differentiated NET's**	**Ki67 index**	**Mitotic index**
NET G1	<=2%	<2 /10 HPF	NET G1	<3%	<2 /10 HPF
NET G2	3-20%	2-20/10 HPF	NET G2	3-20%	2-20/10 HPF
			NET G3	>20%	>20/10 HPF
poorly differentiated NEC's			**poorly differentiated NEC's**		
NEC	>20%	>2 /10 HPF	NEC	>20%	>2 /10 HPF

Part-4 Colon Carcinoma

With the rapid therapeutic advancement in the era of personalized medicine, the role of pathologists in the management of patients with colorectal carcinoma has greatly expanded from traditional morphologists to clinical consultants for gastroenterologists, colorectal surgeons, oncologists and medical geneticists. In addition to providing accurate histopathologic diagnosis, pathologists are responsible for accurately assessing pathologic staging, analyzing surgical margins, searching for prognostic parameters that are not included in the staging such as lymphovascular and perineural invasion, and assessing therapeutic effect in patients who have received neoadjavant therapy. Pathologists also play a central role in analyzing histologic features of the tumors that are suggestive of microsatellite instability (MSI), selecting appropriate tissue sections for MSI testing and mutation analysis for KRAS and BRAF, and interpreting the results of these important therapeutic and prognostic tests.

More than 90% of colorectal carcinomas are adenocarcinomas originating from epithelial cells of the colorectal mucosa. Other rare types of colorectal carcinomas include neuroendocrine, squamous cell, adenosquamous, spindle cell and undifferentiated carcinomas. Conventional adenocarcinoma is characterized by glandular formation, which is the basis for histologic tumor grading. In well differentiated adenocarcinoma >95% of the tumor is gland forming. Moderately differentiated adenocarcinoma shows 50-95% gland formation. Poorly differentiated adenocarcinoma is mostly solid with <50% gland formation. In practice, most colorectal adenocarcinomas (~70%) are diagnosed as moderately differentiated. Well and poorly differentiated carcinomas account for 10% and 20%, respectively.

The most widely used immunohistochemical markers for colorectal adenocarcinoma are cytokeratin (CK) 20, CK7 and CDX2. The most common immunophenotype of colorectal adenocarcinoma is positivity for CK20 and negativity for CK7, which is a relatively specific staining pattern for colorectal origin. However, up to 20% of the tumors may exhibit a CK7-positive/CK20 negative or CK7-negative/CK20-negative staining pattern. It has been suggested that reduced or absent CK20 expression in colorectal carcinoma is associated with MSI-H. CDX2 is a marker of enteric differentiation and is positive in >90% of colorectal adenocarcinomas . However, CDX2 can be positive in any carcinoma that shows enteric differentiation, and thus is not entirely colorectal-specific. Interestingly, medullary carcinomas of the colorectum are frequently CK20-negative and CDX2-negative, in line with the concept of MSI.

Colorectal cancer is a heterogeneous group of diseases with distinctive genetic and epigenetic background. In order to improve clinical management and better predict patient outcome, attempts have been made to classify colorectal cancers based on location, histology, etiologic factors, and molecular mechanisms of tumorigenesis. As early as in the 1980's, it has been recognized that cancers arising in the proximal colon and distal colon involve different genetic mechanisms. For instance, Lynch syndrome preferentially involves the proximal colon whereas FAP tends to show more polyps in the left colon. These familial forms of colorectal cancer have served as prototypes for understanding distinct molecular mechanisms of tumorigenesis. As discussed earlier, Lynch syndrome results from loss of function in one of the MMR genes and follows the MSI pathway ("mutator" pathway). In contrast, FAP arises in patient with inherited mutations in the APC gene,

which has been the center of the original Fearon-Vogelstein model of colorectal tumorigenesisthat forms the basis of chromosomal instability (CIN) pathway ("suppressor" pathway).

Both MSI and CIN pathways describe colorectal cancer pathogenesis based on genetic abnormities that lead to loss of function of tumor suppressor genes and/or gain of function of oncogenes. In the last decade, epigenetic instability has gained considerable attention and is now believed to be implicated in the pathogenesis of almost one third of colorectal cancers. In addition to DNA sequence and structure, gene expression is controlled by a number of epigenetic modifications that include DNA methylation, histone alterations and chromatin remodeling. One of the best characterized epigenetic modifications associated with colorectal tumorigenesis is silencing of genes (tumor suppressor and/or MMR genes) through hypermethylation of their promoter regions. Although it was debated whether the phenomenon of epigenetic instability represents an adaptive cellular mechanism during carcinogenesis aimed to abort cellular proliferation, a secondary alteration to yet unidentified genetic mutations, a phenomenon expected to occur during tumor cell senescence, or simply an artifact, transcriptional silencing of certain genes by hypermethylation has undoubtedly shown to result in tumor development. In particular, promoter hypermethylation of the MLH1, one of the MMR genes, is demonstrated in the majority of sporadic colorectal cancers with a MSI phenotype. Since many genes are rich in cytosine and guanine dinucleotides (CpG islands) in their promoters, methylation of the cytosine residues in CpG islands is a common phenomenon, which leads to alterations of the chromosomal structure and suppression of gene expression. Colorectal cancers with CpG island methylator phenotype (CIMP) are characterized by epigenetic loss of function of tumor suppressor genes without mutations.

Interpretation of Liver Biopsies

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Introduction

The relationship between the liver biopsy and the science and art of medicine is unique. The foundation of many, if not most, liver diseases is based on the evaluation of liver biopsy.

Liver biopsy remains the gold standard in the evaluation of patients with liver disease, particularly chronic liver diseases. With current laboratory and imaging studies liver biopsy is resorted to only when the diagnosis is unclear despite thorough clinical and non-invasive investigation. However in a given clinical situation the liver biopsy, if adequate and assessed properly, invariably has an important bearing in the overall diagnosis and management of liver diseases.

In general, the uses of liver biopsy material are as follows:

1. Making or confirming a diagnosis
2. Assessing the severity of liver damage
3. Assessing the prognosis in a given case
4. Monitoring response to therapy

Indications for Liver Biopsies

Note: A thorough noninvasive investigation *must* have been carried out before performing a liver biopsy.

1. Evaluation, Grading & Staging of Chronic Hepatitis – Cirrhosis
2. Evaluation of the cause of abnormal liver function test
3. Identification and assessment of alcoholic liver disease
4. Recognition of systemic inflammatory or Granulomatous disease
5. Evaluation of fevers of unknown origin
6. Evaluation of the type and extent of liver injury caused by therapeutic drugs
7. Detection of intrahepatic cholestasis
8. Diagnosis of multisystem infiltrative diseases
9. Evaluation of cholestatic liver disease
10. Diagnosis of metabolic liver disease
11. Screening of relatives of patients with familial disease
12. Evaluation of effectiveness of therapy
13. Evaluation of status of liver following liver transplantation
14. Diagnosis of neoplastic diseases
15. Provision of tissue for culture and molecular biology tests

Procedure

Methods:

The methods in use for sampling the liver for histopathological examination are, broadly:

1. Needle biopsy
   i. Percutaneous (most common)
      a. "Blind"
      b. Ultrasound- or CT-guided
   ii. Transjugular (used in patients with ascites or bleeding diatheses)
2. Open biopsy
   i. At surgery
      1. Laparoscopic biopsies
      2. Wedge biopsy
      3. Resection specimen
   ii. At transplantation

   Explants (native liver of the recipient)

Percutaneous liver biopsy inadults and children are by far the most common method of liver biopsies. Transjugular biopsy avoids puncture of the peritoneum and the liver capsule. The technique may be used when coagulation parameters are too far deranged to allow a safe percutaneous biopsy.

In the normal liver, the capsular fibrous tissue dips into the subcapsular parenchyma for a variable distance (around 5mm generally). It is therefore recommended that wedge biopsies be taken in such a manner that deep tissue is included.

Needles:

1) Aspiration-type Needles: Menghini Needle and its variants Klatskin needles, Jamshidi needle

2) Cutting-type Needles: Vim Silverman needle, Trucut needle

Processing A Liver Biopsy

Avoid squeezing the specimen with forceps. The resultant artifacts render interpretation of morphology impossible. In general a core of tissue adequately fixed in formalin in 10% neutral buffered formalin for H&E and other stains (minimum of 2.5 cm in length) is all that is necessary for most indications.

In special circumstances such as in the diagnosis of metabolic liver disease or obscure infections other examinations may be necessary. *Always insist on discussing with clinical colleagues regarding how the biopsy should be sent including the appropriate fixative to be used based on the likely tests that are necessary inturn depending on the clinical differential diagnosis*. Very often this important step is overlooked.

Special Stains That May be used on Liver Biopsy Material

(* = Routine stains)

1. PAS: Stains a wide range of glycoproteins; very sensitive but extremely non-specific.
2. *PAS with diastase: Specific for glycogen if diastase sensitive; useful for identifying diastase-resistant α-1 antitrypsin globules and ceroid pigment.
3. *Reticulin: Outlines the reticulin framework of the liver.
4. *Masson's trichrome: Identifies collagen.
5. Prussian blue: Stains hemosiderin.
6. Shikata's Orcein: Stains elastin fibers, HbsAg and copper-associated protein.
7. Rhodanine (not to be confused with Rhoda*m*ine used for detection of the tubercle bacillus) or rubeanic acid: Stains copper
8. Hall: Stains bile
9. Fontana Masson: Stains melanin.
10. PTAH: Stains fibrin and mitochondria.
11. CR/CV: Identifies Amyloid; permanganate resistance favors AL over AA Amyloid
12. AFB: For tubercle bacilli, schistosome eggs and hooklets of hydatid scolices.
13. Warthin-Starry: For spirochetes.
14. Giemsa: For LD bodies.
15. Oil Red O: Stains lipid.
16. Schultz modification of the Lieberman-Burchard reaction: Stains cholesterol.
17. Toluidine blue: Stains mast cells metachromatically (different from the color of the stain).

Immunohistochemistry

Antibodies raised against the following antigens can be used to determine whether the antigen is present in the tissue being studied (only an indicative list):

1. HBsAg (cytoplasmic staining)
2. HBcAg (nuclear staining)
3. HCV (problematic due to antigenic variation in the Hepatitis C virus)
4. HDV
5. Herpes viruses
6. Adenovirus
7. CMV
8. HIV [19]
9. Ubiquitin: Mallory bodies
10. Cytokeratins ("CK"s)
    a. Pan-CK: Mallory bodies
    b. 8, 18: Hepatocytes

c. 8, 18, 7, 19: Bile duct epithelium
d. Polyclonal CEA: Bile canaliculi
e. Other cytokeratins in neoplastic diseases

11. HepPar 1
12. Alpha 1 antitrypsin

Electron Microscopy

Can be helpful in the following circumstances:

1. Metabolic Diseases: Alpha -1 Antitrypsin Disease, Gauchers Disease etc.
2. Drug-induced injury
3. Viruses: May identify the causal virus
4. Differentiation of Dubin-Johnson pigment from lipofuscin
5. Congenital Cholestatic Diseases such a Progressive Familial Intrahepatic Cholestasis

Fluorescence Microscopy

Fluorescent microscopy is not routinely used in liver biopsy interpretation, but its use has been described to detect autofluorescence in erythropoietic protoporphyria and porphyria cutanea tarda.

Polarizing Microscopy

Polarizing microscopy is another non-routine technique that has been described to be useful in detecting the following substances:

1. Talc
2. Amyloid
3. Malaria pigment
4. Uroporphyrin

Examination of the Liver Biopsy

While interpreting the liver biopsy it must be appreciated that the liver has a limited array of histological changes to a wide variety of diseases. The major reaction patterns that are generally seen are

Hepatocellular damage:

Hepatitis

Cholestasis

Pigment deposition

Storage of material within cells

Hemorrhage and congestion

Tumours

Diagnostic Categories In Hepatic Histopathology

The major *disease entities* for which liver biopsies are performed are:

1. Neonatal cholestasis (neonatal hepatitis syndromes)
2. Chronic hepatitis
3. Acute viral hepatitis versus drug-induced hepatitis
4. Metabolic disorders
5. Cirrhosis
6. Tumors
7. Pyrexia of unknown origin (PUO)
8. Hepatosplenomegaly of unknown origin
9. Post-transplant evaluation
10. Autoimmune hepatitis
11. Liver abscesses
12. Reye's syndrome
13. Congenital hepatic fibrosis and infantile polycystic kidney/liver disease
14. Budd-Chiari syndrome

The hyperbilirubinemias

Broad Categories of Differential Diagnoses of some common lesions

(Adapted from Snover DC Non-neoplastic liver disease In Sternberg SS Diagnostic Surgical Pathology 2nd Ed. New York's Raven Press).

The following is a list of common differential diagnoses found on examination of a liver biopsy.

Lobular mononuclear infiltration with or without necrosis

Acute Hepatitis

Autoimmune hepatitis

Primary biliary cirrhosis

Lymphoma/Leukemia

Non specific reactive hepatitis

Lobular Lymphocyte/Plasma Cell Infiltration with or without Hepatocellular Degeneration

Acute viral hepatitis

Hepatitis A

Hepatitis B (with or without delta)

Hepatitis C

Other hepatitis

Non-A, Non-B, Non C

Cytomegalovirus (CMV)

Epstein-Barr virus (EBV)

Possibly others

Acute drug-induced hepatitis

Autoimmune (Lupoid) hepatitis

Chronic lobular hepatitis

Primary biliary cirrhosis

Leukemia/lymphoma

Nonspecific reactive hepatitis

Lobular Polymorphonuclear Cell Infiltrate with or without Hepatocellular Degeneration

Surgical hepatitis

Sepsis without direct

Infection of the liver

Direct hepatic bacterial or fungal infection

Viral infections (CMV, rarely herpes) in the immunocompromixed host

Alcoholic hepatitis

Non-alcoholic steatohepatitis

Drug reaction

Jejunoileal bypass

Portal Polymorphonuclear Cell Infiltrate with Minimal Lobular Inflammation or Degeneration

Acute biliary obstruction

Ascending cholangitis

Sepsis, including toxic shock syndrome

Drug reactions

Hyperalimentation

Cholangiolytic viral hepatitis

Primary biliary cirrhosis

Confluent Hepatocellular Necrosis with Minimal Inflammation

Acute viral infection

Cytomegalovirus

Herpes simplex

Varicella zoster

Adenovirus

Echovirus

Massive hepatic necrosis

Due to

Hepatitis A

Hepatitis B

Hepatitis delta

Hepatitis C

Other hepatitis Non-A, Non-B

Drug reaction

Ischemia

Toxic drug reaction

Trauma

Artifact of poor fixation

Solitary necrotic nodule

Necrotic tumor

Portal Lymphocyte and/or Plasma Cell Infiltrate with Minimal Lobular Inflammation or Degeneration

Resolving acute hepatitis

Chronic persistent hepatitis

Chronic active hepatitis

Primary biliary cirrhosis

Primary sclerosing cholangitis

Wilson's disease

Chronic low grade or intermittent biliary obstruction

Liver adjacent to a mass lesion

Malignant infiltrate, particularly lymphoma

Portal Eosinophil Infiltrate (Not necessarily Predominant but Easily Identifiable)

Drug reaction

Primary biliary cirrhosis

Primary sclerosing cholangitis

Parasitic infestation

Some malignancies, especially Hodgkin's disease and mastocytosis

Viral infection

Rickettsial infection (Q-fever)

Fungal infection

Granulomatous Inflammation

Mycobacterial infection Bacterial infection such as Typhoid Primary biliary cirrhosis

Sarcoidosis

Idiopathic granulomatosis

Histiocytosis X

Drug reaction

Foreign material
Lipogranuloma
Crohn's disease
Malignancy such as Hodgkins Disease
Chronic Granulomatous disease

Fibrosis

Cirrhosis
Non-cirrhotic bridging fibrosis
Congenital hepatic fibrosis
Hepatoportal sclerosis
Sclerosing hyaline necrosis
Pericentral sclerosis
Chronic outflow obstruction
Heart failure
Budd Chiari syndrome
Venocclusive disease
Focal biliary fibrosis of cystic fibrosis
Fibrolamellar hepatoma
Sclerosing hepatocellular carcinoma
Cholangiocarcinoma
Metastatic carcinoma
Congenital syphilis
Amyloid
Diabetes mellitus
Crohn's disease

Cholestasis in Relative Isolation

Postoperative cholestasis
Sepsis
Drugs
Early bile duct obstruction
Liver adjacent to mass lesions
Benign recurrent familial cholestasis
Cholestasis of pregnancy
Metabolic diseases

Congestion or Hemorrhage, often in Association with Sinusoidal Dilatation

Outflow obstruction
Budd-Chiari syndrome
Venocclusive disease
Heart failure
Portal vein or hepatic arterial obstruction
Infarction
Drug reaction
Peliosis hepatis
Nodular regenerative hyerplasia
Hepatoportal sclerosis
Liver adjacent to a mass lesion
Neoplasms

Sinusoidal Dilatation

Artifact
Drug reaction
Hepatic venous outflow obstruction
Low grade hepatic blood inflow obstruction
Peliosis
Nodular regenerative hyperplasia
Mass lesion

Pigments in the Liver

Bile
Lipofuscin
Iron
Formalin
Dubin-Johnson pigment
Other exogenous pigments

Intranuclear Inclusions

Glycogenated nuclei
Prominent nucleoli
Cytomegalovirus
Herpes simplex or varicella zoster
Adenovirus

Intracytoplasmic Inclusions

Ground glass cells
Hepatitis B

Induction of Endoplasmic Reticulum
Fibrinogen
Drug associated inclusions
Lafora's disease
Microvesicular fat
Mallory hyaline
Giant mitochondria
Alpha-1-antitrypsin
Amylopectin
Cytoplasmic serum protein hyaline inclusions
Endoplasmic storage disease of liver
Hepatic oncocytes

Extracellular Infiltrates

Amyloid
Collagen
Fibrin thrombi

Unusual Cells in the Liver

Megakaryocytes
Extramedullary hematopoiesis
Metastatic tumor
Storage tumor
Storage cells
Adipocytes

The Nearly Normal Biopsy

Storage or metabolic diseases
Nodular regenerative hyperplasia
Hepatoportal sclerosis
Hepatoportal sclerosis
Carrier state of viral hepatitis
Drug reactions

Absence of Normal Structures

Central veins
Portal tracts
Portal veins (in the presence of portal tracts)
Interlobular bile ducts
Sinusoids
Hepatocytes

Bile Duct and Ductular Proliferation

Large duct obstruction
Sepsis
Congenital hepatic fibrosis
Fibrosis or cirrhosis of any etiology
Meyenberg complex (bile duct hamkartoma)
Bile duct adenoma
Focal nodular hyperplasia
Cholangiocarcinoma

Further Reading

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Effective Management of Laboratory Errors

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Creating an environment of minimal error is what every laboratory professional strives to achieve. "Zero Error" is a myth that evades even the best of laboratories. Good Laboratory Practice – the foundation for minimal error comes out of the melting pot of setting good processes, management of nonconformities, risk management and error management. As defined by ISO 9000:2005, a process denotes a set of inter-related activities that transform inputs to outputs. In the laboratory context, we need to define the sequence of events that cover the entire spectrum of activities from pre-examination through examination to post examination.Developing process flow charts have been found to be very effective means of ensuring that everyone in the does the same activity in the same manner bringing in consistency and hence reducing scope for error.

Non-conformities and errors are integral parts of any laboratory system. Though these two terms appear to mean the same there are subtle differences between the two. Defined in the simplest manner, a non-conformity occurs when one does not do what is to be done whereas an error occurs when one does what is not supposed to be done. A non-conformity unlike error does not necessarily result in harm to the patient provided it is detected and checked before it results in an error.

The concept of risk in healthcare in general has been in existence since two decades. Risk indicates the chance of something that may impact the objectives or outcome – which in our case would be an accurate test report. Risk management involves detailed review of new as well as existing processes with a view of picking out potential nonconformities. In other words, it involves looking at a process while repeatedly asking the question "What can go wrong". Once this is done, the data collected should be stratified based on frequency of occurrence and frequency of occurrence. This gives the laboratory an opportunity to address the more serious and frequent non-conformities / potential nonconformities first.

The talk aims to elaborate on the above as some ways by which we can ensure a good night's sleep to our laboratory professionals.

Avatars of Adenocarcinoma

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Lung cancer is the leading cause of cancer death in both men and women worldwide and are said to have distinct variations on the basis of race, ethnicity and region. These variations have additionally lead to variable, unique clinical characteristics, histopathological and molecular heterogeneity of lung cancer patients. It is categorized into two main histological groups: small cell lung carcinoma (SCLC, 15% of all lung cancers) and non-SCLC (NSCLC, 85% of all lung cancers). NSCLCs are generally subcategorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Among these, adenocarcinomas are now the most common subtype. The 2015 WHO classification divides adenocarcinomas into adenocarcinoma*in situ* (AIS, preinvasive lesion), minimally invasive adenocarcinoma (MIA), or overtly invasive adenocarcinoma.AISis defined as an adenocarcinoma comprising a lepidic pattern with a diameter of ≤3 cm.Minimally invasive adenocarcinoma is defined as an adeno-carcinoma with a diameter of ≤3 cm and an invasion size of ≤5 mm but devoid of lymphovascular invasion, pleural invasion, or tumor necrosis. Invasive adenocarcinoma is now classified using five predominant patterns: lepidic, acinar,papillary, micropapillary and solid adenocarcinoma. The variants of invasive tumors also include mucinous, colloid, enteric and fetal types, which can often be the appearances of metastatic lesions. Furthermore, it should be noted that adenocarcinomatous components can also be seen with other carcinomatous variants. Along with that there can also variations in the gross morphology and importantly in the clinical manifestations. The above aspects would be covered in an autopsy scenario.

Postgraduate Training in Pathology: Changing Trends

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Our understanding of the pathogenesis and pathophysiology of disease is rapidly evolving. The realm of diagnostics comes up with new techniques almost every few years. In view of these changing trends, we need to relook at our training of postgraduate students. This talk will deal with evolving trends in curriculum design, training and assessment in pathology training for postgraduates in India.

Pathology is an integrative discipline. The pathologist in this era also needs to have an in-depth understanding of the problems confronting the clinician. And so our pathology training must be grounded in clinical medicine. The curriculum needs to be updated with the latest trends in diagnosis such as molecular biology and genetics. Ethics and professionalism have taken a huge beating and there is need to consciously include these aspects in the curriculum. Managerial, administrative and leadership skills, pathology informatics are some topics which are currently missing from the curriculum.

In view of the Medical Council of India's thrust on competency-based medical education, the initial step, of course, has to be to identify the relevant competencies that need to be imparted at postgraduate levels. Milestones to be achieved at each stage need to be specified, and must be transparent to both students and faculty. Students need comprehensive exposure to all branches of Pathology. Rotations must be clearly planned out. A good balance of theory and practical exposure is needed. More interactive and relevant methods such as case-based learning need to be adopted to make learning clinically relevant. Emphasis needs to be laid on training in communication with clinicians and patients, as well as in proper documentation.

More workplace-based assessment methods need to be incorporated at the postgraduate level. These methods will help in certifying that students are capable of working independently without supervision. Greater weightage has to be given to longitudinal assessment throughout the course, instead of one end-of-the-course summative assessment. Postgraduate students need constant feedback on their performance

Students need to be given skills of self-directed learning. Once they have graduated, they must have capabilities of identifying their learning needs and given opportunities to keep themselves updated.

It must be remembered that we are accountable to society for the quality of training we provide. Given the lure of clinical branches, the number of medical students who make pathology as their career choice is decreasing. And in the near future we will face a shortage of trained pathologists. The challenges we face are of attracting the best brains to this speciality as well as churning out competent postgraduates with skills relevant to present needs of the health system.

Updates in Head and Neck Pathology

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Diagnostic challenges in head and neck pathology is mainly due to its anatomical diversity. With newer immunohistochemical and molecular studies, novel entities have been described; pathognomonic molecular alterations have been uncovered. This has led to a paradigm shift in the approach to head and neck cancers in terms of diagnosis and management

Major changes can be summarized as follows

1. **The recognition of oropharynx (base of tongue, tonsils, adenoids) as a distinctive sub site.**
   - This facilitates the recognition of human papillomavirus related squamous cell carcinoma. HPV–associated tumors occur in younger, healthier individuals with little or no tobacco exposure. It is highly responsive to treatment and has an excellent prognosis. Human papilloma virus related OPSCC generally exhibits non-keratinizing morphology. Grading is not currently advocated. Unlike in HPV-negative cases, dysplasia of the surface epithelium is rarely identified. HPV can be detected by molecular assays (e.g. in situ hybrid ization and PCR-based assays). Diffuse immunoreactivity for p16 is a reliable surrogate marker for the presence of high-risk HPV in oropharyngeal carcinomas, and may be sufficient test for HPV status in tumours with appropriate morphology arising at this site. When p16 or HPV testing is not available, OPSCC can be diagnosed as "squamous cell carcinoma, HPV status unknown" or, if the tumour shows the characteristic non-keratinizing morphology, as "squamous cell carcinoma, HPV not tested, morphology highly suggestive of HPV association". OPSCC-HPV is associated with significantly better survival outcomes than is HPV-negative OPSCC
2. **Change in nomenclature/classification of "unknown primary" head & neck cancer**
   - The evaluation of cervical nodal metastases of unknown primary has changed dramatically over the past decade. Many carcinomas previously diagnosed as cervical nodal metastases of unknown primary are now identified as being from occult oropharyngeal primaries. These cases often present with small primaries and large bulky cervical nodal metastases. Evaluation of nodal metastases for p16 and/or by molecular tests helps in the identification of likely HPV-related primaries
3. **Newly described Tumors of the Nasal Cavity, Paranasal Sinuses**
   - New well defined entities
     - Seromucinous Hamartoma
     - NUT Carcinoma
     - Biphenotypic Sinonasal Sarcoma ("low-grade sinonasal sarcoma with neural and myogenic differentiation,")

- Emerging Entities
    - HPV-Related Sinonasal Carcinomas Including HPV-Related Carcinoma with Adenoid Cystic Features recently renamed as Human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma (HMSC)
    - SMARCB1 (INI-1) Deficient Sinonasal Sarcoma
    - Renal Cell-like Adenocarcinoma

4. Newly described salivary gland tumors

i. Mammary analog secretory carcinoma (MASC)

- A distinctive low grade malignant tumour defined by its close resemblance to secretory breast carcinoma, particularly at the genetic level sharing a characteristic chromosomal translocation, t(12;15) (p13;q25) resulting in an ETV6–NTRK3 fusion. These tumors were composed of microcystic and solid areas with abundant vacuolated colloid-like periodic acid–Schiff (PAS)-positive secretory material within the microcystic spaces; and had previously been categorized as either unusual variants of salivary acinic cell carcinoma (AciCC) or cystadenocarcinoma not otherwise specified (NOS).

ii. Sclerosing polycystic adenoma (SPA)

- SPAs are well-circumscribed tumors with multiple, densely sclerotic, irregularly defined lobules composed of abundant hyalinized collagen surrounding variably sized collections of ducts with varying degrees of cystic change . Previously thought to be a reactive fibroinflammatory process, but recent evidence of clonality, recurrences in up 30%, and dysplastic foci suggest it may be truly neoplastic.

iii. Cribriform adenocarcinoma of tongue and other minor salivary glands (CAMSGs).

- CMASC is originally described in 1999 by Michal et al under the name cribriform adenocarcinoma of the tongue. Although CAMSG and PLGA may show morphologic overlap, and both tumor entities have molecular alterations affecting the same gene locus PRKD1/2/3, there are significant differences. It differs from polymorphous low-grade adenocarcinoma (PLGA) by

i. location (ie, most often arising on the tongue),

ii. Prominent nuclear clearing, like that of papillary carcinoma thyroid and

iii. Frequent metastases at the time of presentation of the primary tumor.

iv. Carcinoma ex pleomorphic adenoma

- CAxPA should no longer be considered a standalone diagnosis, biology is determined by both extent and carcinoma subtype. While the majority are as salivary duct carcinomas, other morphologic subtypes including myoepithelial carcinoma and epithelial-myoepithelial carcinoma also exist which are less aggresive than the prototypical CAxPA
- CAxPA can be classified as
    - Intracapsular - completely confined within the capsule of the adenoma, lacking any penetration of the capsule.
    - minimally invasive – invasion ranging from 1.5 to 6 mm
    - (widely)-invasive

- For salivary duct carcinoma arising from pleomorphic adenoma, intracapsular tumors behave indolently. However, once invasive, considered clinically aggressive

v. Grading of salivary gland tunours

- Most salivary gland carcinoma types have an intrinsic biologic behavior, thus, by assigning a histologic type, the tumor grade itself is often implied. As such, a generic grading scheme is no longer recommended for salivary gland carcinomas. The major diagnostic categories amenable to grading include adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, not otherwise specified and polymorphous adenocarcinoma

vi. High-grade transformation (previously known as "dedifferentiation,") has evolved into an important concept of tumor progression in salivary gland carcinomas. It describes progression of a typically monomorphic carcinoma into a pleomorphic, high-grade carcinoma. Tumors for which this phenomenon is well characterized include acinic cell carcinoma, adenoid cystic carcinoma, and epithelial myoepithelial carcinoma

5. Major Changes in Head and Neck Staging - 8th edition AJCC Cancer Staging Manual.

i. Oral cavity cancers now incorporate depth of invasion as a criterion for T designation.

- Thickness and DOI are not the same. Thickness is usually measured from the mucosal surface of the tumor to the deepest point of tissue invasion in a perpendicular fashion, while DOI is measured from the basement membrane of adjacent normal to the deepest point of invasion of the tumor.

ii. A novel staging system has been introduced for high-risk HPV-associated oropharyngeal cancers.

iii. Extranodal extension is now used on all head and neck nodal disease except nasopharynx and high-risk HPV oropharyngeal cancers

- Extranodal extension is now used on all head and neck nodal disease except nasopharynx and high-risk HPV oropharyngeal cancers.
- Pathologic ENE is defined as extension of metastatic carcinoma through the fibrous capsule of a lymph node into the surrounding connective tissue, regardless of the presence of stromal reaction. Tumor that stretches the capsule without breaching it does not constitute ENE.
- The extent of ENE is subcategorized.
  - ENE ma (macroscopic or gross ENE that is apparent to the pathologist's naked eye or extends > 2 mm beyond the nodal capsule under the microscope, or a solid tissue deposit that has completely destroyed nodal architecture) or
  - ENE mi (microscopic ENE that is restricted to ≤ 2 mm from the nodal capsule).

It is important for the Pathologists and Oncologist to understand these changes for accurate diagnosis and staging for better patient management

Gleason Grading in Prostate Biopsies

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The diagnosis of prostate cancer is suspected in an elderly patient who has lower urinary tract symptoms and issues of micturition. Digital rectal examination and raised serum PSA, if abnormal will trigger the need for a prostate biopsy. In current era, a 12-core biopsy is the recommended procedure. 6 cores are obtained from each lobe.

In 1966-67, Sir Donald Gleason established a grading system based upon the growth pattern and glandular arrangement of a prostate tumor, as seen under the microscope. These patterns were found to correlate with clinical outcome. This Original Gleason system, comprised of summing up the two most common grades or patterns to give a Gleason score in a given core.

In 2005, the International Society of Urological Pathology (ISUP), formulated revisions in the original Gleason scoring system. According to this system, the commonest pattern and the highest pattern were summed up to give a Gleason score, irrespective of the percentage or amount of the higher grade. This Modified scoring of 2005 had better correlation with outcome of patient.

In the latest 2016 ISUP/WHO Gleason grading, there was a major revision in assigning the patients to what is now established as "Prognostic grade groups" or just referred to as Grade Groups.

This was developed with the understanding that a patient of Gleason score 6 is actually the minimal score which a patient can be diagnosed in a core. So, for a patient this is the lowest end of spectrum of prostate cancer as against a score of 6/10 which conveys a "somewhere in the middle of the spectrum". Hence, a score of 6 was assigned a Prognostic grade group 1, to allay fears of patient and prevent overtreatment in this group, which hardly had any chances of developing metastatic disease. The score of Gleason 7 was split into two groups with different prognostic connotations (Score 3+4=7 as Grade group 2 and Gleason score 4+3 =7 as Grade Group 3) The prognostic groups are as follows:

Table : Histological Definition of New Gleason Grading System (2015)

- Grade Group 1 (Gleason score 6)
- Grade Group 2 (Gleason score 3+4=7)
- Grade Group 3 (Gleason score 4+3=7)
- Grade Group 4 (Gleason score 4+4=8; 3+5=8; 5+3=8)
- Grade Group 5 (Gleason scores 9-10)

Suggested reading

6. Phillip M. Pierorazio,* Patrick C. Walsh,* Alan W. Partin,* and Jonathan I. Epstein.† Prognostic Gleason grade grouping: data based on the modified Gleason scoring system.BJU Int. 2013 May; 111(5): 753–760.

IHC in Soft Tissue Tumors

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Introduction

Soft tissue tumors (STTs) comprise of complex group of diagnostic entities that represent a major diagnostic challenge to general pathologist in view of overall rarity of many of these lesions and ever increasing list of new entities.

Immunohistochemistry (IHC) plays a key role in solving these challenges. The utility of IHC falls into 3 categories:

a. Identification of rare or 'atypical' benign pseudosarcomatous lesions.
b. Exclusion of non-sarcomatous neoplasms.
c. Classifying these tumors by trying to define their mesenchymal cell lineage.

In addition, development of new markers that can detect tumor-specific fusion proteins that is either over expressed or aberrantly expressed as a result of translocation has made use of IHC as a surrogate for the presence of tumor-specific molecular alterations.

Identification of rare or 'atypical' benign pseudosarcomatous lesions.

Immunohistochemistry is generally not useful in differentiating benign from malignant STTs with exception of few situations.

Benign nerve sheath tumors with pseudosarcomatous features

Cellular schwannoma or ancient schwannoma with degenerative atypia show strong and diffuse S-100 positivity, whereas malignant peripheral nerve sheath tumors (MPNSTs) show only focal positivity in, 50-60% of cases.

Solitary fibrous tumor (SFT) (benign in 90%)

It can be mistaken for spindle cell sarcoma like synovial sarcoma (SS). Diffuse positivity for CD34 in SFT differentiates it from SS which is regularly negative.

Reactive myofibroblastic proliferations

The immunophenotype of myofibroblasts is variable (SMA +/-, desmin +/-) but the vast majority of benign pseudosarcomatous proliferations (fasciitis) focally express smooth muscle actin.

Histiocytic lesions

Lesions like histiocytic reaction to endogenous and exogenous material, juvenile xanthogranuloma, tenosynovial giant cell tumor (diffuse form may be mistaken for small round cell tumor) and Rosai-Dorfmann disease may be mistaken for a malignant tumor. A strong diffuse positivity for CD68 could be helpful in diagnosing these lesions.

Myoepitheloma

Myoepithelioma of soft tissue may be mistaken for extraskeletal myxoid chondrosarcoma. Immunohistochemistry plays a important role in diagnosis of this lesion by showing positivity to S-100 and cytokeratin.

Diagnosis of rare STTs

Paraganglioma: It may be mistaken for a carcinoma or other malignant tumors. Positivity for chromogranin A in chief cells and S-100 in sustentacular cells is characteristic

Glomus tumor: Glomus tumor may be mistaken for malignant small round cell tumor (SRCT). Positivity of tumor cells for SMA and h-caldesmon is helpful for diagnosis. Type IV collagen can also be helpful, which outlines the cells.

Angiomyolipoma: In renal or extrarenal location, may be mistaken for several malignant tumors: well-differeniated liposarcoma when it is predominantly lipomatous, leiomyosarcoma when it is predominantly smooth muscular with nuclear atypia and carcinoma when it is epithelioid. Immunohistochemistry is helpful by showing positivity to HMB-45, SMA and h-caldesmon.

Exclusion of non-sarcomatous neoplasms:

It is important to exclude the possibility of non-mesenchymal tumor such as carcinoma, melanoma and lymphoma as the treatment is different. One has to be careful in following situations.

a. Tumors located in skin, mucosae, lymphnode areas, kidney, thyroid, lung and breast.
b. When there is previous history of non-mesenchymal malignant tumor.
c. When dealing with tumor which looks like fibrosarcoma, storiform MFH, hemangiopericytoma or unclassified sarcoma.

Immunohistochemistry is helpful in most of these situations in allowing identification of carcinoma (cytokeratin + and EMA +), a melanoma (S-100 +, HMB-45 and Melan–A +) or a lymphoma (CD45+)

Limitations:

Some sarcomatoid carcinomas are negative for epithelial markers whereas some sarcomas are positive for such markers.

Sarcomatoid carcinoma *vs* synovial sarcoma arising in kidney or lung: In such cases molecular biologic technique (RT-PCR or FISH) are helpful by showing t(X;18) in synovial sarcoma

Epithelioid sarcoma *vs* carcinoma: CD 34 staining (positive in 50% cases of epithelioid sarcoma) is help by being regularly negative in carcinomas

Melanoma: Spindle cell melanoma may be usually negative for HMB-45 and melan-A

Lymphomas: Some lymphomas may be CD45 negative and these may be mistaken for sarcoma

Anaplastic large cell lymphoma may be mistaken for pleomorphic sarcoma. In such cases CD3, CD 30 and ALK-1 are necessary for diagnosis

Lymphoblastic lymphoma may be mistaken for PNET since they are often positive for CD99. Additional markers like Tdt, CD 3, CD20 and FLI-1 are helpful in differentiation.

Classification of sarcomas

Tumors for which IHC is determinant for the diagnosis:

In these case IHC is part of the definition of tumor and /or because of therapeutic implications Rhabdomyosarcoma (RMS) (desmin and myogenin positive in >90% tumors)

The sequence of expression of striated muscle differentiation markers includes myogenin/MYOD1, desmin, fast myosin and myoglobin. In alveolar RMS myogenin is positive in >50% cells whereas in embryonal RMS it ispositive in lesser number of tumor cells.

Epithelioid sarcoma (>90% positive for cytokeratin and EMA)

CD34 positive in 50% of cases and can help in excluding carcinoma

Clear cell sarcoma (S-100 positive in 100%; HMB-45 and melan-A positive in >80%)

Demonstration of specific translocation t(12;22) is the only way to distinguish this tumor from melanoma.

Desmoplastic small round cell tumor (DSRCT) (co-expression of epithelial markers, desmin and less often neuronal markers). Cytokeratin, EMA and desmin are positive in 90% cases. WT1 is positive in all cases but not specific.

Gastrointestinal stromal tmor (GIST)

The diagnosis of this entity is based on CD117 positivity on IHC. Few cases are CD117 negative and demonstration of c-kit mutation may be helpful in those cases. Other markers for GIST – Protein kinase C, DOG1.

Mailgnant vascular tumors

These tumors may show wide spectrum of histological appearances (spindle cell/ epithelioid) that may render the definitive diagnosis difficult.

Useful antibodies include CD31, CD34, FVIII related antigen and FLI-1, ERG, Claudin 5, Type IV collagen. Recent studies have documented superior sensitivity and specificity of nuclear ERG expression for vascular endothelium over FLI1, CD31 and CD34. Markers that suggest lymphatic endothelial differentiation include VEGFR-3, Podoplanin (D2-40), Prox1

Synovial sarcoma (SS)

Immunohistochemistry is particularly useful for diagnosing monophasic fibrous and poorly differentiated SS.

Useful antibodies:

Cytokeratin AE1/AE3 – positive in 70% monophasic and 50% PDSS

EMA – positive in virtually every SS

CD 34 – regularly negative

TLE-1 (80%), also expressed by other tumor (MPNST, SFT)

Sarcomas in which IHC may be useful

Ewings sarcoma(ES)/PNET: CD99 is positive in virtually all ES/PNET but it is not specific. It is helpful in differentiating ES/PNET from neuroblastoma where CD99 is always negative. FLI-1 is more specific but positive in only 70% cases. Recently described NKX2-2 is reported to be expressed in 93% of ES, but this is also expressed by other tumors like MCS, olfactory neuroblastoma, SS, DRCT, myoepithelioma and malignant melanoma. Molecular proof of specific translocation involving EWS gene and several other genes is being increasingly used nowadays.

Leiomyosarcoma: IHC is helpful in confirming the diagnosis. SMA is most sensitive marker but it is not specific. Desmin is more specific (positive in only 50-70%). Other marker that can be used is h-caldesmon (more specific).

Malignant peripheral nerve sheath tumors (MPNST): IHC is helpful when tumor cells are positive for S-100 (50-80% cases). Epithelioid MPNSTs regularly show diffuse positivity for S-100. The pattern of S-100 staining is helpful in differentiating MPNST from benign nerve sheath tumors. Loss of expression of H3K27me is observed in 50% of MPNST except in epithelioid variant.

Dermatofibrosarcoma protruberance (DFSP) and giant cell fibroblastoma: These are consistently positive for CD34. This marker is helpful in differentiating DFSP from dermatofibroma where it is negative.

Adipocytic tumors: IHC has minor role in the diagnosis of these tumors. The spindle cell component of spindle cell lipoma and pleomorphic lipoma stain strongly with CD 34. Negative staining for this marker is helpful in ruling out these tumors.

MDM2 and CDK4 are helpful in differential diagnosis of well differentiated liposarcoma (WLDS) and dedifferentiated liposarcoma(DDLS). These two markers are positive in most of (90%) the WDLS, whereas benign lipomatous tumors are negative for both. These two markers are retained even in DDLS.

Myxoid liposarcomas are characterized by distinct translocation including t(12;16) resulting in FUS-DDIT3 and t(12;22) resulting in production of EWSR1-DDIT3 fusion proteins.

Alveolar soft part sarcoma (ASPS): This tumor is characterized by t(X;17) resulting in ASPL-TFE3 fusion transcript. An antibody to carboxy-terminal portion of TFE3 has been developed which shows strong nuclear positivity in ASPS (upto 100% cases). Nuclear expression of TFE3 also encountered in metastatic Xp11 translocation RCC and small subset of PEComas.

Sarcomas with no specific immunohistochemical profile

Fibrosarcoma, myxofibrosarcoma and pleomorphic undifferentiated sarcoma. In such cases IHC is helpful to rule out non-mesenchymal neoplasms or sarcomas with specific line of differentiation.

IHC as surrogate marker for presence of tumor specific molecular alterations

FLI & ERG for EFT

- t(11;22)(q24;q12) → EWSR1-FLI1 (90%)

- t(21;22)(q22;q12) → EWSR1-ERG (5%)
- Monoclonal/ polyclonal Ab to FLI1 – 70-90%
- FLI1 also positive in tumors with EWSR1-ERG (protein homology)
- FLI –ve in – RMS, Mesenchymal CHS, Wilms tumor
- FLI +ve in – lymphoblastic lymphoma, Merkel cell Ca., Melanoma & DSRCT
- FLI1 & ERG +ve in endothelial tumors

WT1 as a marker of t(11;22)(q13;q24) → EWSR1-WT1

- Ab directed to carboxy terminus of WT1 – highly sensitive (>90%) & relatively specific for DSRCT
- Wild type WT1 Ab – recognizes both carboxy & amino terminus and is positive in Wilms tumor & many RMS

TFE3 as marker of der(17)t(x;17)(p11;q25)

- TFE3 highly sensitive and specific for ASPS (strong nuclear expression)
- Low expression is seen in almost all normal tissues
- Also positive in pediatric renal carcinomas, Granular cell tumors, PEComas (small minority)

MUC4

- Low grade fibromyxoid sarcoma
- Minority of ossifying fibromyxoid tumor of soft parts

β-Catenin

- 90% of fibromatoses

MDM2 & CDK 4 – WDLS, DDL

Bcl-2 – Synovial sarcoma, SFT

RECOMMENDED IHC PANEL

It is difficult to recommend panels as the choice of antibodies will change according to the specific clinicopathological differential diagnosis. However, a few "basic" panels can be suggested, depending on the morphological category of the tumor:

Spindle cell tumors

- Pancytokeratin
- Smooth muscle actin
- S-100
- Desmin
- (CD34)
- (EMA)

Epithelioid tumors

- Cytokeratin
- S-100
- CD45

- CD30
- CD31
- CD34

Round cell tumors:

- Pancytokeratin
- CD45
- Desmin and/or myf-4
- CD99, FLI1/ERG, NKX2.2
- Melanocytic markers
- Synaptophysin

Pleomorphic cell tumors

- CK
- Melanocytic markers, s-100
- SMA
- Desmin and myogenin
- MDM2/ CDK4
- (CD30)

These suggested panels should of course be modified on the basis of the histological features of the tumor and the clinical presentation.

Suggested Readings:

7. Fletcher CDM, Unni KK, Mertens F, editors. WHO classification of tumors: Pathology and genetics of tumors of soft tissue and bone. Lyon: IARC Press;2002.
8. Weiss S, Goldbum JR, (edrs). Soft tissue tumors. Fifth edition 2008; Mosby:Pheladelphia. pp129-174.
9. Heim-Hall J, Yohe SL. Application of Immunohistochemistry to Soft Tissue Neoplasms. Arch Pathol Lab Med. 2008;132:476–489
10. Coindre JM. Immunohistochemistry in the diagnosis of soft tissue tumors.Histopathology 2003;43:1-16.
11. Dabbs DJ (edr). Diagnostic immunohistochemistry : theranostic and genomic applications. Fifth Edition 2019; Elsevier:Philadelphia, PA. pp82-136.

Wrong Strokes in A Paper, How to Take Care

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Scientific publishing is an important aspect of academic carrier in any field including medicine. It is the main source of validation of one's research, and often the key indicator of academic success. Promotion and tenure committees value peer-reviewed publications above all; that is, regrettably, even above clinical performance or community service.

The task of writing a research paper can be daunting, even with groundbreaking research, Paper writing is an art, in which an author has to present a picture of his research work in such a manner that it generates an interest in editors, reviewers and readers to read and understand it. Just like an art work, where one has to take care of finer detail of colours, shades, lines, weights of lines, their directions, proportion of various elements etc. Any discrepancy or wrong proportion of these elements may lead to a bad figure. In paper writing also one has to take care of many factors for acceptance and publication of research worklike–

Title

Style and language

Components (Abstract, Introduction, Material and methods, Results, Discussion and conclusion) and preparation of paper

References

Tables and figures

Jjournal selection

Ethical Issues and plagiarism

Writing a paper is an art and if one wants to publish a paper successfully, it is very important to know some basic aspects. Before submitting a paper for publication to a journal it should be self assessed on the following points -

WHY you want to **publish** your work.

Is it **new and interesting**?

Is it a current **hot topic**?

have you **provided solutions** to some difficult problems?

Are you **ready** to publish at this point?

If yes, then proceed with preparation of the manuscript. Manuscript can be submitted in many formats depending upon the type of research work. Usually following formats are there to submit the work:-

Review papers / perspectives: summarize recent developments on a specific topic. Highlight important previously reported points. It is not the place to introduce new information. **Often invited**

Full articles / Original articles: the most important papers. Often substantial and significant **completed pieces of research**.

Rapid Communications/ Short communications: quick and early communication of significant and original advances. Much shorter than full articles (check limitations).

Case reports and **Images**- More common in medical field specially pathology

Letter to the editor

Before starting the writing of your manuscript, the work should be **self-evaluated for the type of the article.** Is it sufficient for a full article? Or the results are so thrilling that they should be shown as soon as possible in form of short/brief communication. Help of a senior or colleagues can be taken for unbiased assessment.

The first and foremost task is to decide the journal in which the paper to be submitted. For this a look at the references may help in narrowing the choice. While short listing a journal following points should be taken in consideration

Find out the hot topics, the accepted types of articles.

Is the journal **peer-reviewed**?

Who is this journal's **Reader**?

What is the **average time to print**?

What are the **indexing and abstracting**sites?

What is the journal's **Impact Factor**?

Section	**Purpose**
Title	Clearly describes contents
Authors	Ensures recognition for the writer(s)
Abstract	Describes what was done – 150 words
Key Words (some journals)	Ensures the article is correctly identified in abstracting and indexing services
Introduction	Explains the problem
Methods	Explains how the data were collected
Results	Describes what was discovered
Discussion	Discusses the implications of the findings
Acknowledgements	Ensures those who helped in the research are recognised
References	Ensures previously published work is recognised
Appendices (some journals)	Provides supplemental data for the expert reader

A manuscript should be submitted to one journal at a time. DO NOT submit to multiple journals. Do not send your manuscript to a second journal UNTIL you receive the final decision of the first journal. A research study is meaningful only ifit is clearly described, so that someone else can use it in his/her studies. It should be able to arouses other scientists' interest and allow others

to reproduce the results. By submitting a manuscripta scientist basically tries to sell the work to the community. Importance of an article is measured by the citation of the articles.

Before starting to prepare read the **Instructions to authors** carefully. Check the details for type of papers, sections, type of abstract, no of figures and words allowed, how to write and quote references and the number of authors allowed for a particular type of manuscript.

A **good manuscript** contains clear, useful, and exciting scientific message, flows in a logical manner that the reader can follow, properly formatted to show the content and written in a style that transmits the message clearly. Following table shows various sections of a manuscript and what should they contain.

Write in the following order:

- Figures and tables
- Methods, Results and Discussion
- Conclusions and Introduction
- Abstract and title

Each section has a definite purpose.

Good manuscript

Contains a clear, useful, and exciting scientific message.

Flows in a logical manner that the reader can follow.

Is formatted to best showcase the material.

Is written in a style that transmits the message clearly.

In present scenario **Ethical Issues in Publishing** have become very important. Clearance from institutional ethical committee has become mandatory in research projects. Various types of ethical misconducts may be there like-

Scientific misconduct

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Different forms / severities

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Plagiarism that means copying of scientific content that may be the article or photo or any other data without proper permission and acknowledgement of original author is again a serious offense. It has long-term consequences. Plagiarism is considered a *serious offense* by the institute, by journal editors, and by the scientific community. Plagiarism may result in *academic charges*, and will certainly cause rejection / retractionof paper. It will *hurt the author's reputation* in the scientific community.

If all these details are properly followed, a paper may result in a beautiful picture where all the finer details are appreciated in first look, leading to appreciation, acceptance and repeated citation.

Sources for further study

- Significant portions were adapted from a 2005 Elsevier Presentation
- How To Write & Publish a Scientific Paper – A General Guide - Hinari Research in Health.
- A personal view of scientific writing or The mistakes I have made!By John Kirby - Postgraduate tutor

Expectations from the Editor: How Justified?

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Publications are an integral part of all academic activities. The dictum "Publish or Perish" holds true. In the process of publication Editor or Editor-in-Chief (EIC) holds a key position, because the final selection of the suitability for publication or rejection of the manuscript lies with him/her. However, this judgment is purely on the basis of merit and not on the discretion of the EIC, expect for articles that are out of scope of the journal. During this entire process each manuscript undergoes strict screening, vigilance and peer review process. These steps ensure only a quality article to be published in the journal, thus maintaining not only the standard of the journal but also its impact factor which depends on the citations of each article published.

When we talk about the expectations from the EIC they are many, especially by the authors. It is expected by them that an article submitted is immediately accepted or published at a very fast pace. This is practically impossible. Many a time when the manuscript is sent back to the authors for corrections or modifications, they do not reply back early thus delaying the processing time however, on the contrary they expect a very fast action from the other side of the table. Another bottleneck is the review process, which again takes time. Each article is strictly "double-blinded" i.e neither the authors know about the reviewers and neither the reviewers know the identity of the authors or the institution. The submitted articles after technical corrections are sent to experts in the respective field as per the article specialty. The peer review process check for the publication feasibility of the article i.e. plagiarism, scientific content, method used for diagnosis confirmation and also for the grammatical errors if any. Each step takes time but in between the entire process the authors start sending emails to the Editor asking for their articles status inspite of the fact that for each editorial activity a message is being sent to the corresponding author for any updates etc.

Editors of scientific journals have responsibilities toward the authors who provide the content of the journals, the peer reviewers who comment on the suitability of manuscripts for publication, the journal's readers and the scientific community, the owners, the publishers of the journals, and finally the public as a whole.

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Editors are responsible for monitoring and ensuring the fairness, timeliness and thoroughness of the peer-review editorial process. Peer review by external reviewers with the proper expertise is the most common method to ensure manuscript quality. Editors may sometimes reject manuscripts without external peer review the manuscript is outside the scope of the journal, does not meet the journal's quality standards, is of limited scientific merit, or lacks originality or any innovation. Ideal is to have a double masked or double blind process with masking the identities of both the authors and reviewers.

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- Complying with the guidelines and procedures of the Publishers.
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- Adhering to the agreed-upon mission, publication practices, and schedule.

Editors' roles have benefited society in many ways, from quality-control measures taken when considering manuscripts for publication to requiring authors to abide by standards that would advance the scientific content and also provide access to others interested in the same subject (i.e data sharing). Some of the points that need highlighting include -

Conflicts of Interest: It is defined as conditions in which an individual holds conflicting or competing interests that could bias the editorial decisions. It may include - Personal conflicts, financial conflicts and, non-financial conflicts. EIC needs to ensure that there is no conflict of interest – neither by the authors, nor by the reviewers or the editorial board members.

Citation Manipulation: Most metrics of scholarly performance, including the Journal Impact Factor (JIF), are based on citations to the published articles. At some point during the peer-review process, editors or the reviewers request that the authors add citations from their own journal. Editors may write editorials in which a disproportionate number of articles from their own journal

are cited. Reviewers may that authors cite their articles. Self-citation is another aspect wherein the authors cite disproportionately large numbers of their own articles in all or most of their publications. Lastly, a group of researchers agree to preferentially and regularly cite each other's articles in all or most of their publications.

Timeliness of the Publication Process: Editors are responsible for monitoring the turnaround time (TAT) for every article from the time of manuscript receipt to publication or rejection. Processing data and evaluating trends can help editors scrutinize acceptance and rejection rates of specific types of manuscripts, manage the inventory/backlog of accepted manuscripts, track reviewers' and editors' performance, and assess staffing needs.

Errata, Retractions, and Expressions of Concern: Editor's need to maintain the integrity of the literature by publishing errata or corrections identifying anything of significance, retractions, and expressions of concern as quickly as possible.

Addressing Authorship Disputes: This is a major problem these days especially when it is a matter of academic promotion. There are disputes related to authorship or contributorship. Editors' need to resolve these matters also.

Considering Appeals for Reconsideration of Rejected Manuscripts: Despite editors' best efforts to publish fair and unbiased reviews to evaluate manuscripts fairly, and to make decisions that are in the best interest of the journal and its readers, authors may still want to challenge the editorial decisions. Although it is not easy to explain to an author that the research reported in his or her manuscript does not warrant publication in comparison with the many others under consideration. Editors then determine whether the decision was clearly explained to the author and whether it may have been based on wrong or questionable information. They may even reconsider rejected manuscripts if the author provides good reasons why the decision may have been wrong and is willing to revise the manuscript in response to the valid comments of the reviewers and editors and, finally editors' encourage resubmission of manuscripts that are potentially acceptable but were rejected because major revision or additional data were suggested but not done by the authors.

Addressing Allegations or Findings of Misconduct: Concerns of possible scientific misconduct are usually expressed first to the editors of a journal about a manuscript that is under consideration or has already been published. The publishers have a responsibility to inform readers and secondary services of work formally proven to be plagiarized, fabricated, or faked.

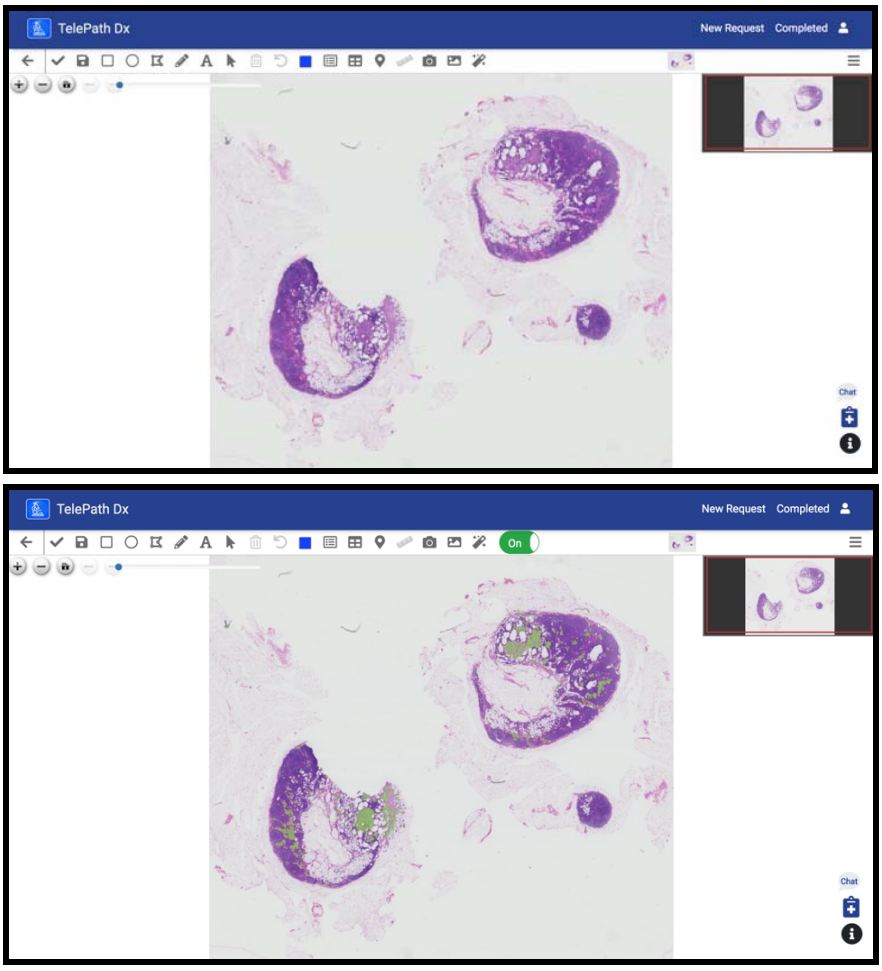
Digital Pathology: CV/ML

Vikas Ramachandra & Harish Prabhala

Onward Assist

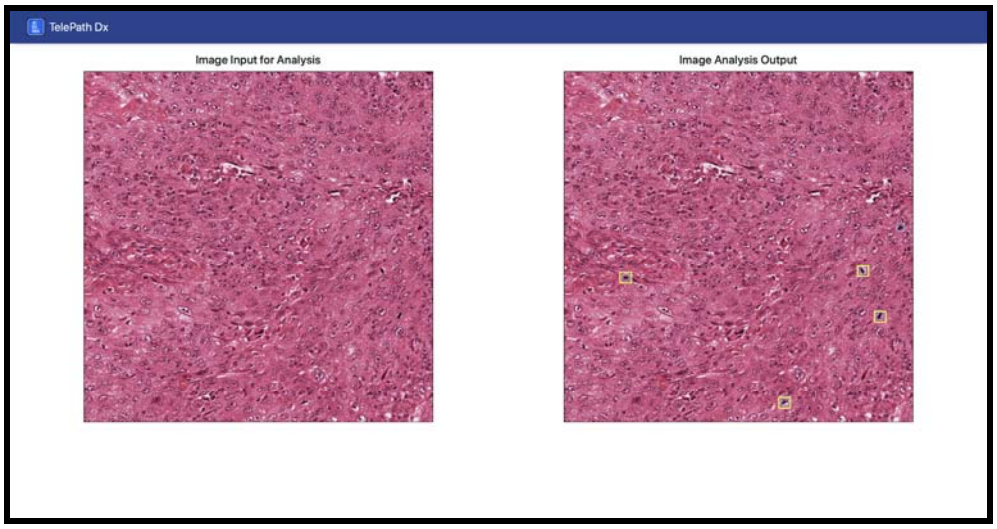
When biopsy tissue slides arrive at the pathologist's desk, they have to scout through the whole tissue slide to find the malignant regions and report on the various parameters such as cell grade, stage, mitotic count etc. Using digital pathology and computer vision, Onward Assist provides tools to help the pathologist reduce some of their burden. These tools include; tumor heatmap, mitosis counting and HER2+ detection and scoring.

Imaging ML algorithms have been trained to detect tumor islands and show a spatial heatmap of benign and malignant regions. Once the heatmap is displayed on the whole slide image, the pathologist can directly go to that location and report on it rather than searching the whole slide image themselves. The below figure shows a whole slide image (WSI) with malignant tumor regions highlighted in green, when the heatmap tool is turned on.



One of the important biomarkers of tumor cell proliferation is the mitotic activity. Today, one of the most tedious, straining and cumbersome task for a pathologist is to do the mitotic count per field of view. We have developed an algorithm that will aid the pathologist in the mitotic counting

activity. Our algorithm has shown promising early results in automatically detecting and counting mitosis in one field of view. The below figure shows input field of view on the left and the right side image shows output where the mitosis are marked with a yellow box.



Another tool from Onward Assist, assists pathologists in scoring of HER2 slides. The IHC stained HER2 images have three scores; score 0, score 1, score 2 and score 3. HER2 status is determined using the scores. We have trained our algorithm to score patches of the IHC image based on staining intensity. An overall recommendation of the HER2 status is computed based on the percentage of cells/patches with the staining according to the guidelines given by the College of American Pathologists.

In the below images, the algorithm determines the score based on the intensity and produces a colormap/heatmap of the distribution of the scores. Based on the distribution and our suggested recommendation, the pathologist can make a decision on the HER2 status.

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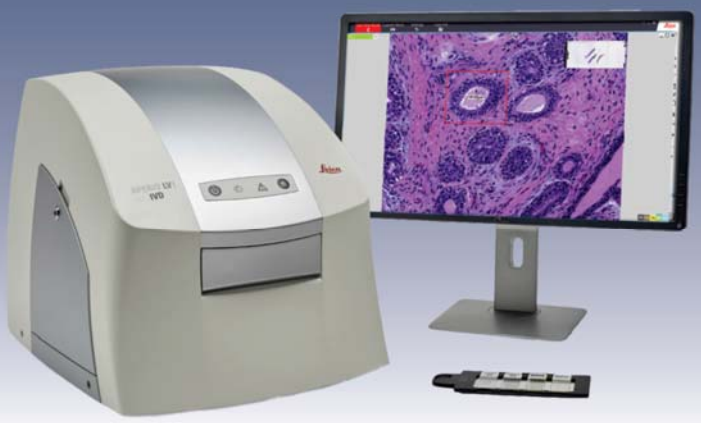

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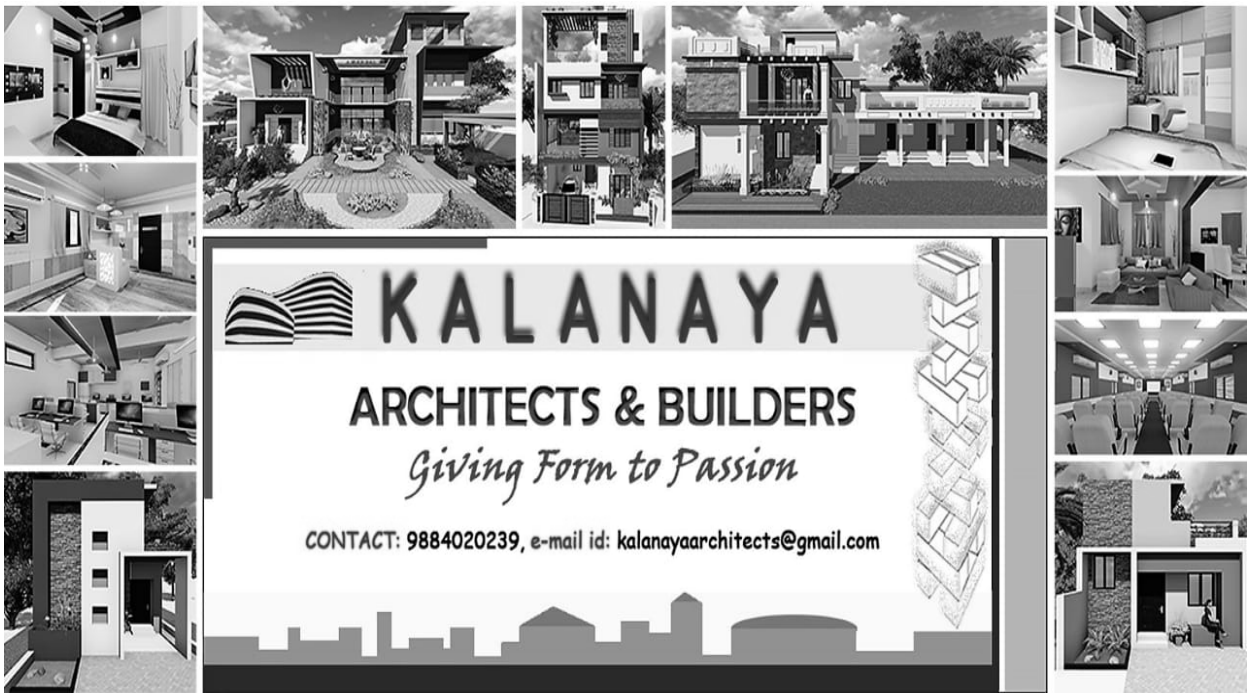

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