LAPORAN ABDIMAS MANDIRI
DOSEN FAKULTAS KEDOKTERAN
UNIVERSITAS TARUMANAGARA

Judul Abdimas : Peran Patologi Anatomik dalam Diagnosis dan Terapi Kanker Payudara [RS. Sumber Waras -24 Oktober 2023]

Ketua Tim : Sony Sugiharto, Dr. dr, SpPA (0322126601/10499002)

1. PENDAHULUAN

Kanker Payudara merupakan kanker yang menduduki urutan pertama di dunia dan Indonesia. Insiden kanker payudara di Indonesia 42,1 per 100,000 penduduk dengan angka kematian 17 per 100,000 penduduk (Kementrian Kesehatan Republik Indonesia 2019). Di Indonesia > 80% kanker payudara di diagnosis dalam stadium lanjut (Komite Nasional Penanggulangan Kanker 2015). Kanker payudara stadium lanjut adalah kanker yang sudah menyebar dari payudara ke jaringan lain seperti kelenjar getah bening, paru, hati, tulang, dan otak.

Saat ini peran dokter spesialis patologi anatomi tidak hanya mendiagnosis kanker payudara dengan pemeriksaan rutin Hematoksilin-Eosin (HE) yang dapat menentukan jenis tumor, grade, invasi limfovaskular, batas sayatan, keterlibatan kelenjar getah bening, Tumor Infiltrating Lymphocytes (TILs), dan staging.(1) Peran ini terus berkembang seiring dengan penemuan obat-obat kanker payudara. Pemeriksaan selanjutnya adalah pemeriksaan imunohistokimia untuk panel kanker payudara (Estrogen Receptor/ER, Progesteron Receptor/PR, human epidermal growth factor receptor 2 (HER 2), dan Ki67). Bila ER positif maka pasien akan diterapi dengan terapi seperti Tamoxifen, sedangkan bila HER2 positif maka pasien akan diberi terapi target seperti trastuzumab.(2) Bila ER, PR, dan HER2 negatif maka selain kemoterapi, untuk penderita kanker stadium lanjut dan metastasis dapat diperiksa PD-L1. Ada 2 clone yang berbeda yaitu Sp142(3) dan 22C3 (4) dengan cut-off yang berbeda dan obat yang berbeda pula. Pemeriksaan genomik untuk prognosis, memprediksi metastasis jauh dan benefit kemoterapi dapat dilakukan dengan MammaPrint®(5) & Oncotype DX®(6). Semua pemeriksaan ini dilakukan pada massa tumor yang sudah dibuat blok paraffin.

Target Abdimas: Dokter spesialis, dokter umum dan mahasiswa Kedokteran di RS Sumber Waras.

Permasalahan Mitra: Terapi kanker payudara yang dulu hanya menggunakan kemoterapi sudah berkembang pesat. Perlunya dokter dan mahasiwa kedokteran mengetahui pemeriksaan dan terapi terkini kanker payudara, walaupun RS. Sumber Waras belum memiliki fasilitas pemeriksaan yang lebih lanjut.

2. METODE PELAKSANAAN

Webinar menggunakan aplikasi Zoom. Pada Webinar ini ada 3 Pembicara yaitu dari bagian Patologi Anatomi, Bedah dan Radiologi.

3. HASIL KEGIATAN

Pada tanggal 24 Oktober 2023, pk 09.00 – 12.00 PKM dilaksanakan. Webinar dihadiri 19 peserta dokter dengan berbagai bidang keahlian dan mahasiswa/i kedokteran. Acara dimulai dengan pemaparan dari ketiga dokter spesialis dan diakhiri dengan diskusi yang dipimpin oleh Moderator.

4. KESIMPULAN DAN SARAN

Pelaksanaan PKM berjalan dengan baik dengan antusiasme yang besar dari peserta. Walaupun RS. Sumber Waras belum memiliki fasilitas pemeriksaan patologi yang lebih lanjut webinar ini bermanfaat untuk memperlengkapi dokter dan mahasiswa kedokteran ke depannya dalam mendiagnosis dan terapi Kanker Payudara

Saran: PKM dengan pembicara multidisiplin.

5. DAFTAR PUSTAKA

1. Board WC of TE. Breast Tumours [Internet]. [cited 2024 Feb 29]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Breast-Tumours-2019

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3. Ahn SG, Kim SK, Shepherd JH, Cha YJ, Bae SJ, Kim C, et al. Clinical and genomic assessment of PD-L1 SP142 expression in triple-negative breast cancer. Breast Cancer Res Treat. 2021 Jul;188(1):165–78.

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5. Sapino A, Roepman P, Linn SC, Snel MHJ, Delahaye LJMJ, van den Akker J, et al. MammaPrint Molecular Diagnostics on Formalin-Fixed, Paraffin-Embedded Tissue. The Journal of Molecular Diagnostics. 2014 Mar 1;16(2):190–7.

6. Abdelhakam DA, Hanna H, Nassar A. Oncotype DX and Prosigna in breast cancer patients: A comparison study. Cancer Treatment and Research Communications. 2021 Jan 1;26:100306.

Siang Klinik Oktober

Breast Cancer

AWARENESS MONTH

dr. Ratih Adira, Sp. B
Kanker Payudara

Dr. dr. Sonny Sugiharto, Sp. PA
Peranan Patologi Anatomi dalam diagnosis & terapi
kanker payudara

dr. Verawati Sutedjo, Sp.Rad(K)-TR
Breast Imaging

Selasa, 24 Oktober 2023
pkl 09.00 by Zoom

Peran Patologi Anatomik dalam Diagnosis dan Terapi Kanker Payudara

Sony Sugiharto

Outline

- Epidemiologi
- Penanganan spesimen
- Pemeriksaan Histopatologi
- Pemeriksaan Imunohistokimia

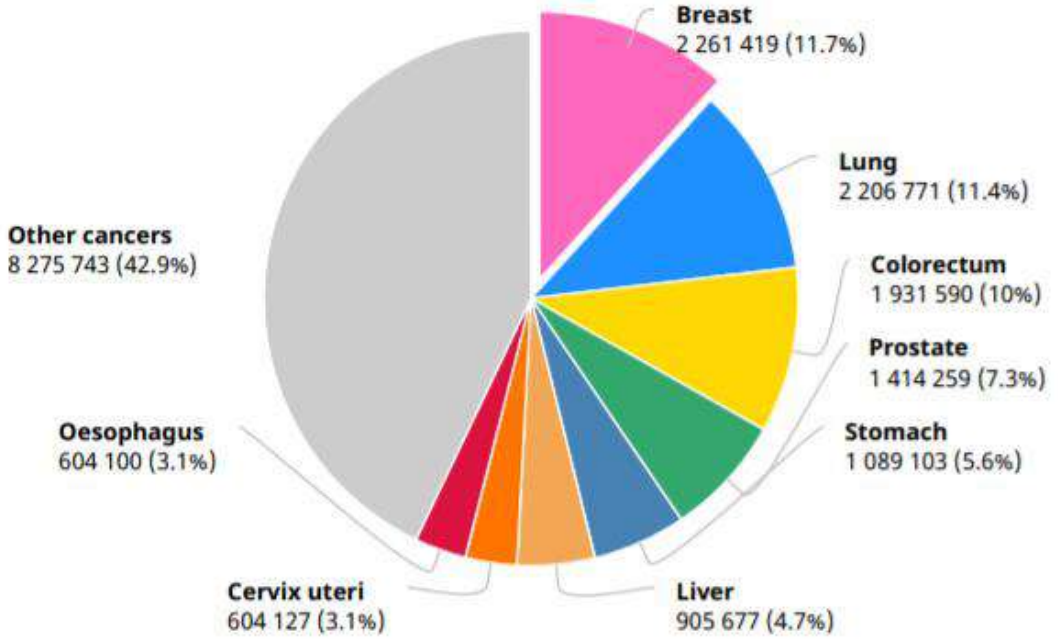
EPIDEMIOLOGI

International Agency for Research on Cancer
World Health Organization

Breast

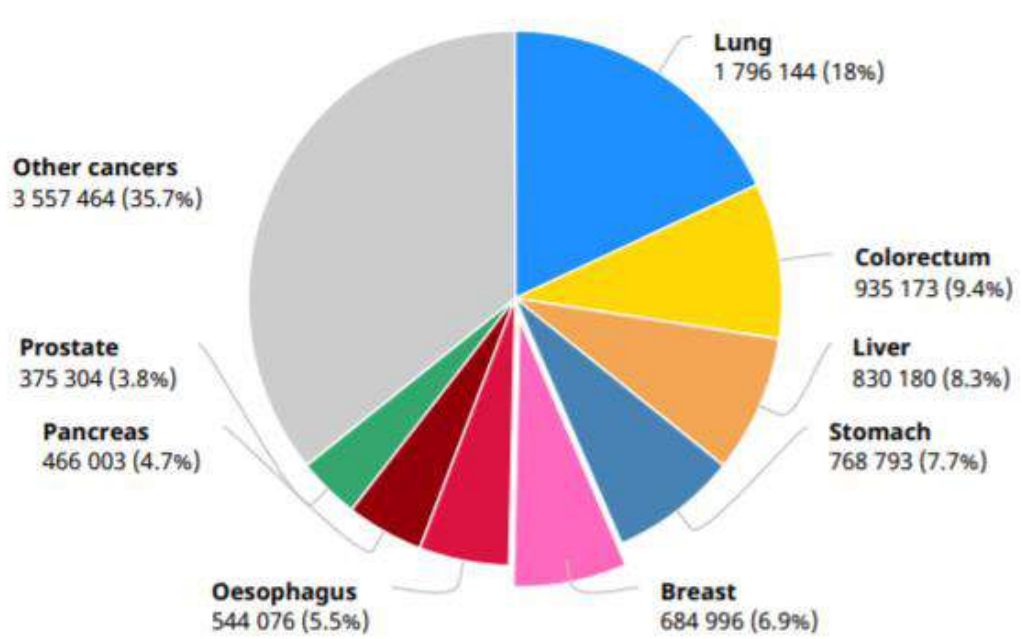
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages

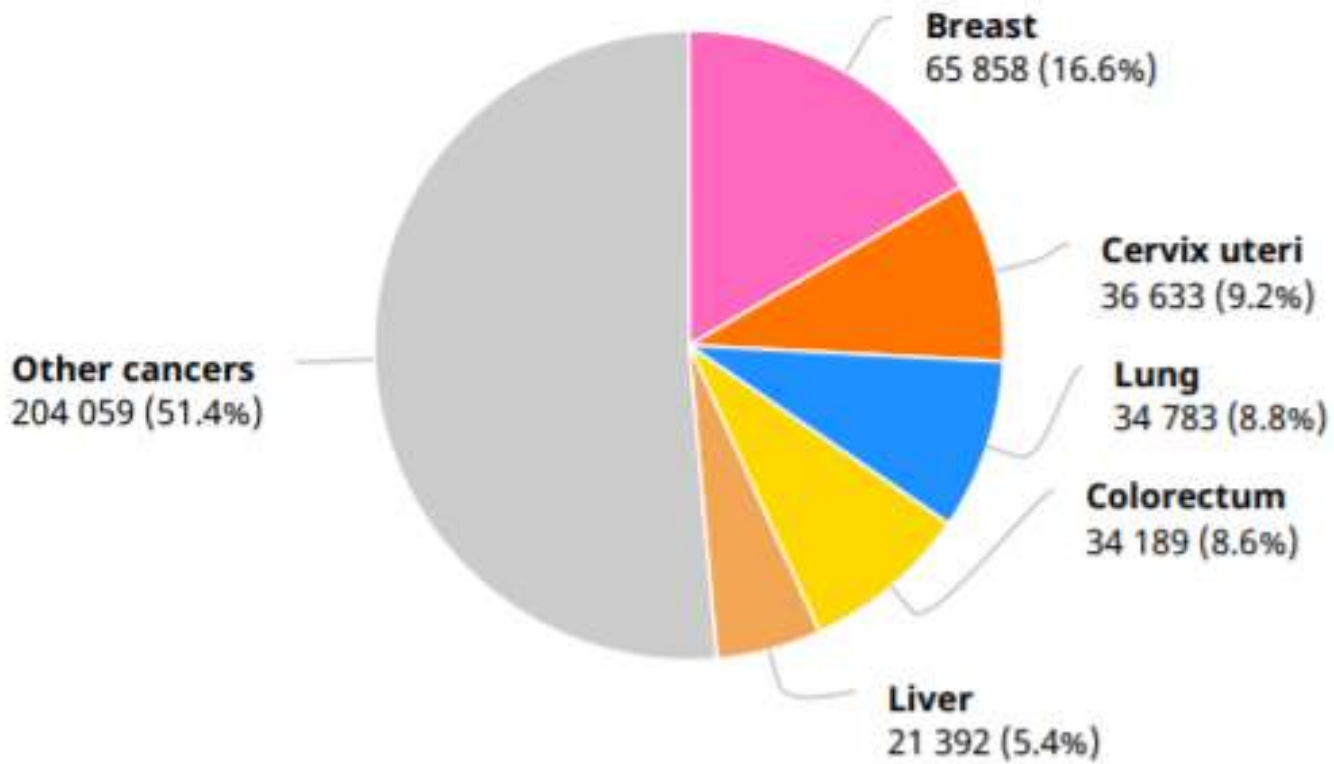


Total: 9 958 133 deaths

Indonesia

Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages

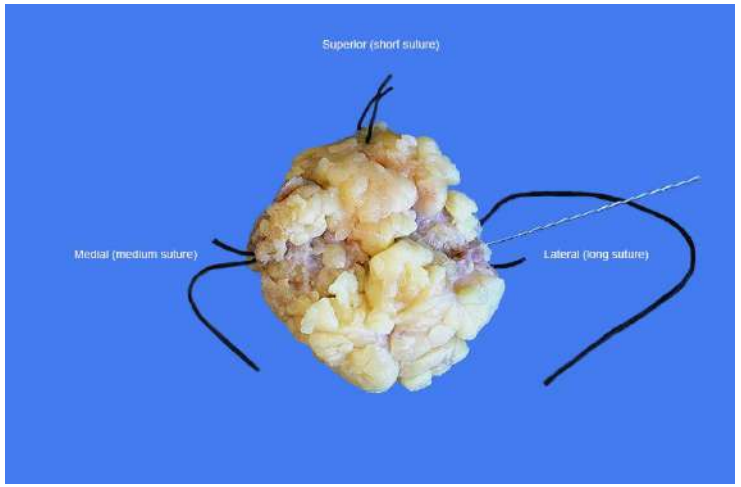


Total: 396 914

Spesimen Kanker Payudara

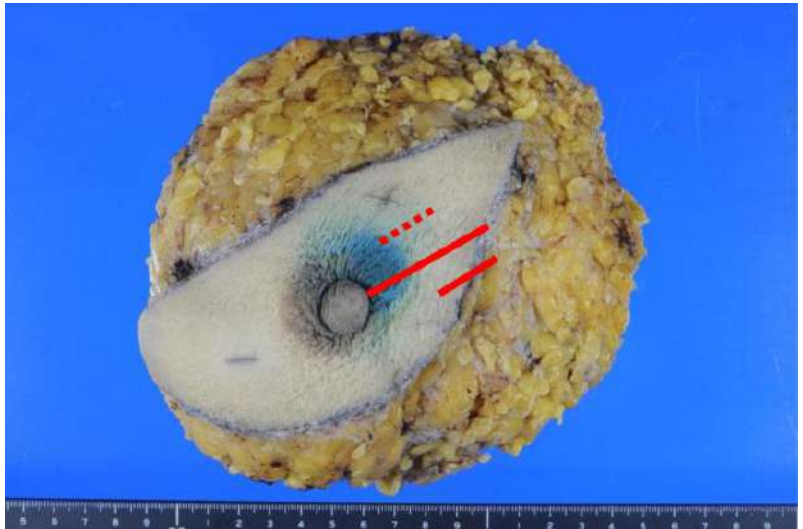
Tahap lanjut

- Core biopsy
- Biopsi insisi



Tahap awal

- Biopsi eksisi
- Breast conserving surgery
- Mastektomi



Penanganan spesimen

Bagian bedah

- Identitas pasien
- 10% *neutral buffer formalin* (NBF) dengan pH 5-7
- Ratio Volume jaringan: NBF =1:10
- Waktu antara pengambilan massa tumor sampai masuk NBF < 1 jam
- Waktu pengambilan tumor dan masuknya tumor ke NBF
- *Slicing*

Bagian patologi

- Pendaftaran spesimen
- Lama fiksasi 6-72 jam
- *Grossing*
- *Processing*
- *Embedding:* pembuatan blok parafin
- *Sectioning :* pemotongan dengan mikrotom
- Pewarnaan: H&E
- Diagnosis oleh dokter PA
- Pewarnaan imunohistokimia

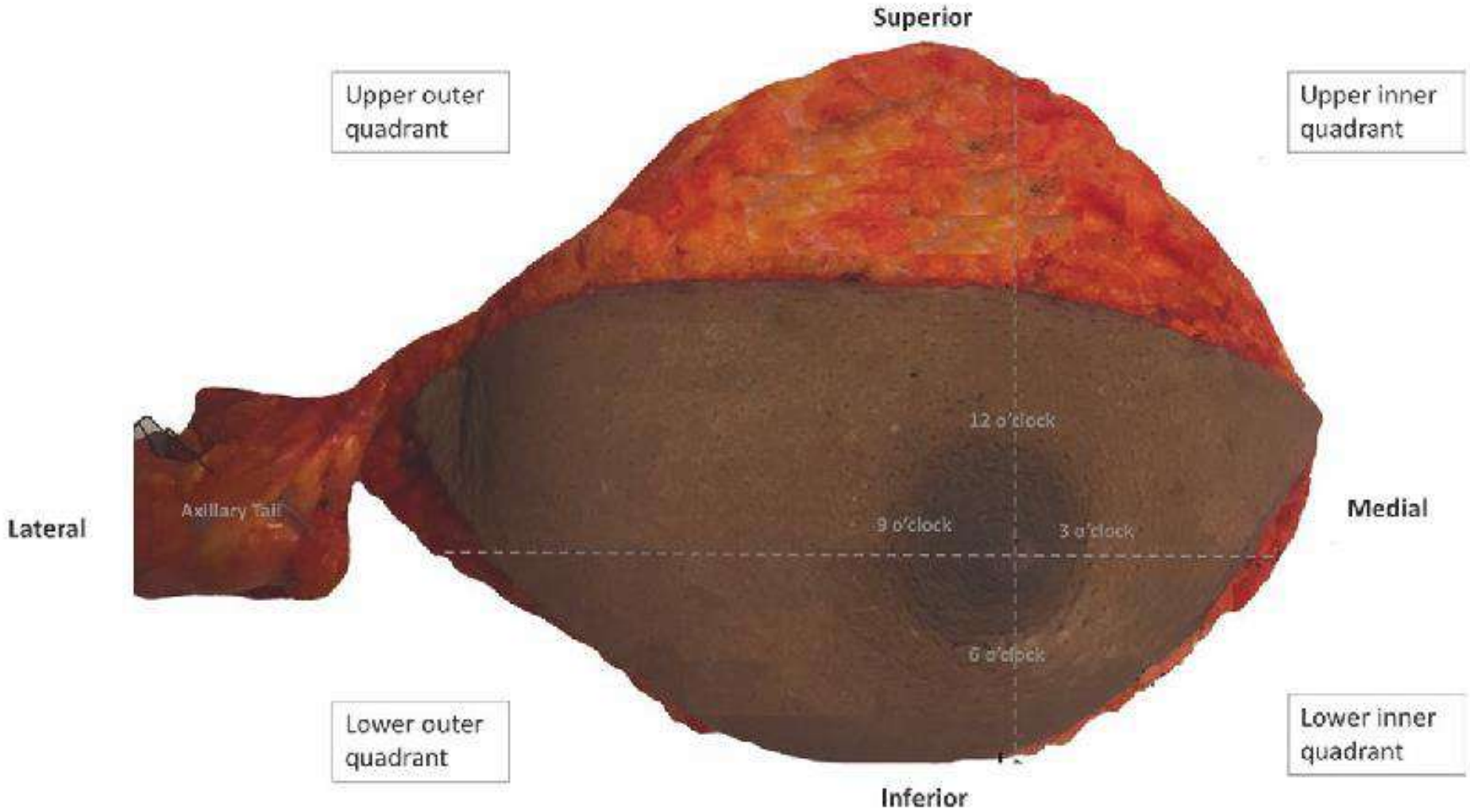


Fig. 2.1 Right mastectomy: Orientation. The mastectomy specimen consists of four quadrants in addition to superior, inferior, medial, and lateral sides. The specimen pictured also includes an axillary tail. The orientation can be described by clock positions, with 12 o'clock superiorly, 3 o'clock medially, 6 o'clock inferiorly, and 9 o'clock laterally. Note that the 3 o'clock and 9 o'clock positions would be switched with respect to the medial and lateral sides in a left mastectomy specimen. The nipple (or the base of nipple excision in nipple-sparing mastectomies) is considered the center point around which the four quadrants are arranged. This orientation scheme is used to describe the position of masses or other breast lesions

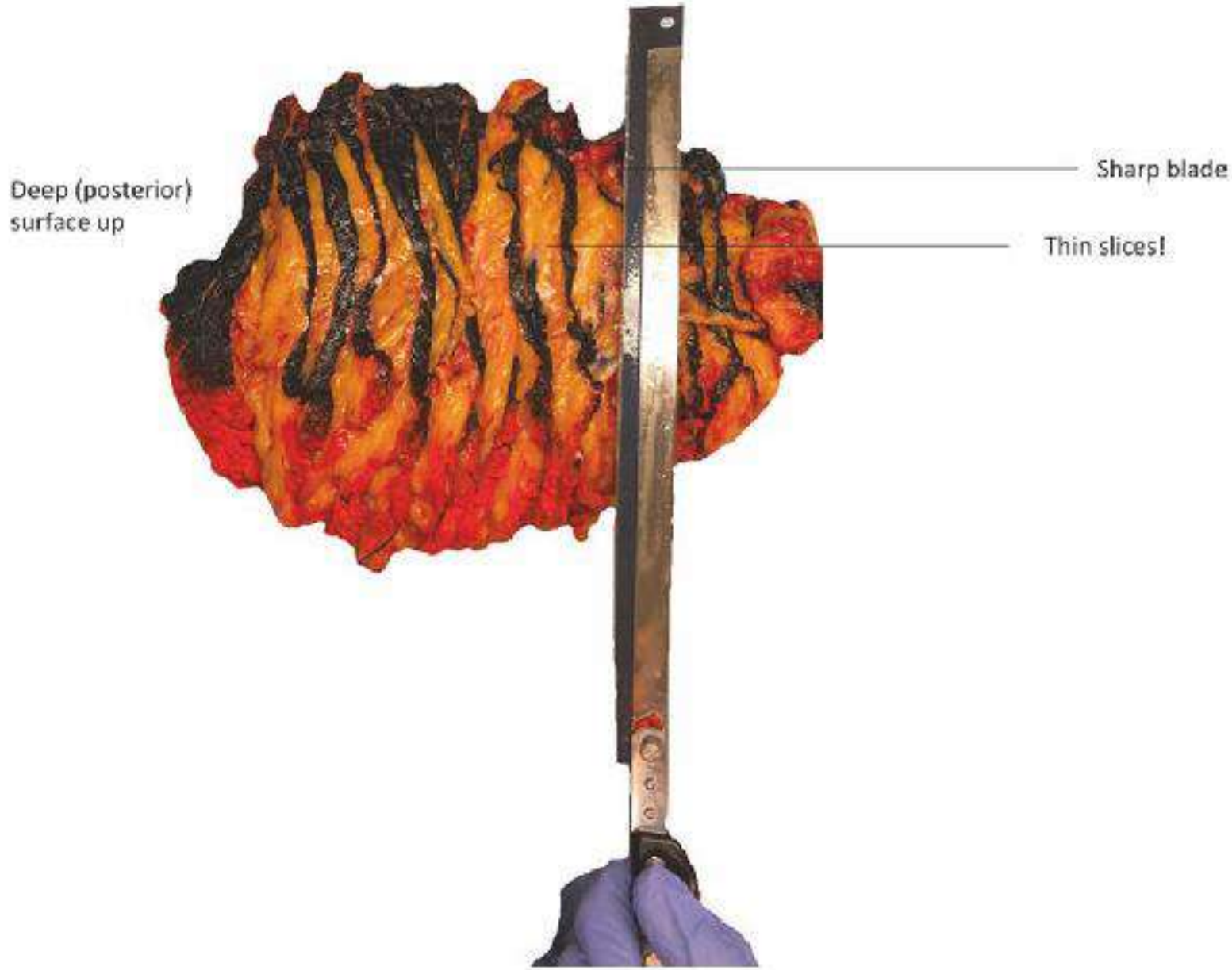
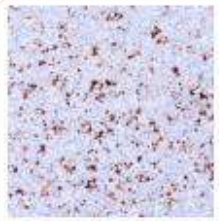
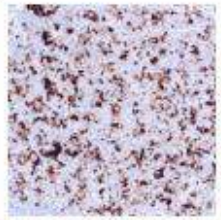
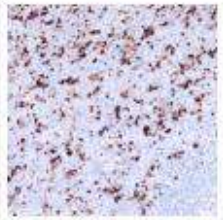
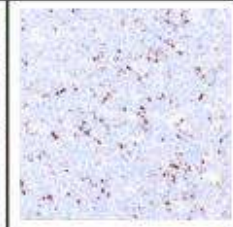
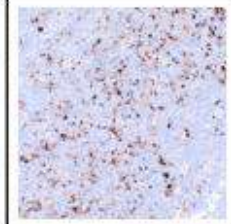
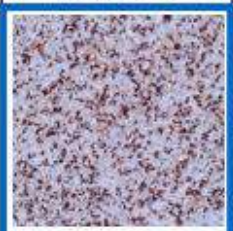
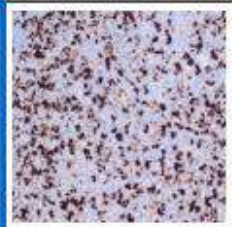
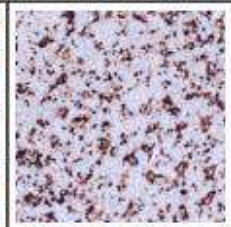
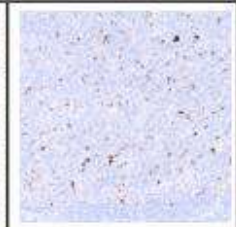
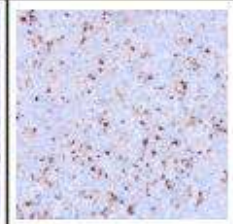
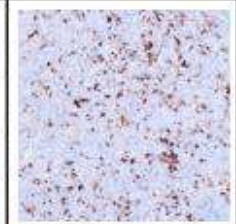
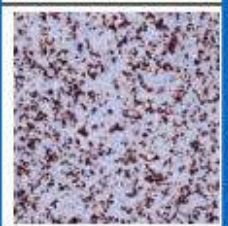
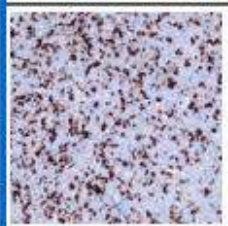
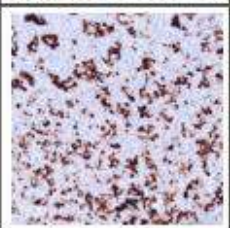
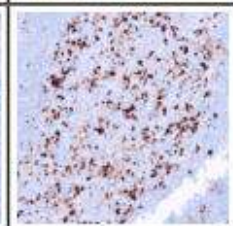
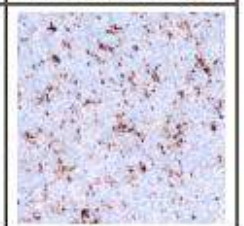
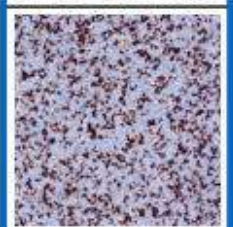
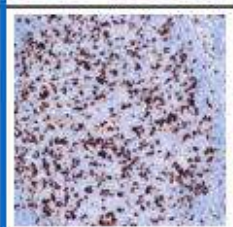
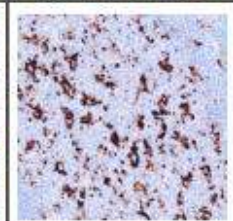
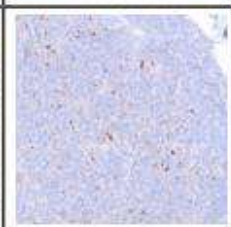
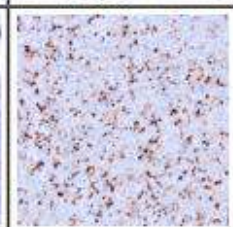
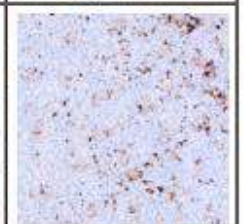
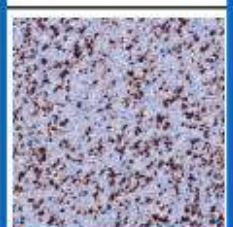
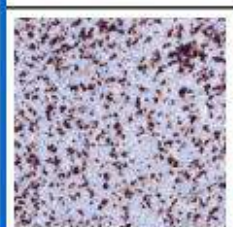
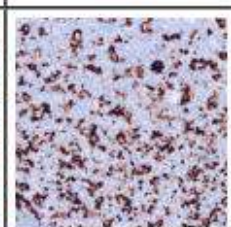
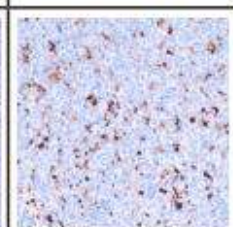
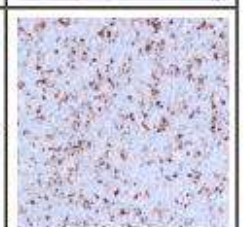


Fig. 2.3 Sectioning a mastectomy. The mastectomy specimen should be sliced along the long axis (medial to lateral, or lateral to medial), with the deep aspect always facing the prosector. The slices should be made as thin as possible so that lesions on the cut surface can be effectively detected. To cut effectively and keep track of orientation, always slice the breast with the skin (superficial aspect) facing down on the cutting board and the superior aspect directed upwards

Pengaruh lama fiksasi pada hasil pewarnaan IHK

Time Hours	Fixative					
	10% NBF	Zinc Formalin	Z-5*	PREFER*	AFA*	95% Alcohol*
1*						
6						
12						
24						
72						

(all images 20x magnification)

Workflow with Instrumentation Examples

1 **Grossing Workstations for gross cutting**

Analyze and dissect specimen, transfer selected areas of the specimen into labeled plastic cassettes.

2 **Tissue Processing**

Remove lipid and water from the tissues and replace with paraffin wax

3 **Embedding Center**

Specimen is embedded into paraffin wax to prepare tissue blocks for sectioning

4 **Sectioning**

Microtomes are used to cut and mount thin tissue sections into microscopic slides

5 **Staining Slides & Adding Cover Slip**

Slides are stained to highlight features; the tissue sections are then sealed into the slides with coverslips for use at the microscope

6 **Slide Case Assembly**

Slides are gathered and assembled in slide folders by case number and assigned a pathologist for distribuition.

7 **Future WSI & NGS**

New technology information processing functions

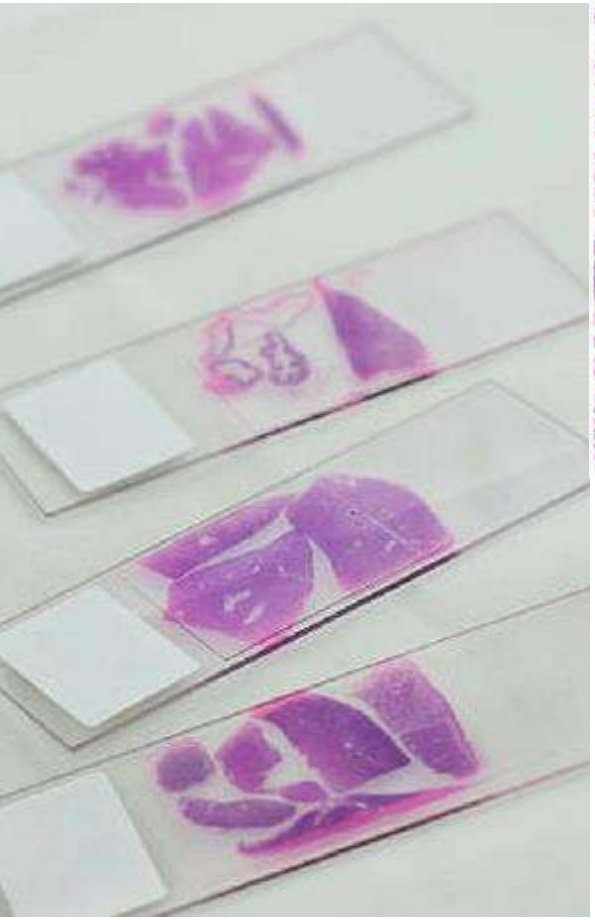
(Future WSI & NGS Function)

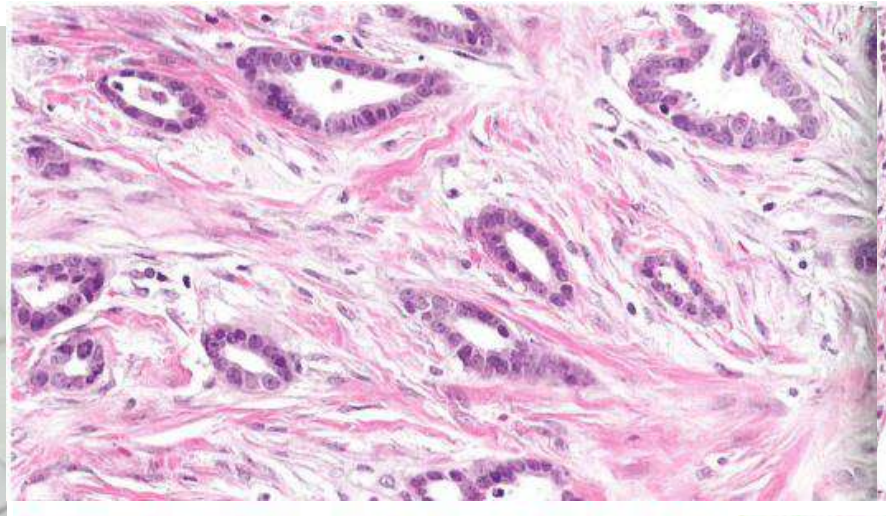
8 **Analysis & Review**

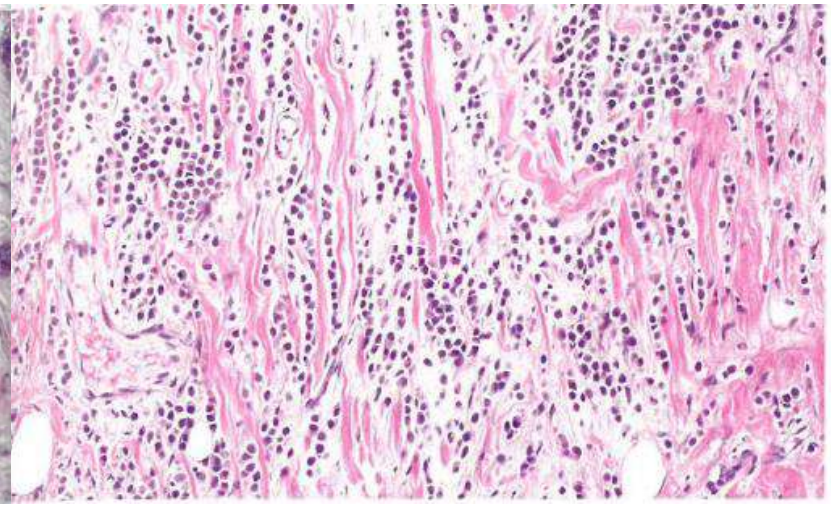
Pathologist microscopically examine slides for interpretation and diagnosis of disease.

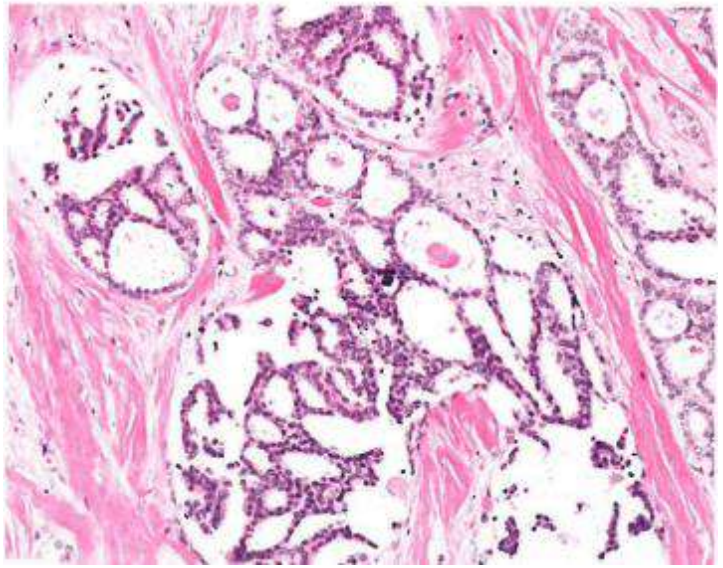
Mullay et al. Medicallab management 2017, Vol 6 no 10:8

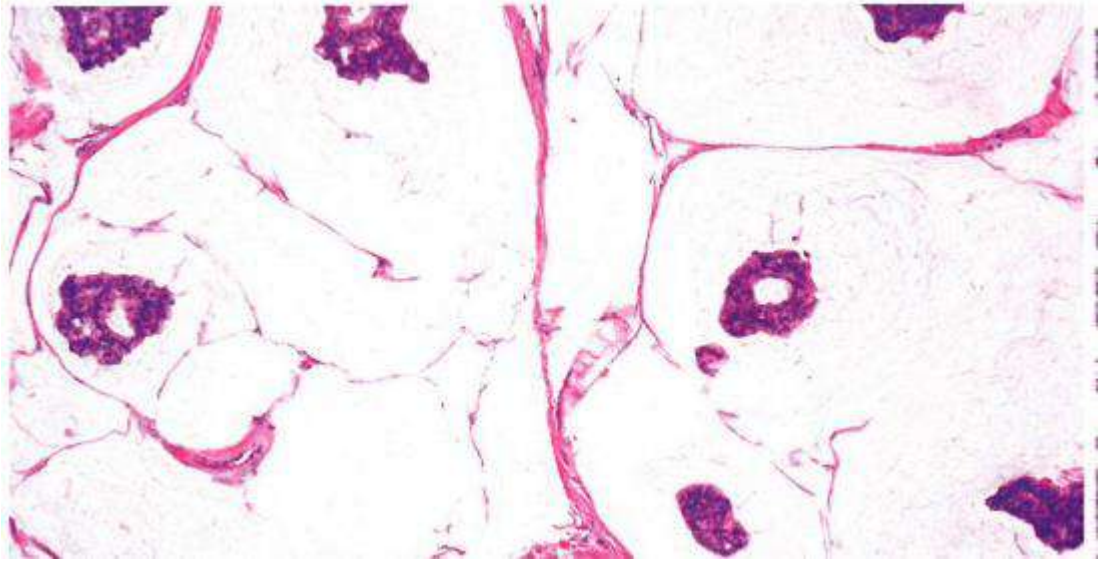
Pewarnaan Hematoksillin Eosin











Ekspertise Histopatologi

- Identitas pasien
- Diagnosis klinik
- Lokasi
- Deskripsi makroskopik
- Deskripsi mikroskopik
  - Jenis tumor
  - Grade
  - Invasi Limfovaskular
  - Batas sayatan
  - Kelenjar getah bening
  - Sebukan limfosit
  - Stage

Histological Type

Insitu
Ductal carcinoma insitu
Lobular carcinoma insitu

Invasive
Invasive breast carcinoma of no special type
Microinvasive carcinoma
Invasive lobular carcinoma
Tubular carcinoma
Cribriform carcinoma
Mucinous carcinoma
Mucinous cystadenocarcinoma
Invasive micropapillary carcinoma
Carcinoma with apocrine differentiation
Metaplastic carcinoma

WHO 5thed, 2019

Others
Papillary carcinoma
Papillary ductal carcinoma insitu
Encapsulated papillary carcinoma
Solid papillary carcinoma (insitu & invasive)
Invasive papillary carcinoma
Rare and salivary gland-type tumours
Acinic cell carcinoma
Adenoid cystic carcinoma
Secretory carcinoma
Mucoepidermid carcinoma
Polymorphous adenocarcinoma
Tall cell carcinoma with resersed polarity
Neuroendocrine tumour
Neuroendocrine carcinoma

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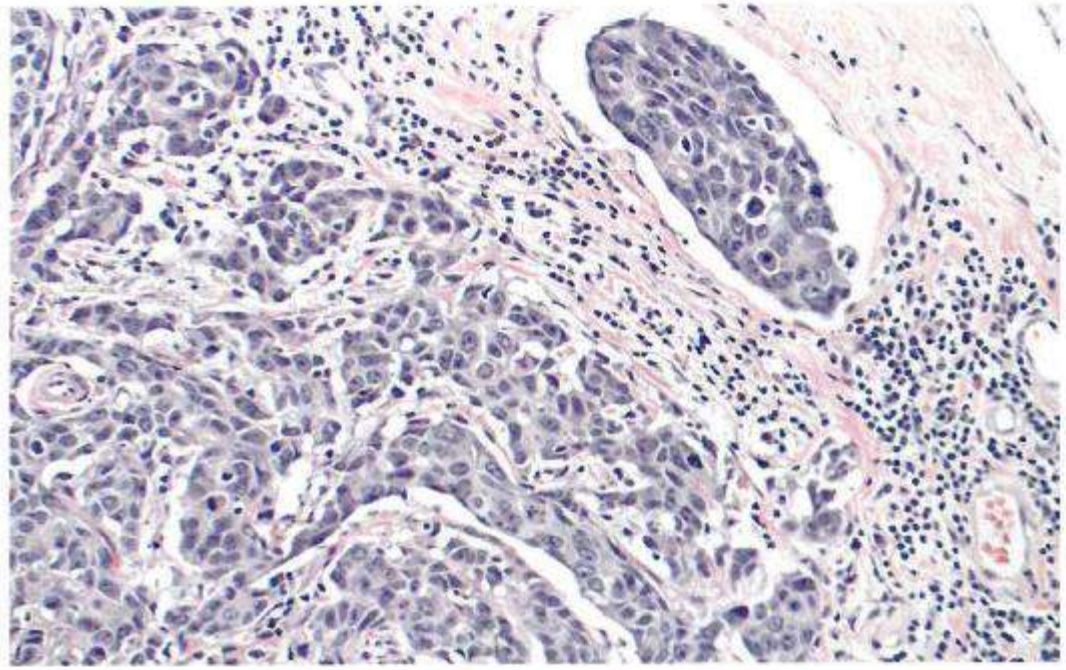

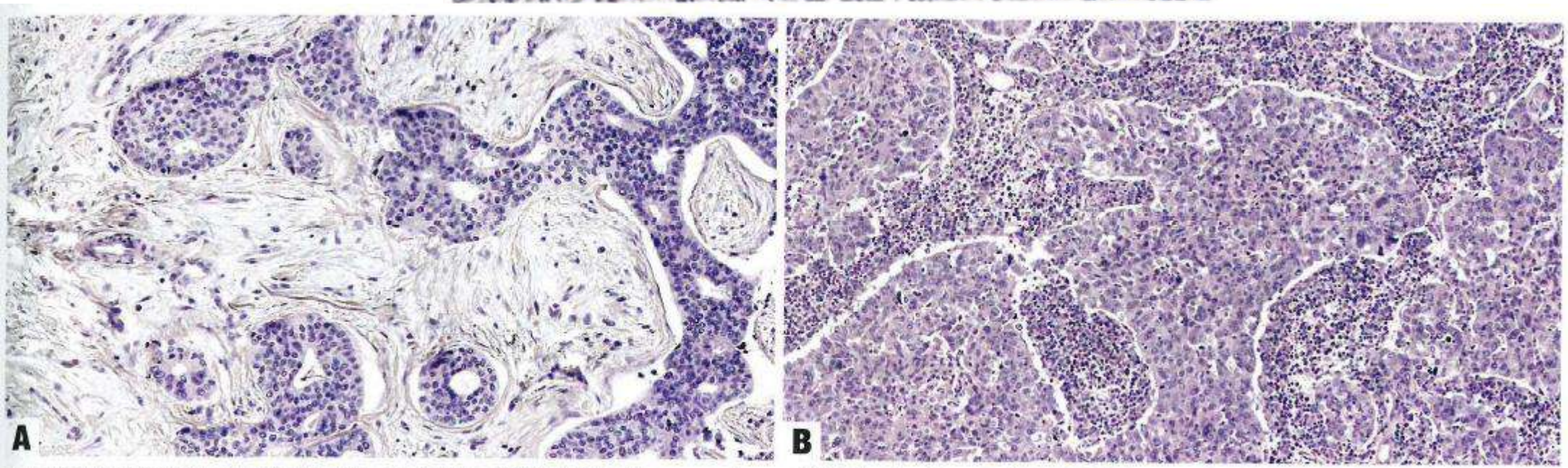

Fig. 2.92 Invasive breast carcinoma of no special type (NST). **A** Note the sparse tumour-infiltrating lymphocytes (~1%). **B** This tumour is rich in tumour-infiltrating lymphocytes (~95%).

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Grading

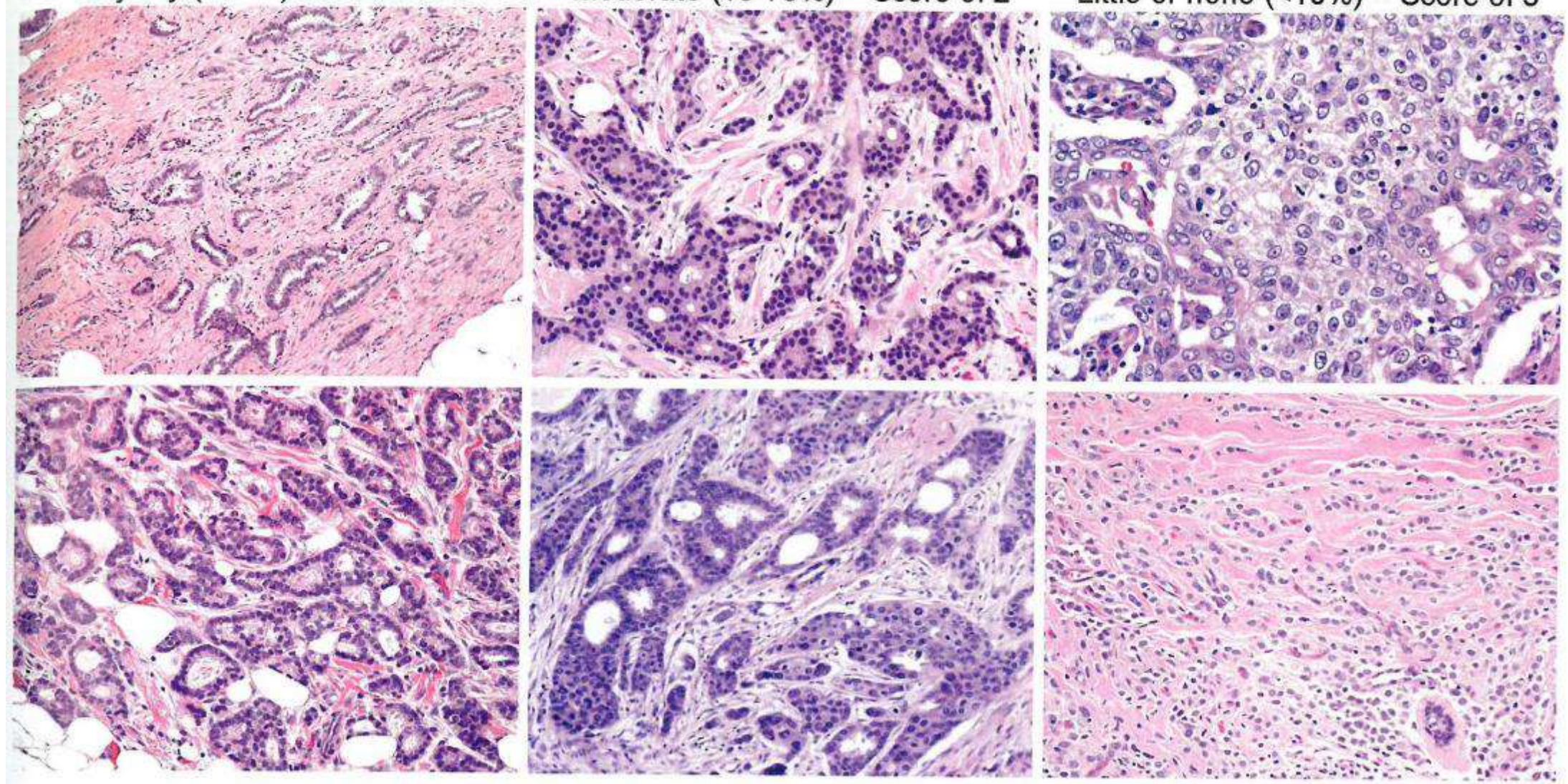
- Tubular formation
- Nuclear pleomorphism
- Mitotic Count

Nottingham Grading Examples: Tubule Formation

Majority (>75%) = Score of 1

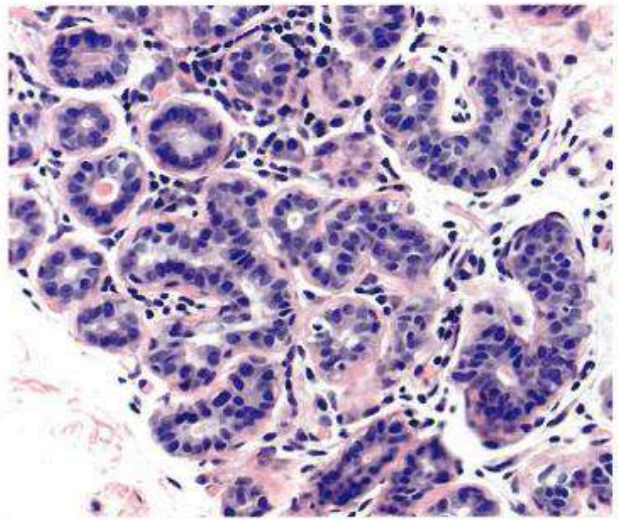
Moderate (10-75%) = Score of 2

Little or none (<10%) = Score of 3

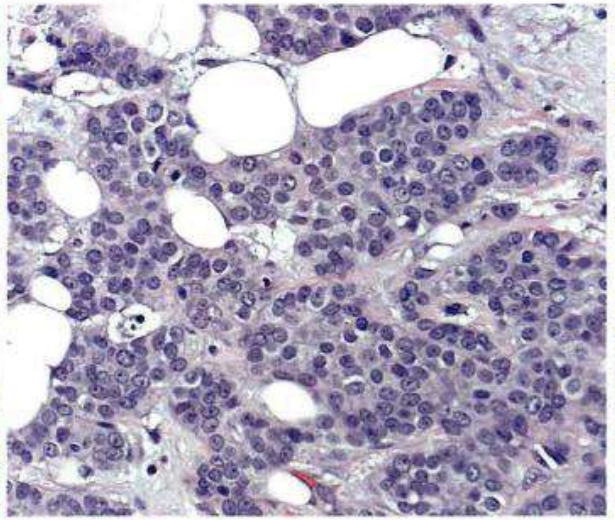


Nottingham Grading Examples: Nuclear Pleomorphism

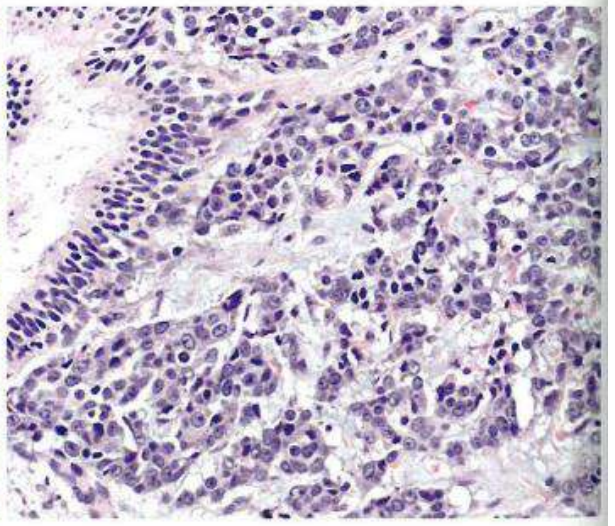
Normal



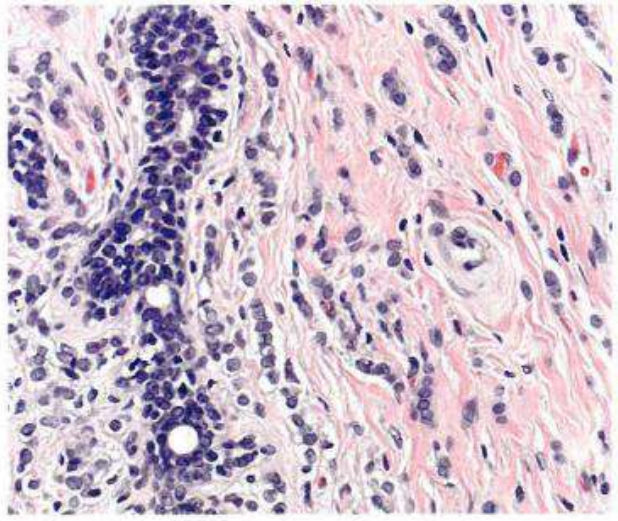
Moderate increase in size + variability = Score of 2



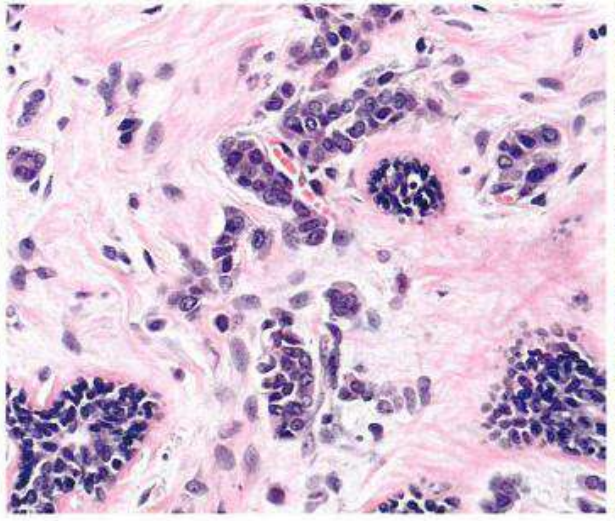
Marked variation = Score of 3



Small, regular uniform = Score of 1



Moderate increase in size + variability = Score of 2



Marked variation = Score of 3

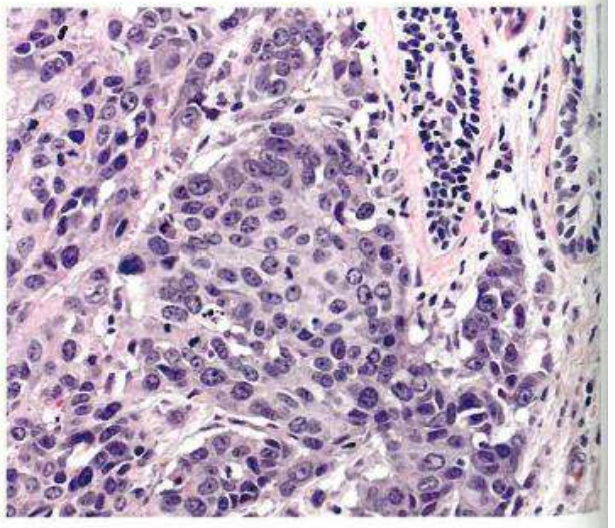


Table 2.06 Semiqualitative method for assessing histological grade in breast tumours {585}

Feature	Score
Tubule and gland formation	
Majority of tumour (> 75%)	1
Moderate degree (10–75%)	2
Little or none (< 10%)	3
Nuclear pleomorphism	
Small, regular, uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic count	
Dependent on microscope field area[a]	1–3
Total score	**Final grading**
Add the scores for gland formation, nuclear polymorphism, and mitotic count:	
3–5	Grade 1
6 or 7	Grade 2
8 or 9	Grade 3

Terapi Kanker Payudara

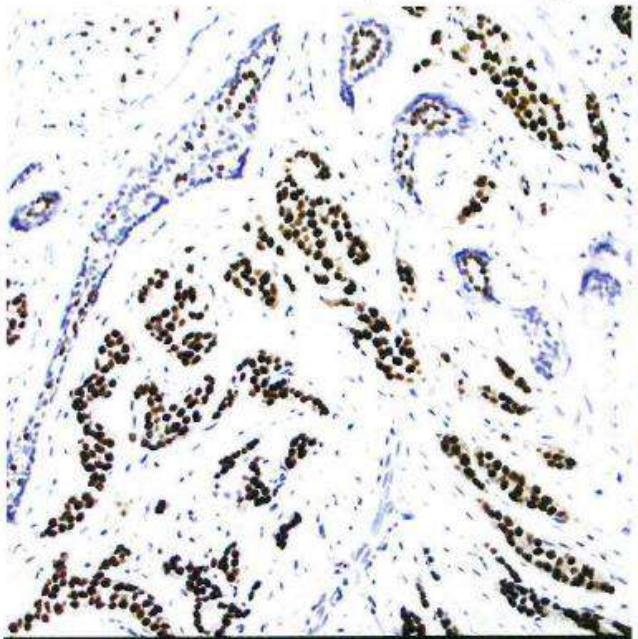
- Bedah
- Kemoterapi
- Radioterapi
- Terapi hormonal
- *Targeted therapy*
- *Imuno therapy*

Pemeriksaan Imunohistokimia

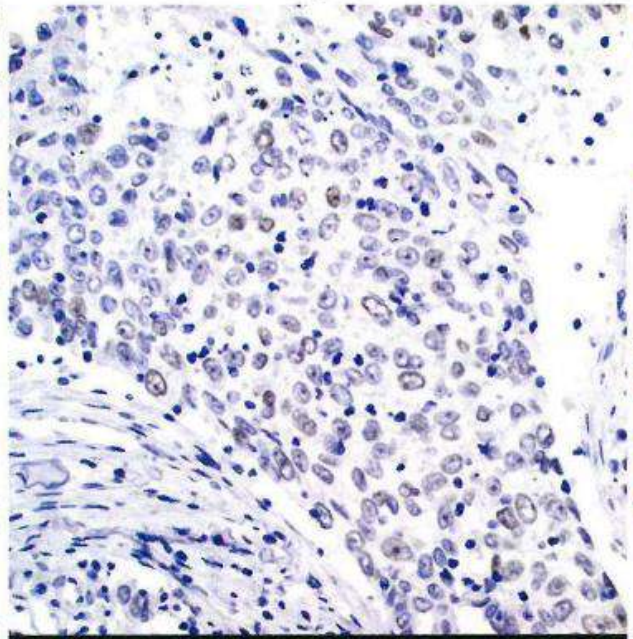
- ER (Estrogen Receptor)
- PR (Progesteron Receptor)
- HER 2(Human epidermal growth Factor receptor-2/ c-erbB-2)
- Ki-67

Hormone receptor staining interpretation (ER and PR)

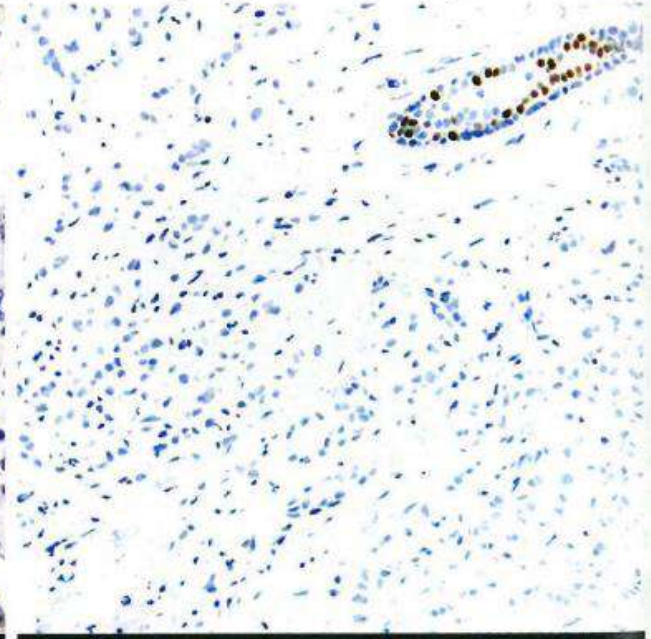
Evaluate overall percentage of cancer in sample with nuclear staining and intensity of stain



Example of a cancer with uniform strong staining



Example of a cancer with weak focal staining



Example of a cancer with no staining and a positive internal control

If ≥ 1% of cells stain

Interpretation: **Positive***

(include % and intensity in report)

*Report as low positive if 1–10% of cells stain

If < 1% or 0% of cells stain

Interpretation: **Negative**

(note whether result was < 1% or 0%)

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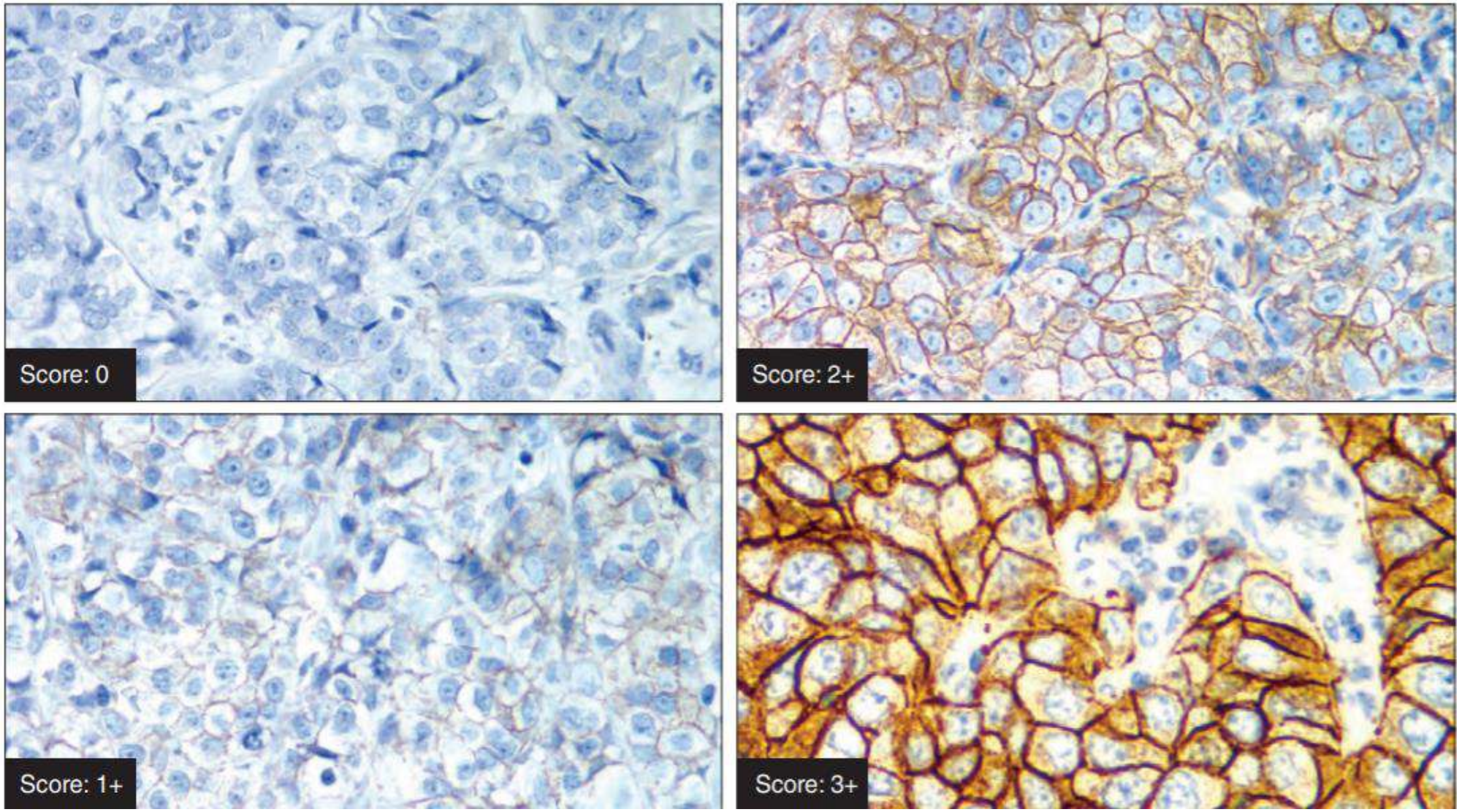
HER 2



Herceptest™ interpretation Manual Breast Cancer

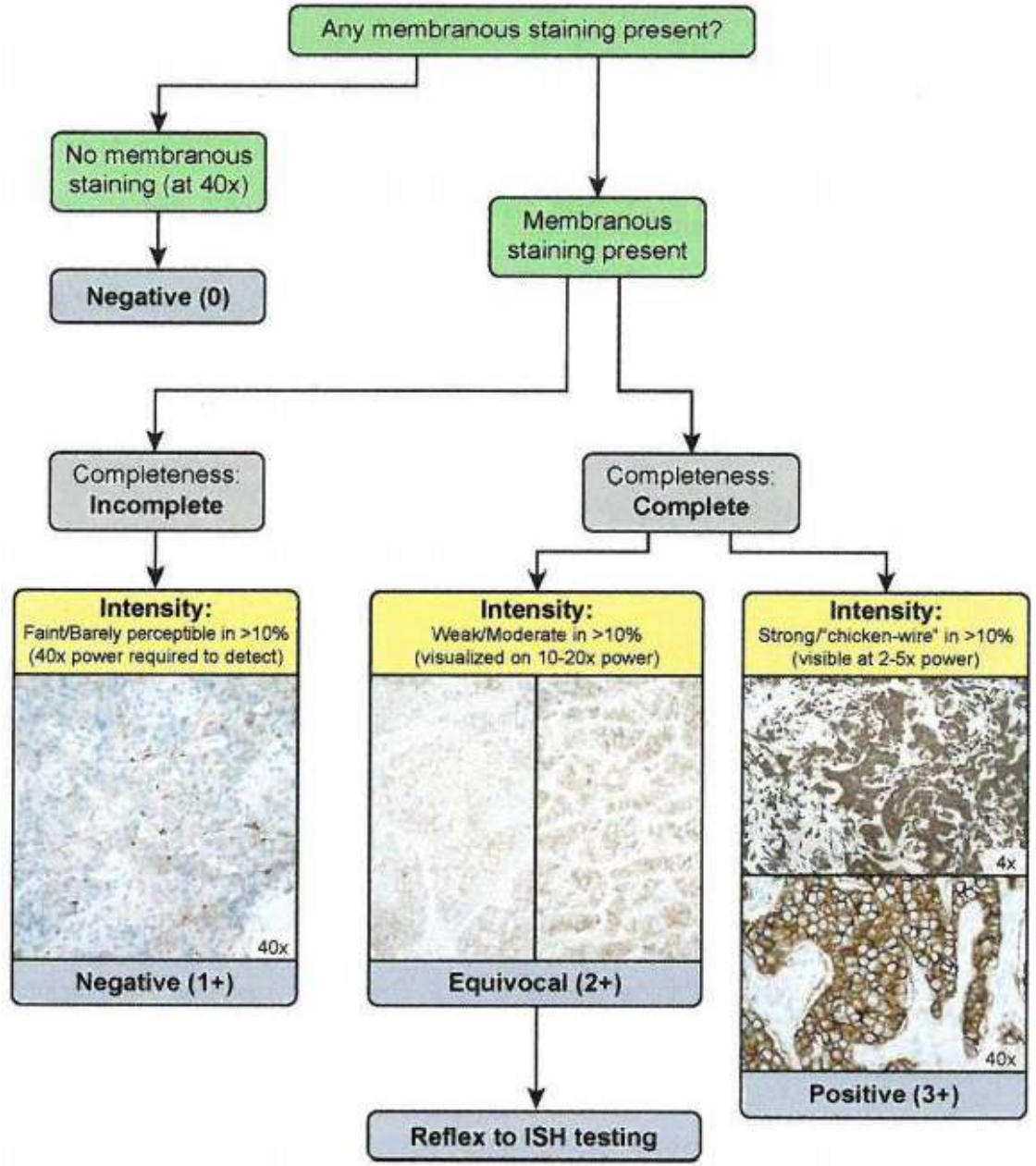


Fig. 2.81 Algorithm for interpreting ERBB2 (HER2) immunohistochemical staining in invasive breast carcinoma. ISH, in situ hybridization.

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Subtipe Kanker Payudara

Intrinsic subtype	Clinicopathology surrogate definition	ER	PR	HER 2	Ki67
Luminal A	Luminal A - like	+	+	-	low
Luminal B	Luminal B – like (HER2 Negative)	+	-/low	-	high
	Luminal B – like (HER2 Positive)	+	any	+	any
Erb-B2 overexpression	HER2 positive (non luminal)	-	-	+	
“Basal like”	Triple Negative	-	-	-	

Goldhirchs 2013 Annals of Oncology 21:2206-2223

Berdasarkan Pemeriksaan Imunohistokimia

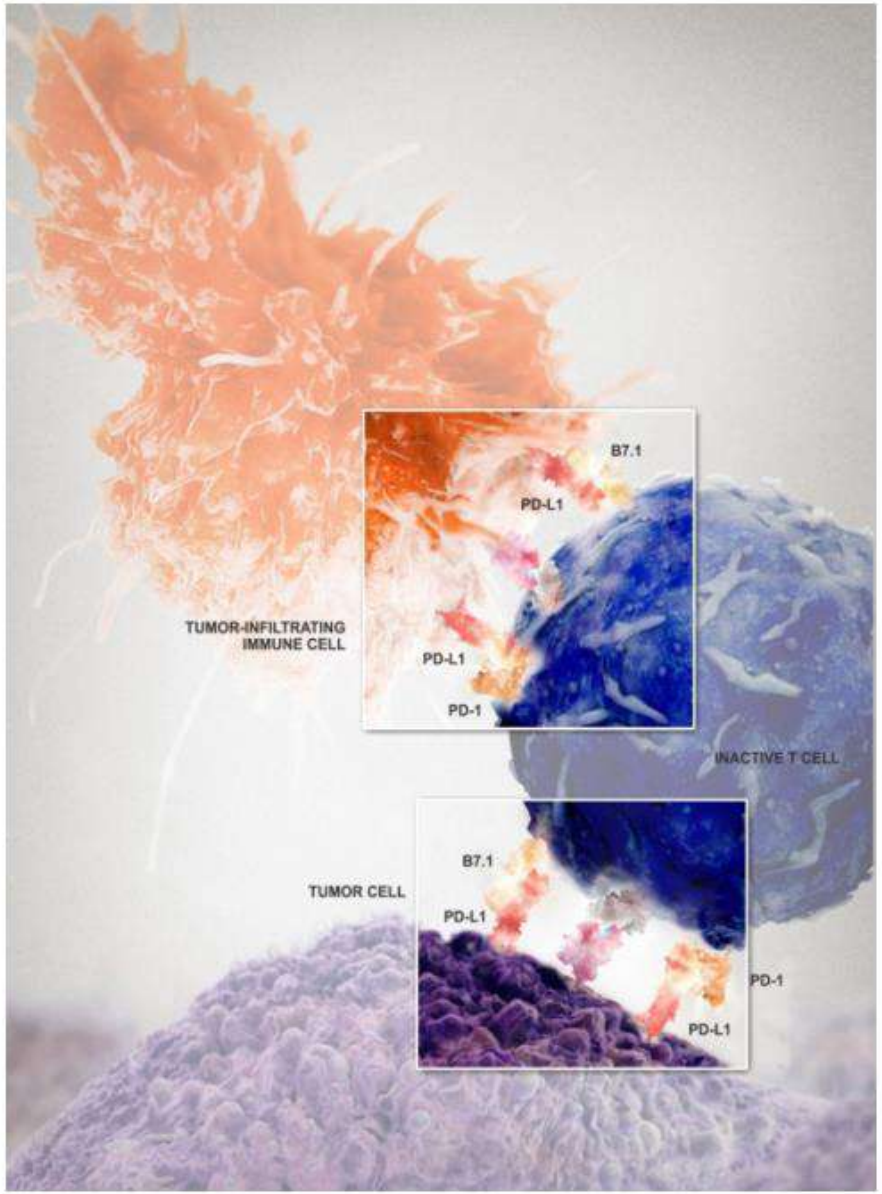
- Jenis Pengobatan
  - ER positif: Hormonal terapi contoh :Tamoxifen, Aromatase inhibitors · Goserelin (Zoladex) · Leuprorelin (Prostap) · Fulvestrant (Faslodex)
  - HER 2 positif +3: Terapi target contoh trastuzumab (Herceptin)

    HER 2 low positif: +1 dan 2: trastuzumab-deruxtecan*
  - Triple Negatif: Kemoterapi→ PDL1
- Prognosis
  - PR

*Breast. 2023 Feb; 67: 116–123

PD-L1 (Program Death-Ligand 1 Immunohistochemistry

- Triple Negative Breast cancer (TNBC) tahap lanjut/ metastasis
- Pewarnaan imunohistokimia menggunakan anti-PD-L1 rabbit monoclonal primary antibody untuk mengenali PD-L1 protein.
- PD-L1: Sel tumor dan sel imun



PD-L1 Clone

- SP 142
- Immune cells (IC): ≥ 1%
- Atezolizumab

- 22C3
- Combined Positive Score (CPS): ≥ 10 %
- Pembrolizumab

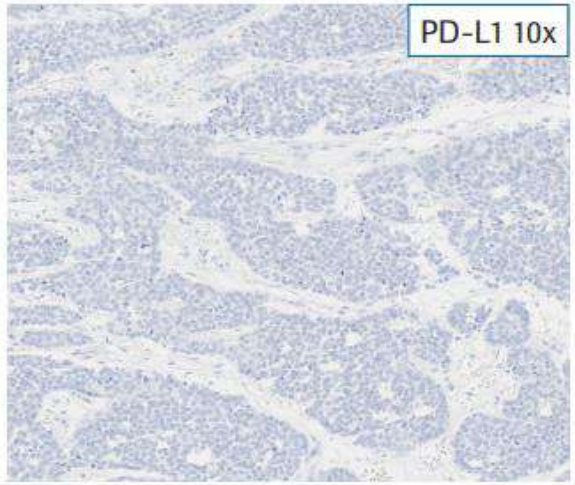
Table 1: VENTANA PD-L1 (SP142) Assay Scoring Algorithm for Triple-Negative Breast Carcinoma

Criteria/Characteristics	PD-L1 Expression
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	< 1% IC
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	≥ 1% IC

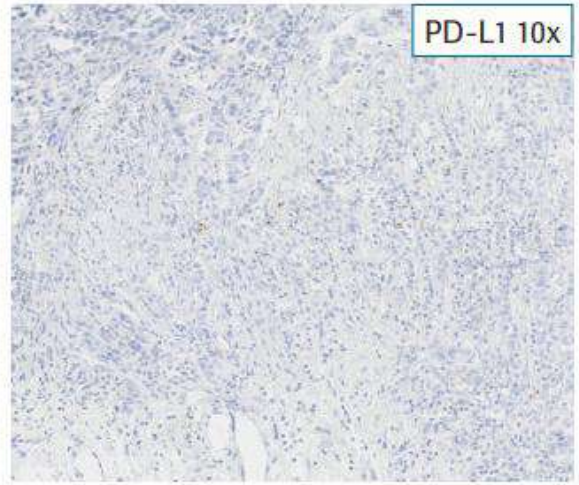
Table 2: Tumor-infiltrating Immune Cell (IC) Interpretation Criteria

Attributes	Descriptions
Type of cells showing staining	Lymphocytes, macrophages, dendritic cells, and granulocytes
Type of cells included in scoring	Lymphocytes, macrophages, dendritic cells, and granulocytes
Pattern	Aggregates in stroma, single cells dispersed among tumor cells with punctate, linear or circumferential staining
Denominator for scoring	Tumor area

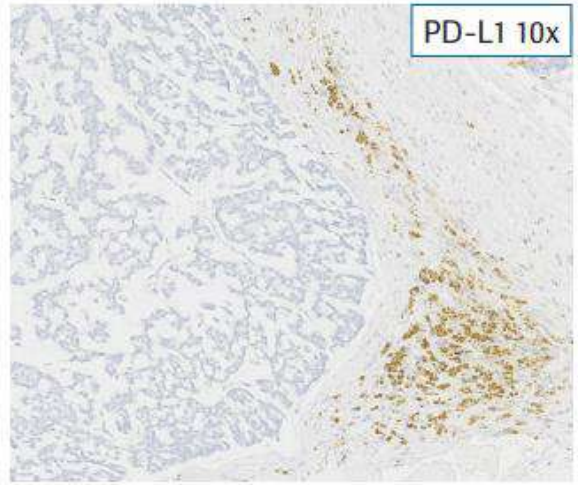
PD-L1 Expression < 1% IC



No Staining

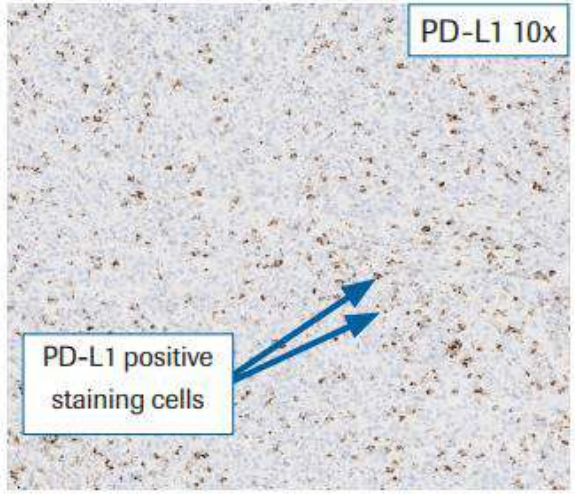


Light speckling and rare IC staining

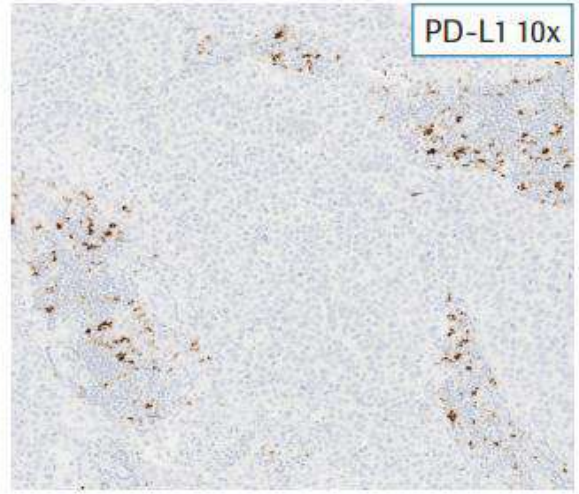


Hemosiderin pigment with no IC staining

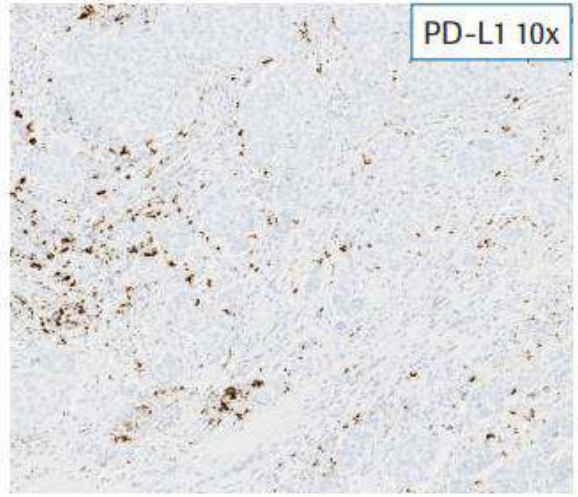
PD-L1 Expression ≥ 1% IC



Single-cell spread staining



Predominantly aggregate staining



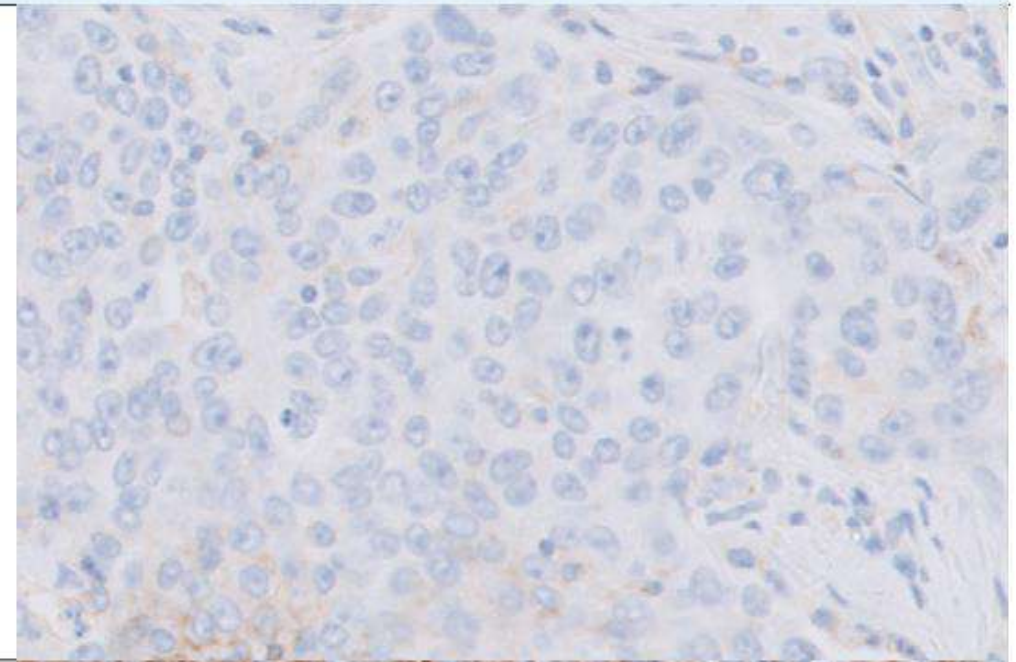
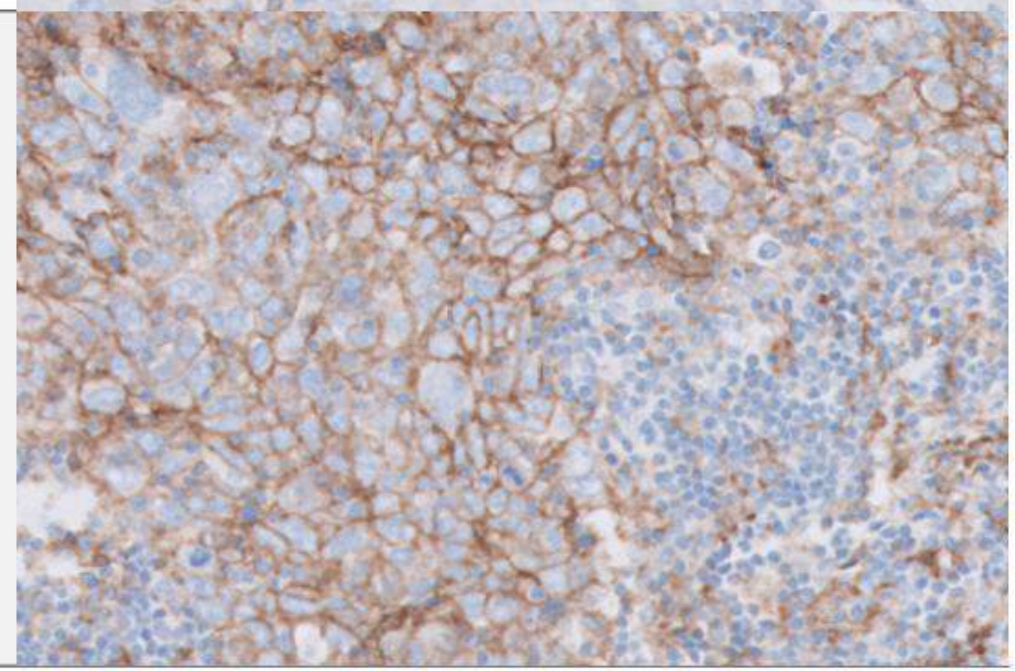
Aggregate and single-cell spread staining

PD-L1 22C3

TNBC tissue specimens that are tested for PD-L1 expression are scored and divided into PD-L1 expression levels based on a Combined Positive Score (CPS):

- CPS < 10
- CPS ≥ 10

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$$

CPS	PD-L1 Expression Level	Image (20× magnification)
< 10	CPS is less than 10	
≥ 10	CPS is greater than or equal to 10	

KESIMPULAN

- Kanker payudara merupakan kanker terbanyak di dunia dan Indonesia
- Penanganan spesimen yang baik sangat penting untuk diagnosis.
- Diagnosis kanker payudara ditegakkan melaui pemeriksaan histopatologi.
- Pemeriksaan Imunohistokimia untuk kanker payudara perlu dilakukan untuk terapi dan prognosis.

TERIMA KASIH

RUMAH SAKIT
SUMBER WARAS

SERTIFIKAT

Diberikan pada

Dr. dr. Sony Sugiharto, Sp.PA

Sebagai Pembicara

Seminar Mini Komite Medik

" Tatalaksana Kanker Payudara Terupdate "

Dilaksanakan pada 24 Oktober 2023

Jakarta, 26 Oktober 2023
Rumah Sakit Sumber Waras

RUMAH SAKIT SUMBER WARAS JAKARTA

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Pjs.Direktur Utama