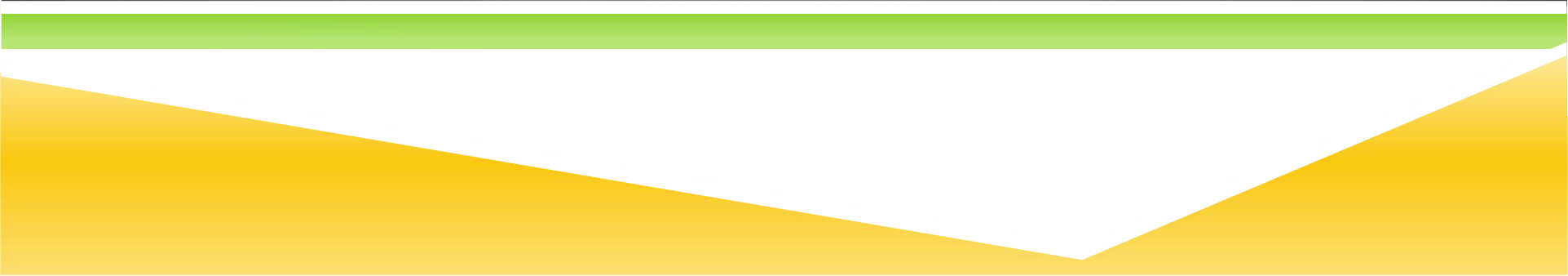


OVERVIEW OF CANCER AND AND ITS TREATMENT



OBJECTIVES

- ▶ What is cancer?
- ▶ Different types of cancer
- ▶ Treatment of cancer
- ▶ Side effects of cancer treatment
- ▶ Oncological emergencies
- ▶ The Cancer pharmacist's role
- ▶ Further Information
- ▶ Suggested reading

I. WHAT IS CANCER?

- Cancer is a disease in which cells of an organ or tissue of the body become *abnormal, failing to respond* to normal control mechanisms, *growing* and *multiplying* out of control
- Tumour is the mass of out of control cells – *benign* or *malignant*
- *Malignant* – invade and destroy surrounding tissue and *spread* to distant locations- metastases
- *Metastases* occur when malignant cells become *detached* from the original primary tumour and *travel in blood or lymphatic system* and establish themselves at a new site

II. CANCER IN INDONESIA

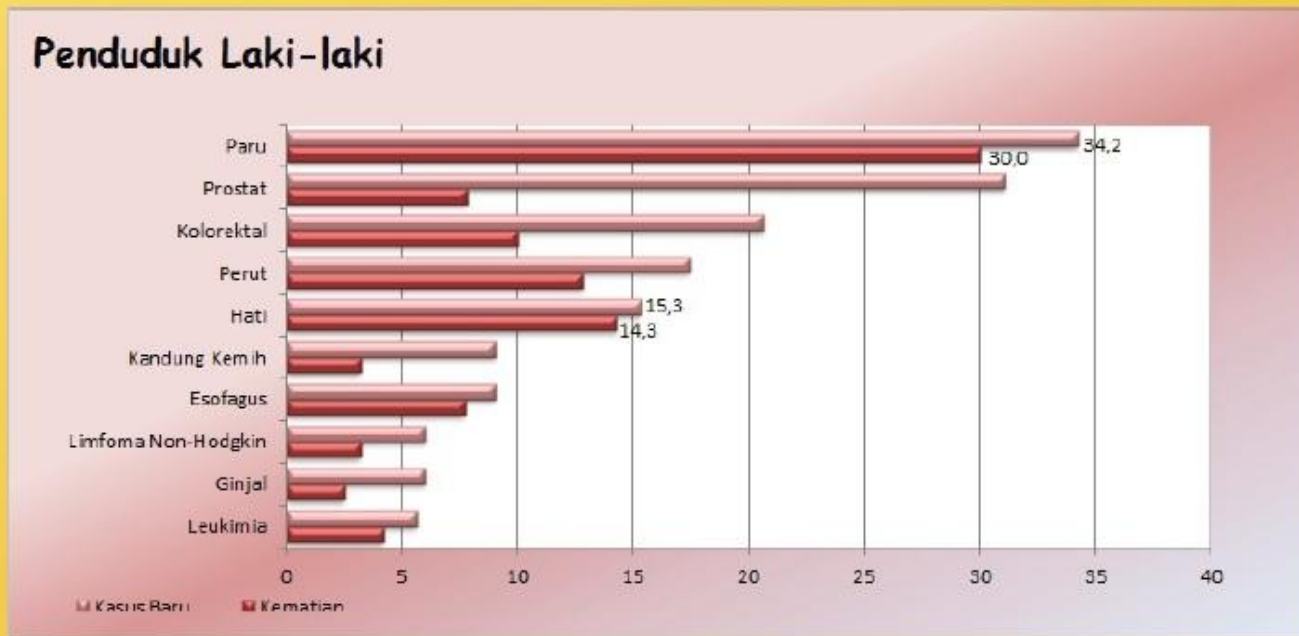
Per 31 Januari 2019 > peringkat kanker di Indonesia menempati urutan *kedelapan* di Asia Tenggara dan 23 di Asia

Prevalence > Meningkat dari 1,4 per seribu penduduk di 2013 menjadi 1,79 per seribu penduduk di 2018.

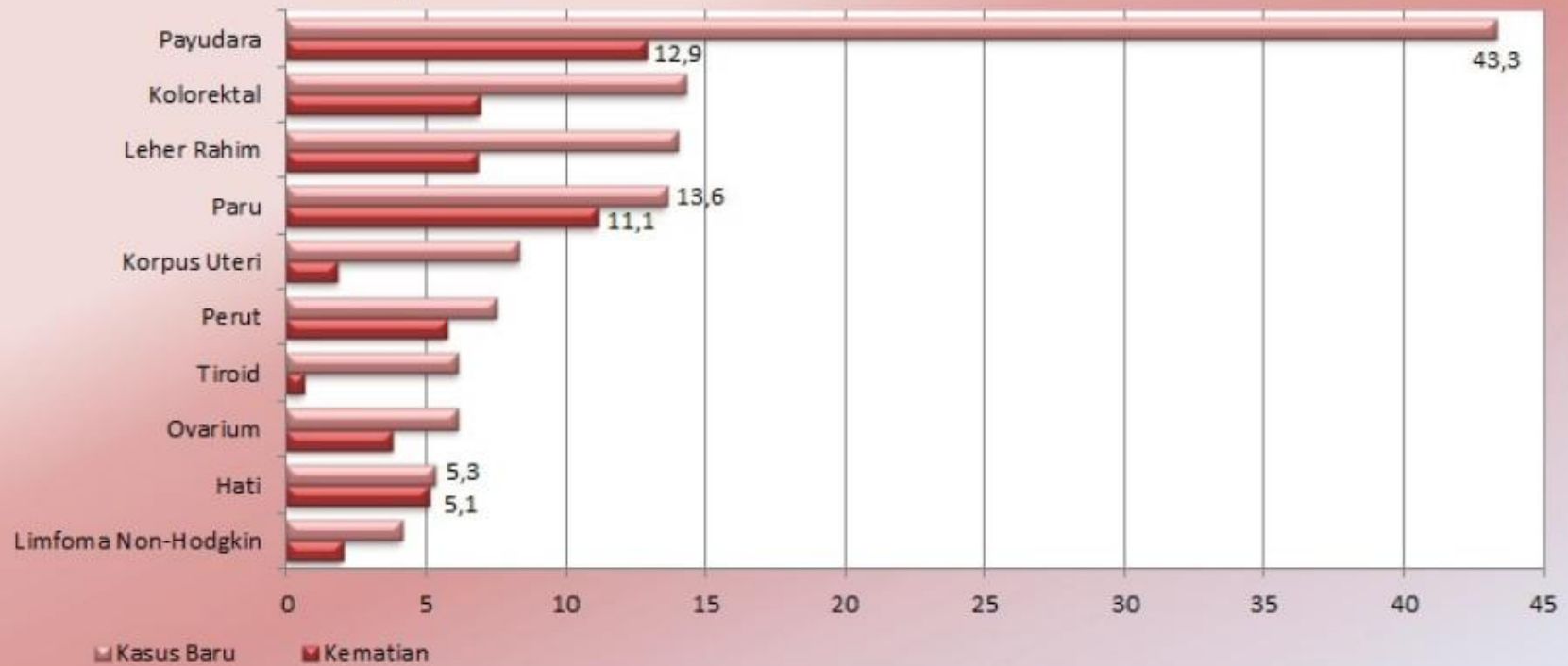
(Riset Kesehatan Dasar 2018 Kementerian Kesehatan Republik Indonesia)

Cancer Incidence Based on Gender

Gambar 1. Estimasi Persentase Kasus Baru dan Kematian Akibat Kanker pada Penduduk Laki-laki dan Perempuan di Dunia Tahun 2012



Penduduk Perempuan



Sumber : *GLOBOCAN, IARC, 2012*

III. CANCER IN THE UK

► **Some statistics**

- More than 200 types of cancer
- 356,860 new cases diagnosed in 2014 in UK
- 163,444 people died from cancer in 2014 in UK
- 50% survive 10+ years as of 2010-11
- 42% preventable

Reference: Cancer Research UK 2016

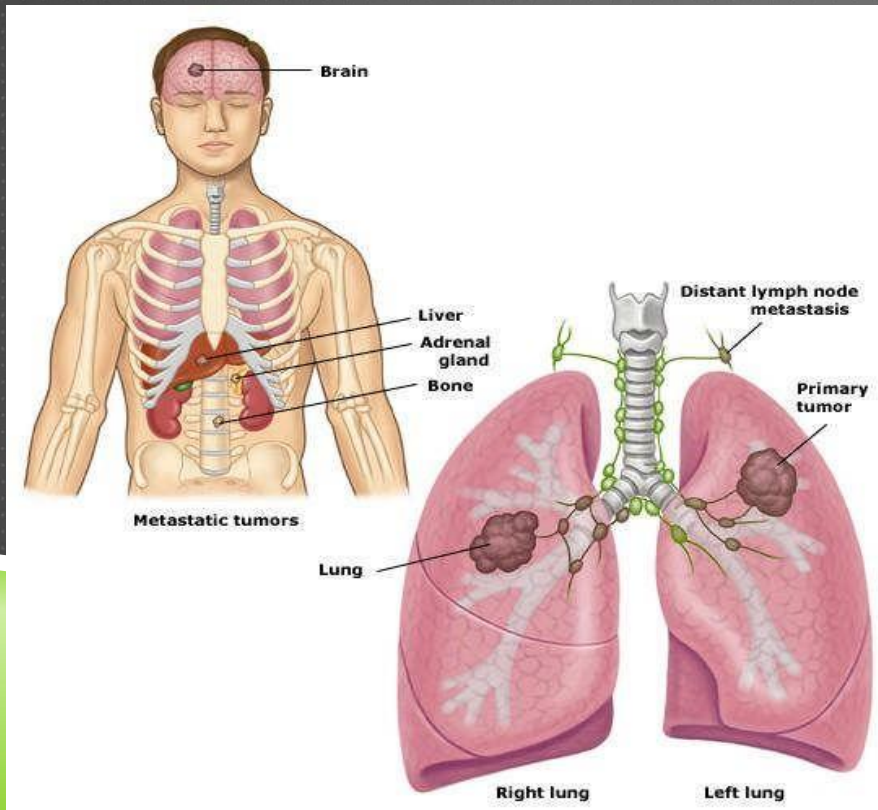
► **Government tackling cancer**

- Cancer Reform Strategy 2011, Five Year Forward View 2014
- **NICE guidance** and technology appraisals
- **Cancer Drug Fund** since 2011
 - New structure for CDF in July 2016 - £340m/yr (no overspend)

IV. DIFFERENT TYPES OF CANCER

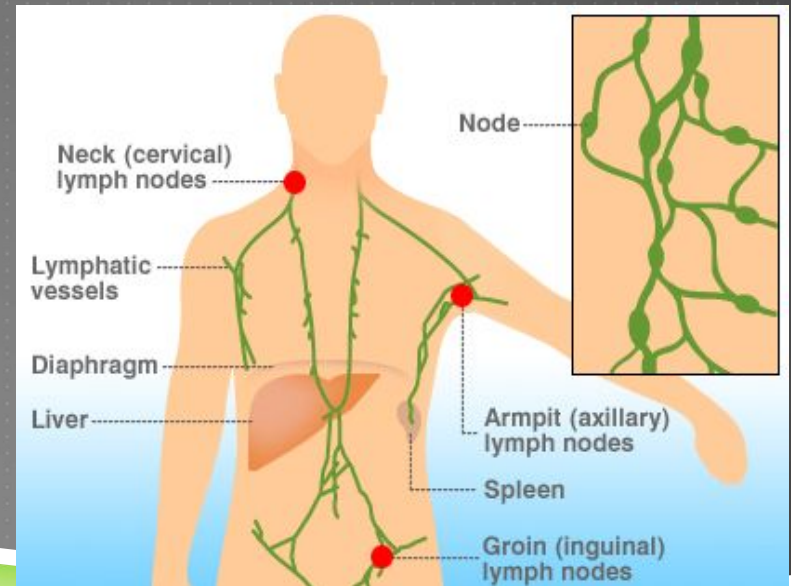
- ▶ Solid Tumours

- ▶ Eg colorectal, breast, lung, brain



- ▶ Haematological malignancy

- ▶ Leukaemia, lymphoma, myeloma



DIFFERENT TYPES OF CANCER (Cont)

- ▶ Solid Tumours
(Tumor
Padat)

- ▶ Carcinoma
- ▶ Sarcoma
- ▶ Melanoma

- ▶ Haematological malignancy
(keganasan di darah)

- ▶ Leukaemia,
- ▶ lymphoma,
- ▶ myeloma

DIFFERENT TYPES OF CANCER (Cont)

► Solid Tumours

► Carcinoma

- Kanker yg berasal dr **lapisan kulit terluar** or **jaringan yg melapisi** or menutupi organ internal (**jaringan epitel**)
- Kanker Nasofaring, Kanker kulit (melanoma), kanker paru, kanker ovarium, kanker usus besar, kanker prostat, kanker pancreas

► Sarcoma

- Kanker dari **mesotel** (jaringan **tengah atau ikat**), misal jar. **Tulang, tulang rawan, lemak**, otot, pembuluh darah, **jaringan ikat** atau penyokong lainnya)
- Kanker tulang, osteosarcoma, liposarcoma, angiosarcoma, fibrosarcoma, lipoma, synovial sarcoma

DIFFERENT TYPES OF CANCER (Cont)

► Haematological malignancy

► Leukemia

- Kanker yg berasal dari jaringan pembentuk darah, seperti sumsum tulang
- ALL (Acute Leukemia Lymphoblastic) & CLL (Chronic Leukemia Lymphoblastic)
- AML (Acute Leukemia Myelogenous) & CML (Chronic Leukemia Myelogenous)

► Lymphoma

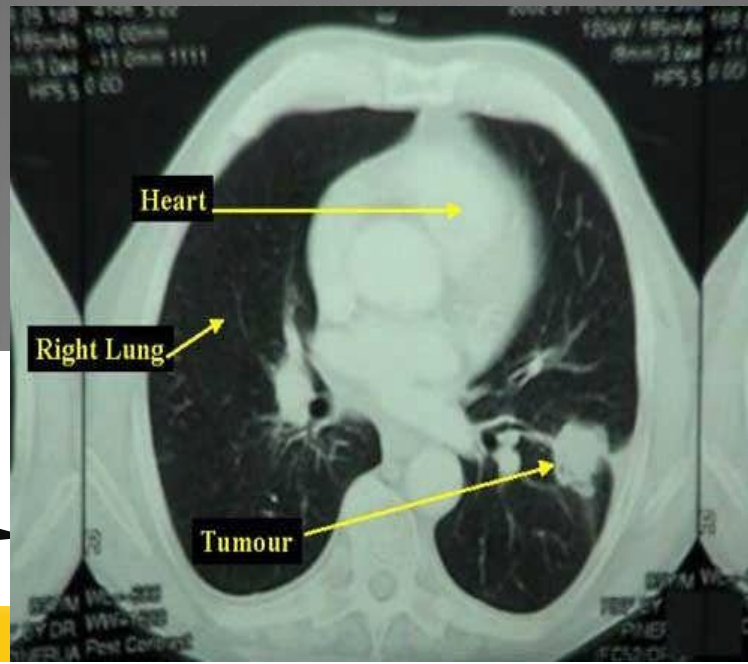
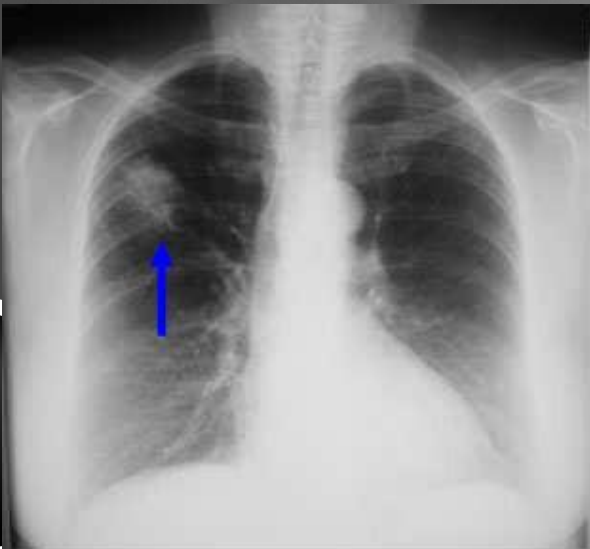
- Kanker Limfosit (kanker yg terbentuk dr sel2x system imun or system limfatik)
- Limfoma sel-T, Limfoma Sel B, Limfoma Hodgkin, Limfoma Non Hodgkin

► Myeloma

- Kanker yang berasal dari sel plasma dari sumsum tulang
- Sel2x plasma ini menghasilkan protein yg dapat ditemukan dalam darah

V. DIAGNOSIS

- ▶ Impairment, change in normal function
- ▶ X-ray – shows lesion
- ▶ CT scan – shows lesion
- ▶ PET scan – shows area of activity



VI. DIAGNOSIS - SYMPTOMS

► Colorectal cancer

- blood in stools = **darah di tinja**
- a change in normal bowel habit (**BAB**) (**diarrhoea or constipation**) for no obvious reason, **lasting** longer than **six weeks**
- **pain** in the **abdomen** or **rectum**
- **a feeling of not havisng emptied** the bowel properly after a bowel motion
- unexplained **weight loss/tiredness**

DIAGNOSIS - SYMPTOMS

► Lung Cancer

- a continuing **cough**, or change in a **long-standing cough**
- a **chest infection** that doesn't improve
- increasing breathlessness = **sesak nafas** and wheezing = **mengi**
- blood-stained sputum = **dahak bernoda darah**
- hoarse voice = **suara serak**
- dull ache = **nyeri tumpul**, or a sharp pain = **nyeri tajam**, when you **cough** or take a **deep breath**
- **loss of appetite** and **weight loss**
- **difficulty swallowing**
- excessive **fatigue** = **lelah** and **lethargy** = **lesu**

DIAGNOSIS - SYMPTOMS

► Breast

- lump (**benjolan**) in the breast
- change in the **size** or **shape** of the breast
- dimpling (**lesung**) of the skin or thickening (**penebalan**) in the breast tissue
- inverted nipple (**puting menonjol ke dalam**)
- rash (**kemerahan**) on the nipple
- discharge (**cairan berbau**) from the nipple
- Swelling (**bengkak**) or a lump (**benjolan**) in the armpit (**ketiak**)

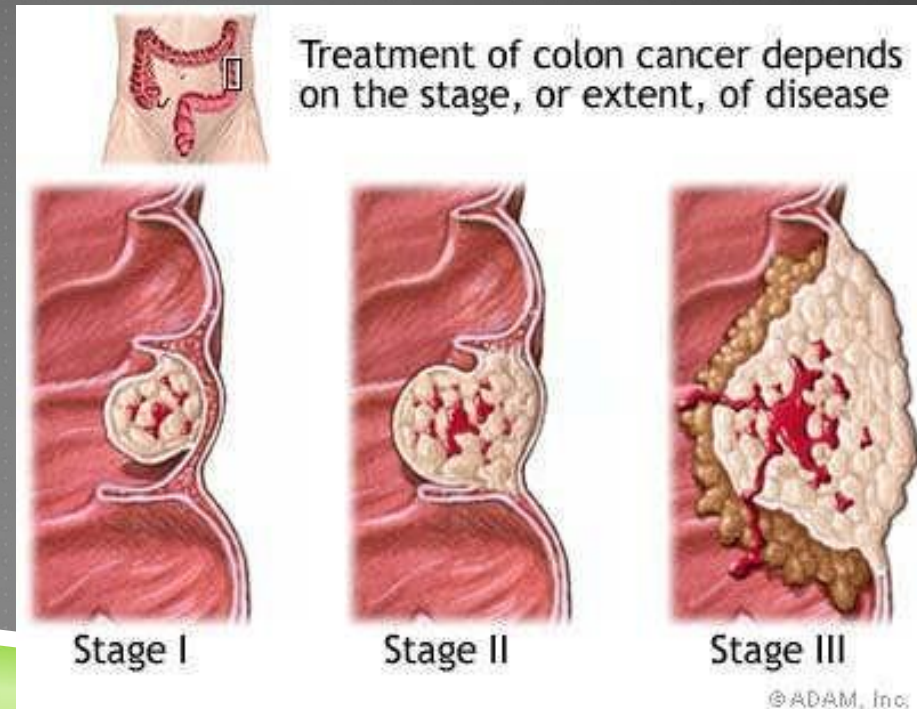
DIAGNOSIS - SYMPTOMS

▶ Prostate

- ▶ Similar for cancer and BPH (**Benign Prostatic Hyperplasia**)
- ▶ **difficulty passing urine**
- ▶ passing urine **more frequently** than usual, especially at **night**
- ▶ **pain** when passing urine
- ▶ **blood** in the urine (this is not common).
- ▶ (Advanced) Nagging ache in bones (**terasa ada sensasi nyeri di tulang**)

DIAGNOSIS - GENERAL

- ▶ Blood/urine- raised tumour markers eg PSA, CEA
- ▶ Biopsy – section of tissue viewed under microscope for malignant cells
- ▶ Staging - TNM
 - ▶ Tumour – size of lump
 - ▶ Node – how many nodes are affected (yg terpengaruh)
 - ▶ Metastases – if there are any or not



VII.TREATMENT OPTIONS

- ▶ A. Surgery – if small enough or debulk (pengurangan volume tumor)
- ▶ B. Radiotherapy
 - ▶ External beam (EBRT)
 - ▶ Radioactive implants – brachytherapy (internal)
- ▶ C. Systemic Anticancer Therapy (SACT)
 - ▶ 1. Chemotherapy – oral, intravenous, intrathecal etc.
 - ▶ Curative – aggressive treatment
 - ▶ Neoadjuvant – given before surgery to decrease tumour size
 - ▶ Adjuvant – given after surgery to ‘mop up’ any cancer cells
 - ▶ Palliative – given to prolong life (months), reduce symptoms
 - ▶ 2. Chemoradiotherapy
 - ▶ 3. Targeted therapies – mAbs, TKIs

I. RADIOTHERAPY

- ▶ Use of **high energy radiation** to **shrink tumours**
- ▶ Radiation damages DNA in the cells beyond repair so **cells stop dividing or die**
- ▶ Takes **several days/weeks** to have **full effect**
- ▶ Either external beam radiotherapy (**EBRT**) or radioactive material being placed inside the body (**brachytherapy**).
- ▶ Used for both **curative** intent and **palliation**

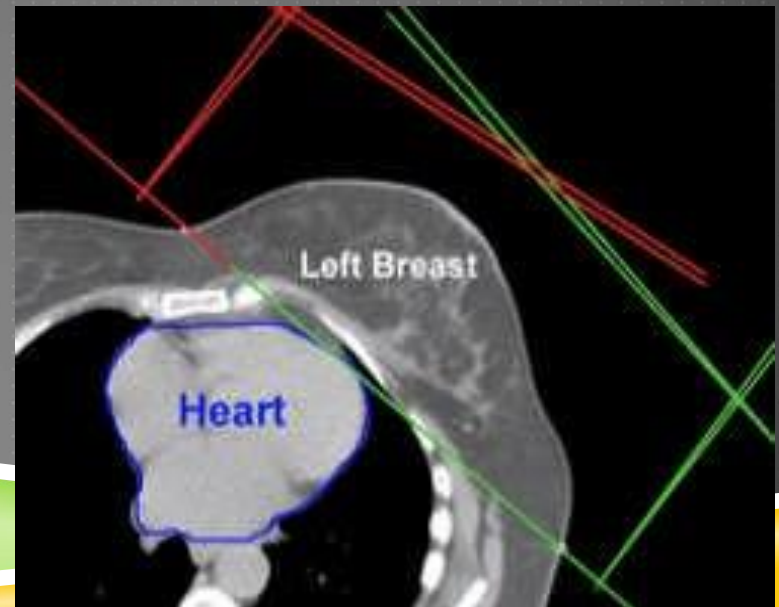


RADIOTHERAPY

- ▶ Different tissues require different levels of radiation – each can only be treated once in a lifetime. Treated to maximum dose.
- ▶ Given in fractions, usually daily (Monday to Friday)



Photo showing a mesh plastic mask used for radiotherapy for the head and neck area
Copyright © CancerHelp UK



RADIOTHERAPY – SIDE EFFECTS

- ▶ Fatigue (**kelelahan**) – can last 12 months
- ▶ Hair loss (at site only, eg. Exit site)
- ▶ Nausea and vomiting (**brain** or **gut/usus** RT)
- ▶ Diarrhoea
- ▶ Skin changes (**avoid sun**, use **high SPF**)
- ▶ Sore mouth (**mulut terasa nyeri/sakit**)

2. CHEMOTHERAPY

- Treatment of cancer with the use of **cytotoxic drugs**
- Different modes of action, act at different stages in the cell cycle (**men target DNA/RNA**)
Most currently-used drugs :
 - **inhibit DNA synthesis** and/or cell division,
 - **Inducing apoptosis**
- **Monotherapy** or **combination** chemo
- Dose intensity - dose and interval
 - Cycles, courses

CHEMOTHERAPY

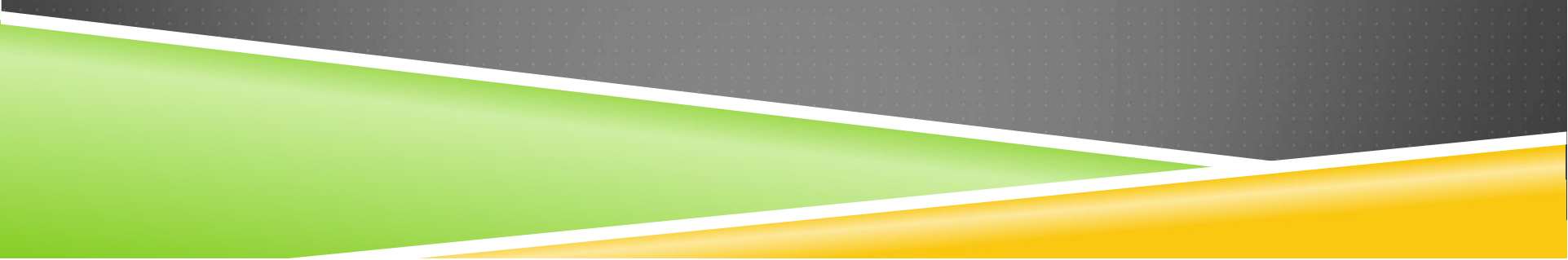
► Systemic Chemo:

given orally, IV, SC, IM with aim of maximal therapeutic cytotoxic effect

► Regional:

aimed at delivering chemo drugs directly into blood vessel supplying tumor or the cavity in which the tumor is located (e.g. Intrathecal/ruang subarachnoid spinal, intravesical/kandung kemih) therefore minimizing side effects.

2A. CYTOTOXIC DRUGS

- ▶ Alkylating agents – bond with DNA
 - ▶ Antimetabolites – inhibit enzymes that form DNA
 - ▶ Cytotoxic antibiotics – intercalating with DNA
 - ▶ Antimitotic agents – bind to microtubules prevent mitosis
 - ▶ Topoisomerase inhibitors – prevent DNA synthesis
- 

2A. CYTOTOXIC DRUGS

- ▶ **Alkylating agents** – merusak DNA
Ex : Cyclophosphamide, Cisplatin
- ▶ **Antimetabolites** – Menghambat pertumbuhan DNA dan RNA dengan memblok pembentukan DNA dan RNA
Ex : 5-fluorouracil (5-FU), 6-merkaptopurin (6 -MP), Capecitabine (Xeloda®)
- ▶ **Cytotoxic antibiotics** – Mengganggu *enzymes involved* dalam replikasi DNA
Ex : Anthracycline : Daunorubicin, Doxorubicin
Non anthracycline : Bleomycin, Mitomycin – C
- ▶ **Antimitotic agents** – Menghentikan mitosis atau menghambat enzim untuk membentuk protein yang dibutuhkan dalam reproduksi sel.
Ex : Taxanes: Paclitaxel (Taxol ®) dan Docetaxel (Taxotere ®)
Epothilones: Ixabepilone (Ixempra ®)
Vinca Alkaloid: Vinblastine (Velban ®), Vincristine (Oncovin ®),
- ▶ **Topoisomerase inhibitors** – Mengganggu enzim yang disebut topoisomerase, enzim yang membantu pemisahan rantai DNA sehingga dapat terbentuk 2 rantai DNA baru yang sama
Ex : Penghambat Topoisomerase I, meliputi: Topotecan dan Irinotecan (CPT –11).
Penghambat Topoisomerase II, meliputi: Etoposid (VP – 16) dan Teniposide.

2B. REGIMENS

- Combinations of drugs for maximum cytotoxic effect
- Doses usually based on **body surface area**
- FEC
 - ▶ Fluorouracil, epirubicin, cyclophosphamide
- CHOP
 - ▶ Cyclophosphamide, doxorubicin, vincristine, prednisolone
- ECX
 - ▶ Epirubicin, cisplatin, capecitabin

3.TARGETED THERAPY

▶ 3A. Monoclonal antibodies

- ▶ Eg trastuzumab, cetuximab

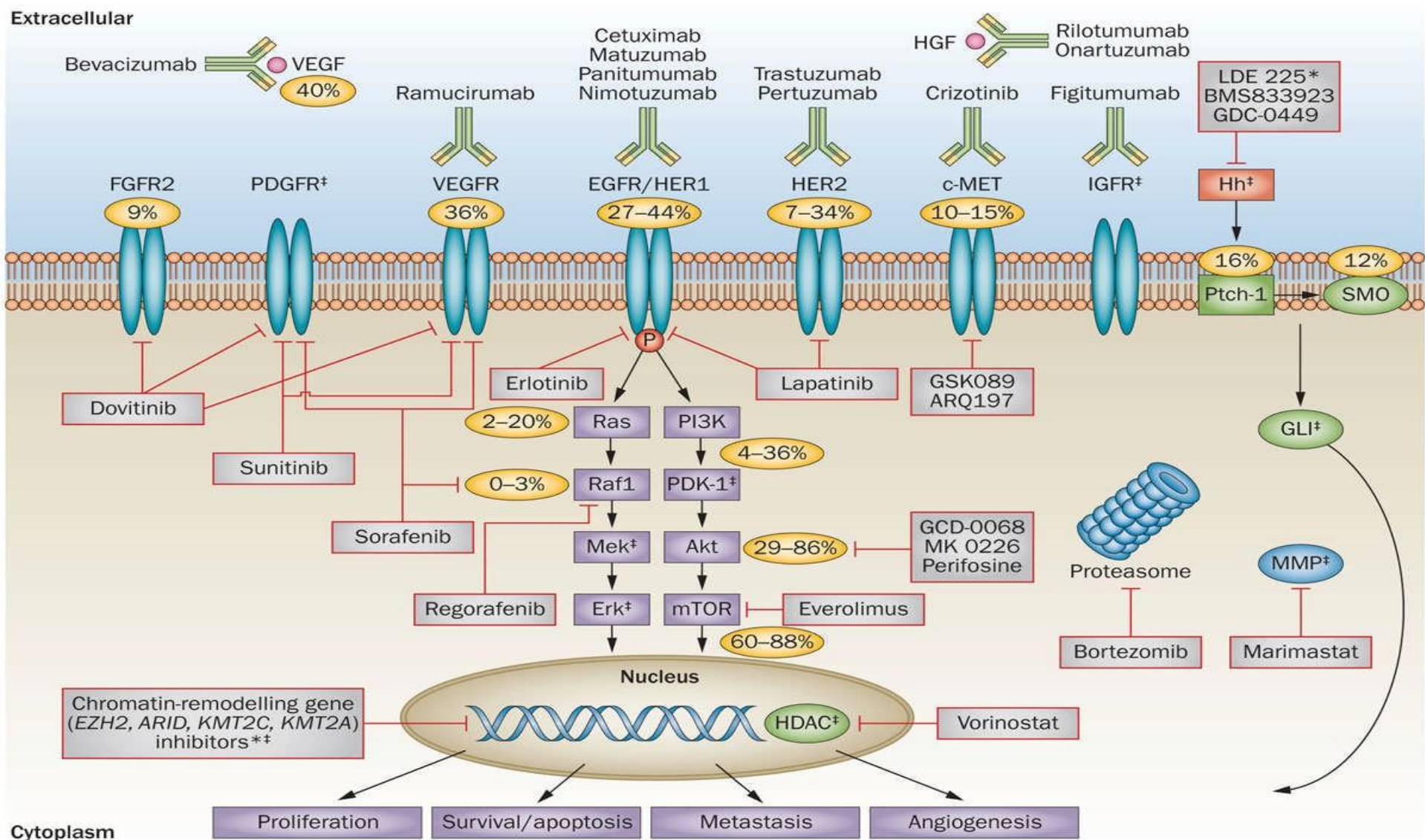
▶ 3B. Protein kinase inhibitors

- ▶ E.g. everolimus, afatinib, erlotinib

▶ 3C. Immunotherapy

- ▶ E.g.pembrolizumab, nivolumab

TARGETED THERAPY



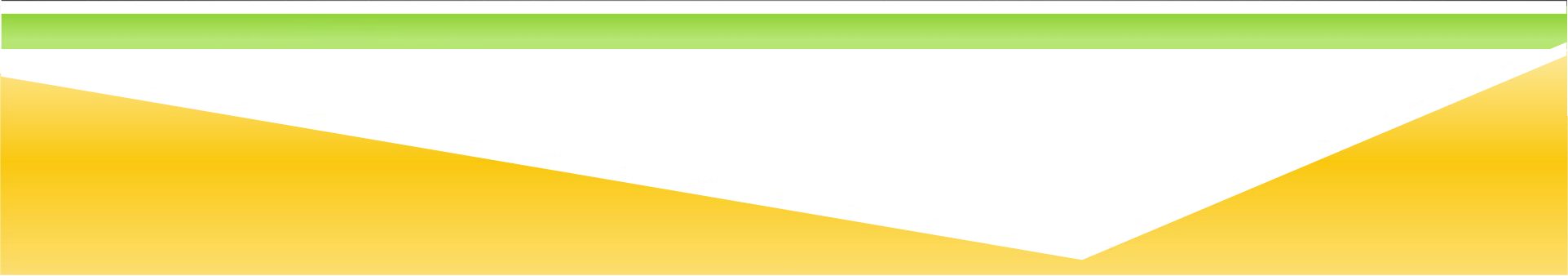
TARGETED THERAPY

- Small molecules eg **tyrosine kinase inhibitors**
- Eg erlotinib, sunitinib
- Oral
- Long term therapy – different models of care required
- Side effects
 - Due to inhibition of proteins on normal cells eg. EGFR
- Interactions
 - Due to metabolism by cytochrome P450 (mainly 3A4)

IMMUNOTHERAPY

- ▶ Rapidly growing area in cancer management
- ▶ Acts by 'waking up' the body's own immune system
- ▶ Includes pembrolizumab, nivolumab, ipilimumab and more
- ▶ Already approved for use in:
 - ▶ Metastatic melanoma
 - ▶ Renal Cell carcinoma
 - ▶ NSCLC (Non-small-cell lung carcinoma)
- ▶ Being tested in many tumour types including brain
- ▶ Different toxicities to conventional chemotherapy

VIII. SIDE EFFECTS OF SACT



VIIIA. COMMON SIDE EFFECTS OF CHEMOTHERAPY

- ▶ General to all chemotherapy
 - ▶ nausea and vomiting, myelosuppression, fatigue
- ▶ Specific toxicity of drug
 - ▶ Mucositis, renal impairment, diarrhoea, palmar- plantar syndrome (hand foot syndrome)

I. FATIGUE = kelelahan

- One of **most** common symptoms
- Under reported
- Massive impact on **QoL**
- Not very well managed/addressed by healthcare professionals
 - **anaemia** correction
 - exercise
 - support

2. LOSS OF APPETITE

- **Contributing factors** can be: constipation, pain, nausea, depression and anxiety
- **Choose foods** that will provide the **most calories** per serving
- **Drink high calorie** beverage
- **Eating small, frequent meals**
- **Serving small portions and using smaller dishes**
- **Dietician involvement**
- **TX** = Use of **steroids** – stimulate appetite
Use of **TPN** and **NG feeds** > Expected mucositis

3. NAUSEA AND VOMITING

- ▶ Chemotherapy agents stimulate the **brain's vomiting centre** and **chemoreceptor trigger zone** - different abilities to do so
- ▶ For any drug that causes severe or moderate **emesis antiemetics should always be prescribed on a regular basis**

NAUSEA AND VOMITING CONT.

- ▶ Acute
- ▶ Delayed
- ▶ Anticipatory

4. EMETOGENIC RISK = faktor resiko terjadinya mual muntah

- ▶ **Treatment related**
 - ▶ Dependent on chemotherapy agent
 - ▶ or combination
 - ▶ Dosage used
- ▶ **Patient factors** eg.
 - ▶ Gender
 - ▶ age
 - ▶ Previous motion or pregnancy sickness
 - ▶ Alcohol intake

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT ₃ + DEX + NK ₁
High AC	5-HT ₃ + DEX + NK ₁
Carboplatin	5-HT ₃ + DEX + NK ₁
Moderate (other than carboplatin)	5-HT ₃ + DEX
Low	5-HT ₃ or DEX or DOP
Minimal	No routine prophylaxis

5-HT₃ = serotonin₃
receptor antagonist

DEX =
DEXAMETHASONE

NK₁ = neurokinin₁ receptor antagonist such as
APREPITANT or FOSAPREPITANT or
ROLAPITANT or NEPA (combination of
netupitant and palonosetron)

DOP = dopamine
receptor antagonist

NOTE: If the NK₁ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃ receptor antagonist.
AC = Anthracyclines & Cyclophosphamide

DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	DEX or (if APR 125mg for acute: (MCP + DEX) or APR)
High AC	None or (if APR 125mg for acute: DEX or APR)
Carboplatin	None or (if APR 125mg for acute: APR)
Oxaliplatin, or anthracycline, or cyclophosphamide	DEX can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE

MCP = METOCLOPRAMIDE

APR = APREPITANT

5.ALOPECIA

- Hair almost **always grows back** but can have a **colour** and/or **texture change**
- Patients should be **prepared for hair loss** and **given practical advice** on coping (**wigs**)
- **TX**: Hair loss can be minimized through **scalp cooling**
 - theory that constricting blood vessels of hair follicles restricts agent from reaching follicle (**PD folikel rambut dibatasi shg agen chemo tdk sampai ke akar rambut**)
- Unpleasant and only **effective for drugs with short half life** of about 30 mins eg. **Doxorubicin**



6. MUCOSITIS

- Mucositis can range in **severity** from **a red**, sore mouth and/or gums to **open sores** that can cause a patient to be **unable to eat**
- Can effect **the lining** of the entire **GIT**
- **Management**:
 - Rationalize regime - spacing between different products eg benzydamine (**NSAID/pain reliever**), chlorhexidine (**antibacterial/antiseptic**)
 - Interaction chlorhexidine/ nystatin (**antijamur**)- separate by half an hour

7. NEUTROPENIA AND SEPSIS

- ▶ ↑ risk: Neutrophils $<0.5 \times 10^9/l$ and temp $> 38^\circ C$,
- ▶ treat **immediately**
- ▶ First line treatment:
 - Tazocin 4.5g tds IV (care if penicillin allergy)
 - +/- **Amikacin** 15mg/kg od (aim for pre-dose below 5mg/l)
- ▶ Vancomycin if line infection
- ▶ **avoid** regular **paracetamol**
- ▶ **G-CSF** (Granulocyte Colony Stimulating Factor) not routine

8. THROMBOCYTOPENIA

- Platelets $<100 \times 10^9/l$
- Management :
- Avoid NSAIDs – resiko bleeding
- Avoid IM preparations – resiko bleeding
- Avoid heparin (antikoagulan/pengencer darah) – resiko bleeding
- Avoid rectal preparations and examination

9. ORGAN TOXICITIES

- Pulmonary toxicity, neurotoxicity and cardiotoxicity
- Are more drug specific and they may not be reversible
 - Vinca alkaloids -
 - Anthracyclines (max cumulative lifetime dose) -
 - Cisplatin -
 - Irinotecan -
 - Neurotoxicity
 - cardiac toxicity
 - renal toxicity
 - cholinergic effects

10. REPRODUCTION

- ▶ Effects on reproduction
- ▶ May **not be apparent** for **months** or **years** after treatment
- ▶ **Patients** with potentially **curable cancers** should be offered **sperm banking** and **females oocyte collection/IVF/embryo cryopreservation**
- ▶ **Goserelin** to preserve ovarian function

II. EXTRAVASATION

The **leakage** of chemotherapy agents from **blood vessel** or tube into the **tissue** surrounding the **intravenous** or **intra-arterial administration site**.

Potentially disastrous- permanent tissue damage

- ▶ might need **plastic surgeons** involvement
- ▶ Eg. **Anthracyclines, vinca-alkaloids**
- ▶ **TX** : Ensure right treatment eg **heat pack** or **cold pack**

AN EXTRAVASATION



VIIIB. SIDE EFFECTS OF

TARGETED AGENTS

▶ Monoclonal antibodies

- ▶ Hypersensitivity reactions, Cardiac dysfunction, Rash

▶ Tyrosine kinase inhibitors

- ▶ Rash/skin toxicity, Diarrhoea, Nausea/vomiting, Hypertension, Proteinuria/kidney dysfunction, Arrhythmias, Pneumonitis

▶ Immunotherapy

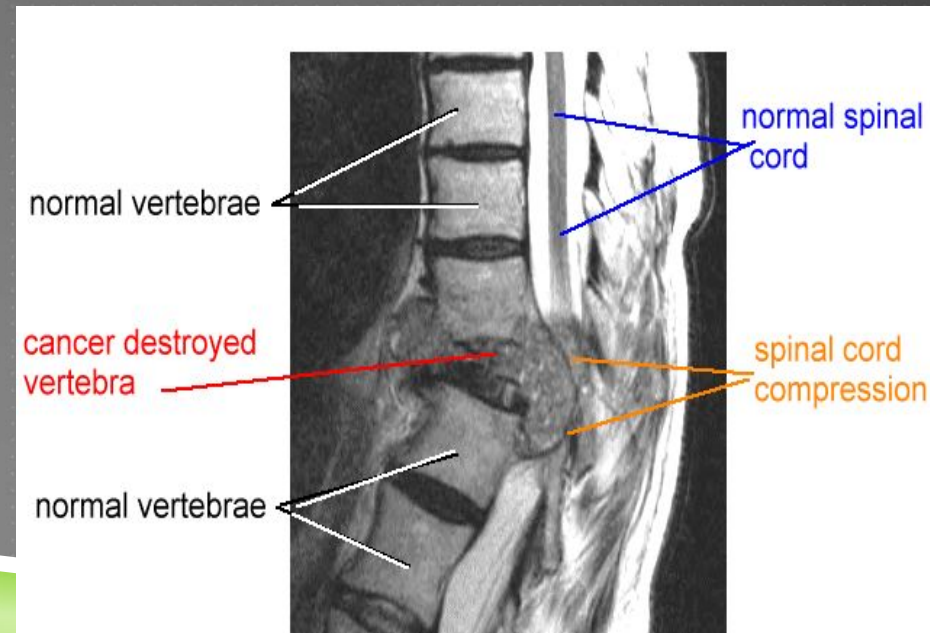
- ▶ Colitis (radang pd usus besar), Hepatotoxicity, Endocrinopathies, Pneumonitis

IX. ONCOLOGICAL EMERGENCIES



I. SPINAL CORD COMPRESSION

- ▶ Tumour pressing on spinal cord (**saraf tulang belakang**)
- ▶ **Paralysis** – **permanent** if not treated straight away
- ▶ **TX** : High dose **dexamethasone**
Radiotherapy to tumour
Sometimes **Surgery** or **Chemotherapy**



2. OTHERS

- ▶ Superior Vena Cava obstruction (SVCO)

- ▶ Restriction of blood flow
- ▶ High dose dexamethasone
- ▶ radiotherapy

- ▶ Hypercalcaemia

- ▶ Bony metastases ??
- ▶ Hydration 3-5 litres 24 hours
- ▶ bisphosphonate

X.THE CANCER PHARMACIST'S ROLE

XA. GENERAL ROLES

- ▶ Clinical service to oncology wards
- ▶ Educate other staff:
 - ▶ Doctors – e-prescribing system, prescribing chemotherapy/dose reductions, Prescribing CD's/other supportive meds
 - ▶ Nurses – guidance on chemotherapy/drug administration
 - ▶ Pharmacists/Pre-registration pharmacists – screening/overview, management of inpatients on SACT
 - ▶ Patients – counselling on SACT
- ▶ Maintain registers of competent staff
 - ▶ Prescribers, pharmacists, dispensers, administration
- ▶ Ensure drugs correctly funded
 - ▶ CDF, IFR, NICE, Trust Protocols
- ▶ Update guidelines/validate e-prescriptions
- ▶ Prescribing SACT/Assessing patients

XB.VERIFICATION ROLES

- ▶ SACT prescriptions
- ▶ Oral and IV – same procedures
- ▶ Check correct
 - ▶ patient
 - ▶ protocol
 - ▶ BSA
 - ▶ doses for renal, hepatic function
 - ▶ dose modifications
 - ▶ administration
 - ▶ Interval
 - ▶ interactions



XC. PATIENT INFORMATION EDUCATION

- Ensure patient has been informed of rationale and possible side effects
- How to manage side effects
- How to take oral chemotherapy – duration of course
- Any problems with administration eg. Difficulty swallowing
- Macmillan information leaflet (UK)
- Grey card, red chemotherapy book (UK)

XI. FURTHER INFORMATION

- Macmillan/Cancer Backup – general info
 - www.macmillan.org.uk
- Cancer Research UK – general info
 - www.cancerresearchuk.org
 - Cancer Reform Strategy – DH
- National Chemotherapy Advisory Group Report
- British Oncology Pharmacy Association
- NICE - www.nice.org.uk
- LCA - www.londoncanceralliance.nhs.uk/

XII. SUGGESTED READING

- ▶ Greene and Harris (2008) 'Neoplastic disease' in *Pathology and Therapeutics for Pharmacists*, Cambridge: Pharmaceutical Press pp.645-704
- ▶ Neal, A. Hoskin, P (2009) *Clinical Oncology- Basic Principles and Practice*. Oxford: Arnold
- ▶ Pharmaceutical Journal – series on cancer

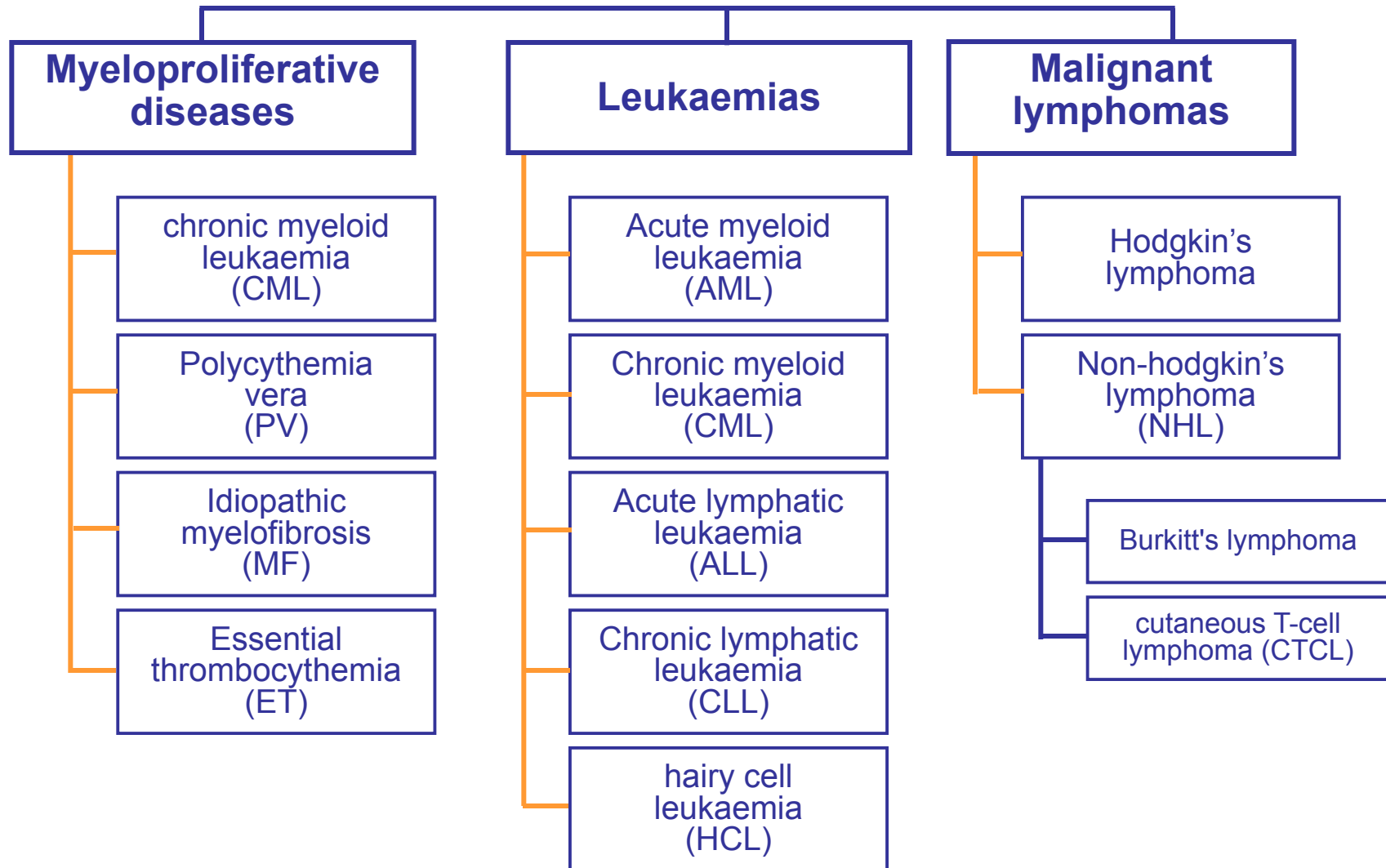
DISCUSSION TIME & GAMES





FARMAKOTERAPI KANKER LIMFOMA NON HODGKINS

Haematopoietic Malignancies



I. DEFINISI

Haematopoietic Malignancies

Myeloproliferative diseases

- Family of chronic neoplastic diseases
- Due to a clonal disorder arising at the level of the pluripotent stem cell
- Characterised by abnormal proliferation of 1 or more blood cell lines

Leukaemias

- Neoplastic disease of a haematopoietic precursor cell
- Characterised by replacement of normal bone marrow
- Often infiltration into other organs
- Malignant clones suppress normal cell formation

Malignant lymphomas

- Neoplastic disease of lymphatic tissue
- Originates in lymph node or spleen
- Hodgkin's (15%)
- non-Hodgkin's (85%)

II. EPIDEMIOLOGI

- ▶ LNH menempati urutan kelima saat ini di Amerika,
di Indonesia sendiri LNH bersama LH dan leukemia menempati urutan keenam tersering.
- ▶ Insiden usia puncak LH : usia 20-30 tahun dan usia diatas 50 tahun
- ▶ Insiden LNH mencapai puncak pada usia 80-84 tahun

III. ETIOLOGI

1. Etiologi sebagian besar LNH tidak diketahui. Namun terdapat beberapa faktor resiko terjadinya LNH, antara lain :

a. Immunodefisiensi

kelainan hereditier langka, seperti : *severe combined immunodeficiency*, *hypogammaglobulinemia*, seringkali dihubungkan pula dengan Epstein-Barr virus (EBV)

- 
2. Agen Infeksius : Epstein-Barr virus (EBV)
 3. Paparan Lingkungan dan Pekerjaan : paparan herbisida dan pelarut organik.
 4. Diet dan Paparan Lainnya
 - ▶ Resiko LNH meningkat pada orang yang mengkonsumsi makanan tinggi lemak hewani, merokok, dan yang terkena paparan ultraviolet.

IV. MANIFESTASI KLINIK

Limfoma memiliki gejala relatif yang khas, berupa :

- ▶ **Demam tinggi 38°C** tanpa sebab jelas (pada LH disebut panas Pel-Ebstein)
- ▶ **Keringat malam hari,**
- ▶ **Penurunan berat badan** 10% dalam waktu 6 bulan
- ▶ Tampak **limfadenopati** bagian leher, aksila, inguinal, dan kelenjar limfe mandibula. Limfadenopati sering kali asimetri, konsistensi padat dan kenyal, tidak nyeri.

V. PENENTUAN STADIUM

Perbandingan Penggolongan stadium Lymphoma Non Hodgkins menurut European Guideline VS American Guideline VS Indonesian Guideline

European Guideline 2019 VS American Guideline 2019
VS Indonesian Guideline 2019

Revised European-American Lymphoma (REAL) Classification: B-Cell Neoplasms

Indolent	Aggressive	Very Aggressive
■ CLL/SLL ■ Lymphoplasmacytic/IMC/WM ■ HCL ■ Splenic marginal zone lymphoma ■ MZL - Extranodal (MALT) - Nodal ■ Follicle center lymphoma, follicular, grade I-II	■ PLL ■ Plasmacytoma/Multiple myeloma ■ MCL ■ Follicle centre lymphoma, follicular, grade III ■ DLCL ■ Primary mediastinal large B-cell lymphoma ■ High-grade B-cell lymphoma/Burkitt's-like	■ Precursor B-lymphoblastic lymphoma/Leukemia ■ Burkitt's lymphoma/B-cell acute leukemia ■ Plasma cell leukemia

REVISED STAGING SYSTEM FOR PRIMARY NODAL LYMPHOMAS



Stage	Involvement	Extranodal status (E)
Limited		
Stage I	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited, contiguous extranodal involvement
Stage II bulky	II as above with bulky disease	N/A

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

REVISED STAGING SYSTEM FOR PRIMARY NODAL LYMPHOMAS



Stage	Involvement	Extranodal status (E)
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	N/A
Stage IV	Additional non-contiguous extranodal involvement	N/A

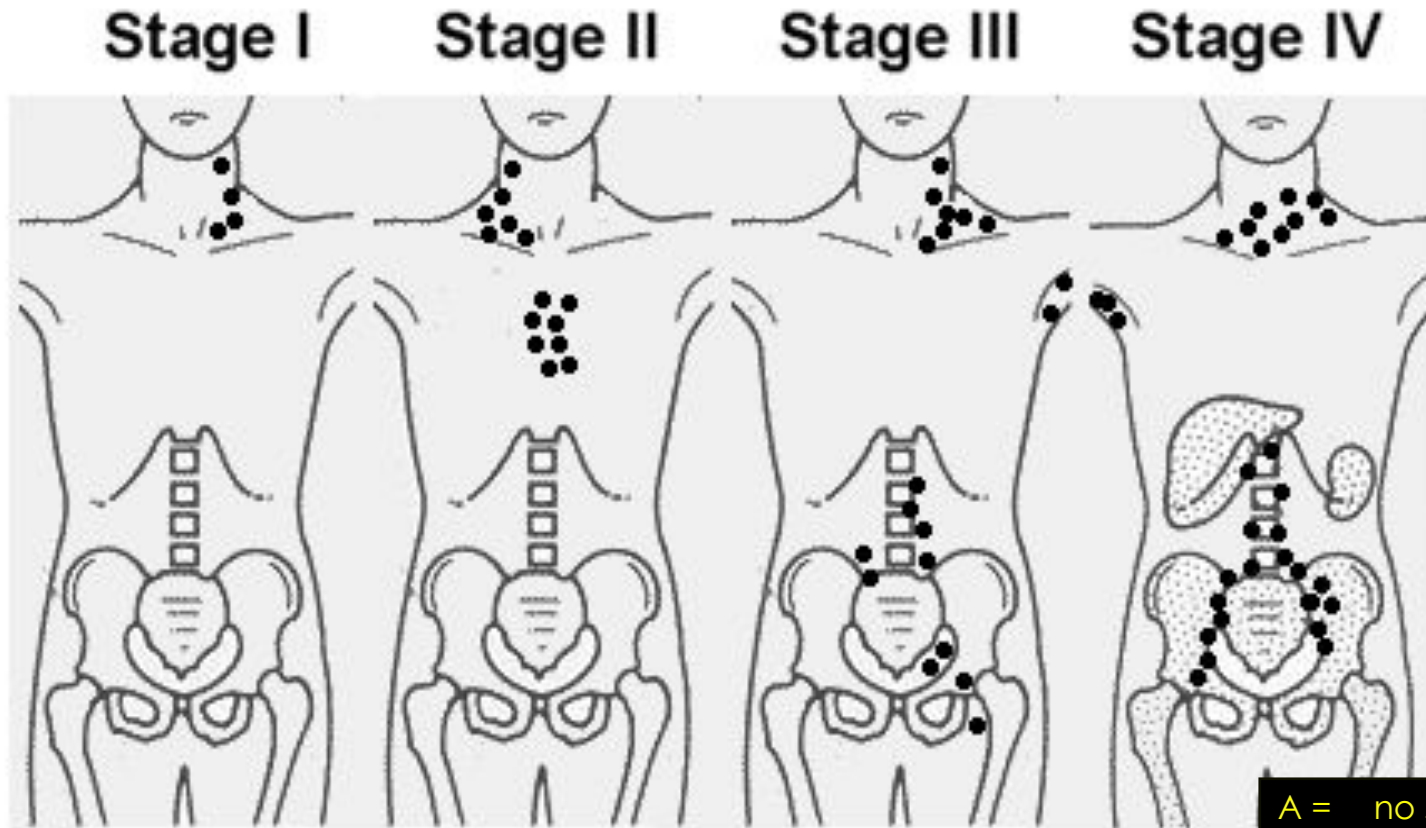
Ann Arbor Classification & Costwold Modification

TABLE 3 Ann Arbor Classification and the Costwold Modifications

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
For all stages	
A	No symptoms
B	Fever ($>38^{\circ}\text{C}$), drenching sweats, weight loss (10% body weight over 6 months)
For Stages I to III	
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site
Cotswold modifications	Massive mediastinal disease has been defined by the Cotswold meeting as a thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography. The number of anatomic regions involved should be indicated by a subscript (eg, II₃) Stage III may be subdivided into: III₁, with or without splenic, hilar, celiac, or portal nodes; III₂, with para-aortic, iliac, mesenteric nodes Staging should be identified as clinical stage (CS) or pathologic stage (PS) A new category of response to therapy, unconfirmed/uncertain complete remission (CR) can be introduced because of the persistent radiologic abnormalities of uncertain significance

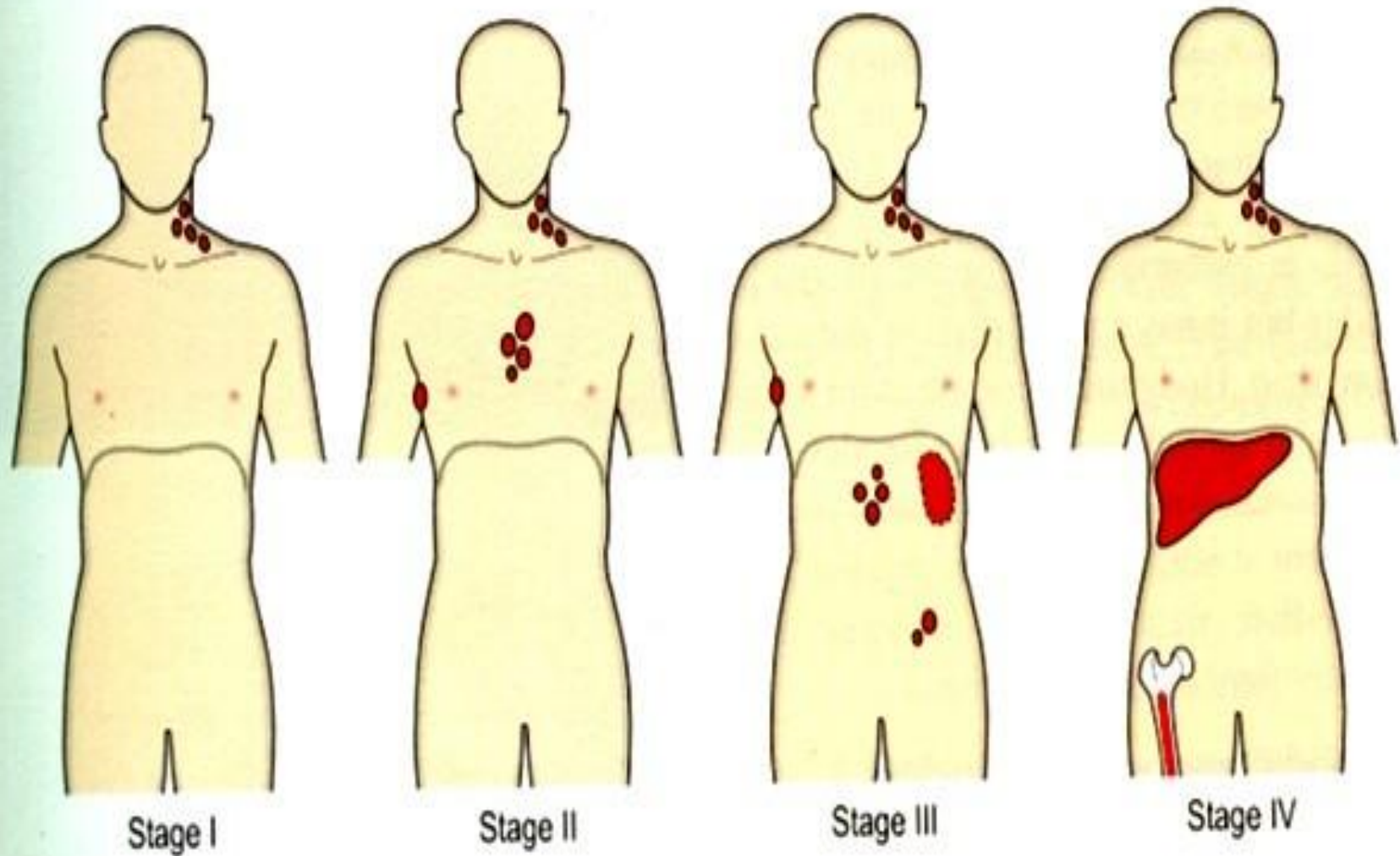
non-Hodgkin Lymphoma

Ann Arbor Staging

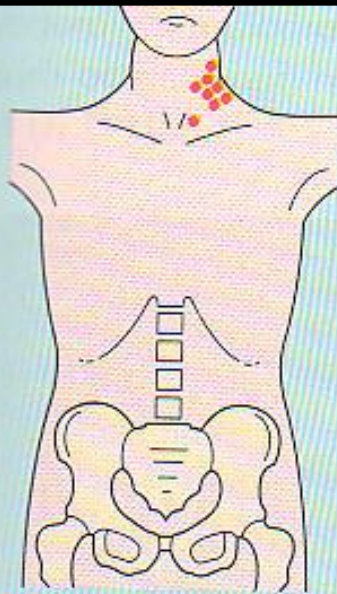


A = no symptoms
B = fever (unexplained)
night sweats
weight loss >10%

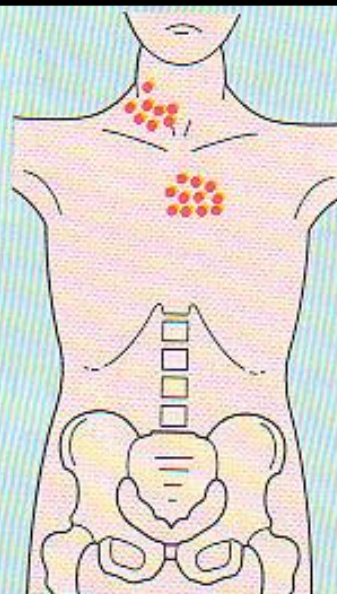
Staging of NHL



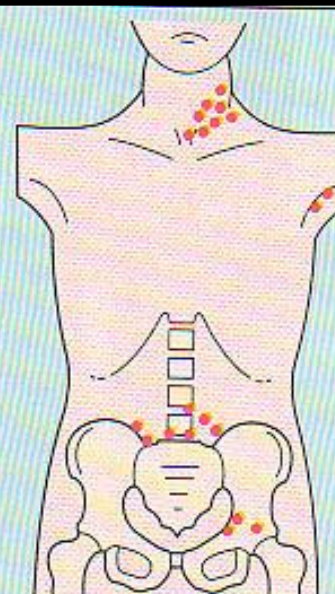
Staging of NHL



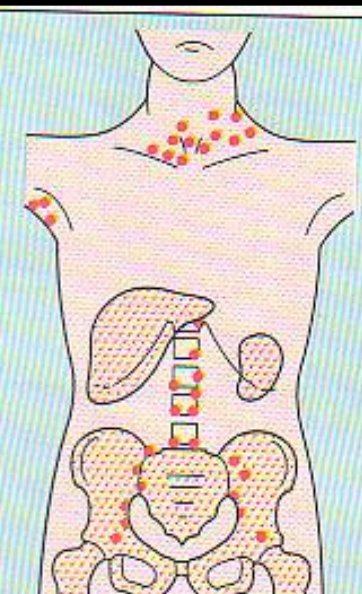
Stage I:
involvement of single lymph node region or single extralymphatic site (I_E)



Stage II:
involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic involvement on same side of diaphragm (II_E)



Stage III:
involvement of lymph node regions on both sides of the diaphragm; may include spleen (III_S) or localized extranodal disease (III_E)



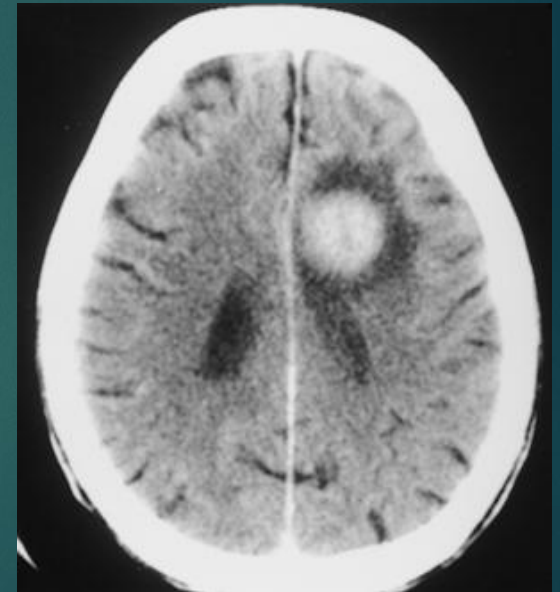
Stage IV:
diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)

VI. DIAGNOSIS

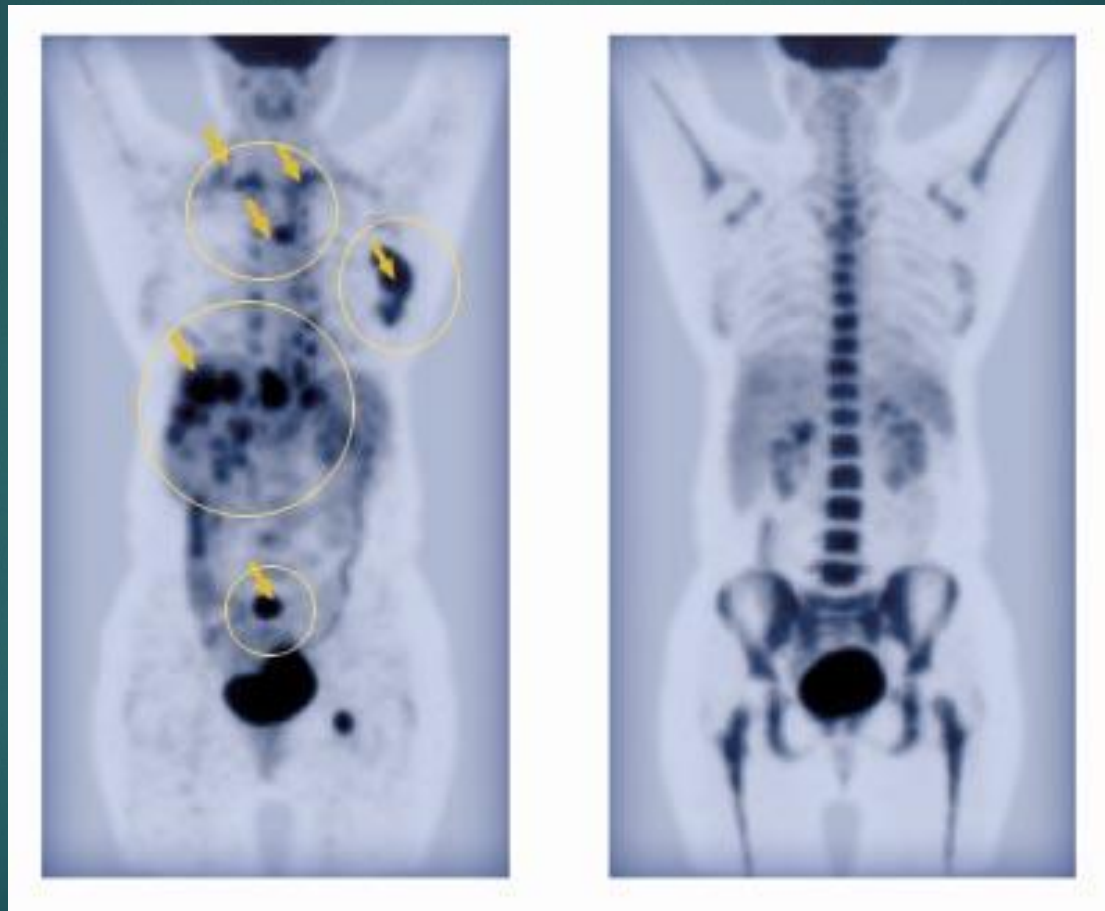


- ▶ History/ Physical examination
- ▶ CT scan thorax
- ▶ CT scan abdomen
- ▶ PET scan: aggressive lymphomas
- ▶ Bone marrow biopsy

CT scans in lymphoma



PET scan in lymphoma



VII. PENATALAKSANAAN



General Principles :

- It is (still) not possible to select a specific treatment for each type of NHL
- Therefore NHL are divided into major subgroups:
 - ▶ **Indolent** types (follicular lymphoma)
 - ▶ **Aggressive** types (diffuse large B cell lymphoma)
 - ▶ **Very aggressive** types (Burkitt)

Treatment of non-Hodgkin lymphoma

considerations as to choice of therapy

- ▶ Type of lymphoma (REAL classification)
- ▶ Ann Arbor stage (I to IV)
- ▶ localizations
- ▶ Risk profile/prognostic score of the patient
- ▶ Which treatment is possible?

Treatment of non-Hodgkin lymphoma

Indolent (stage II-IV)*

- ▶ “Wait and see”
- ▶ (mild) chemotherapy
- ▶ (low dose) radiotherapy

* Stage I(II): high dose radiotherapy

Aggressive (stage II-IV)

**

- CHOP chemotherapy
1x / 3 weeks, 8x

** Stage I: 3x CHOP + radiotherapy

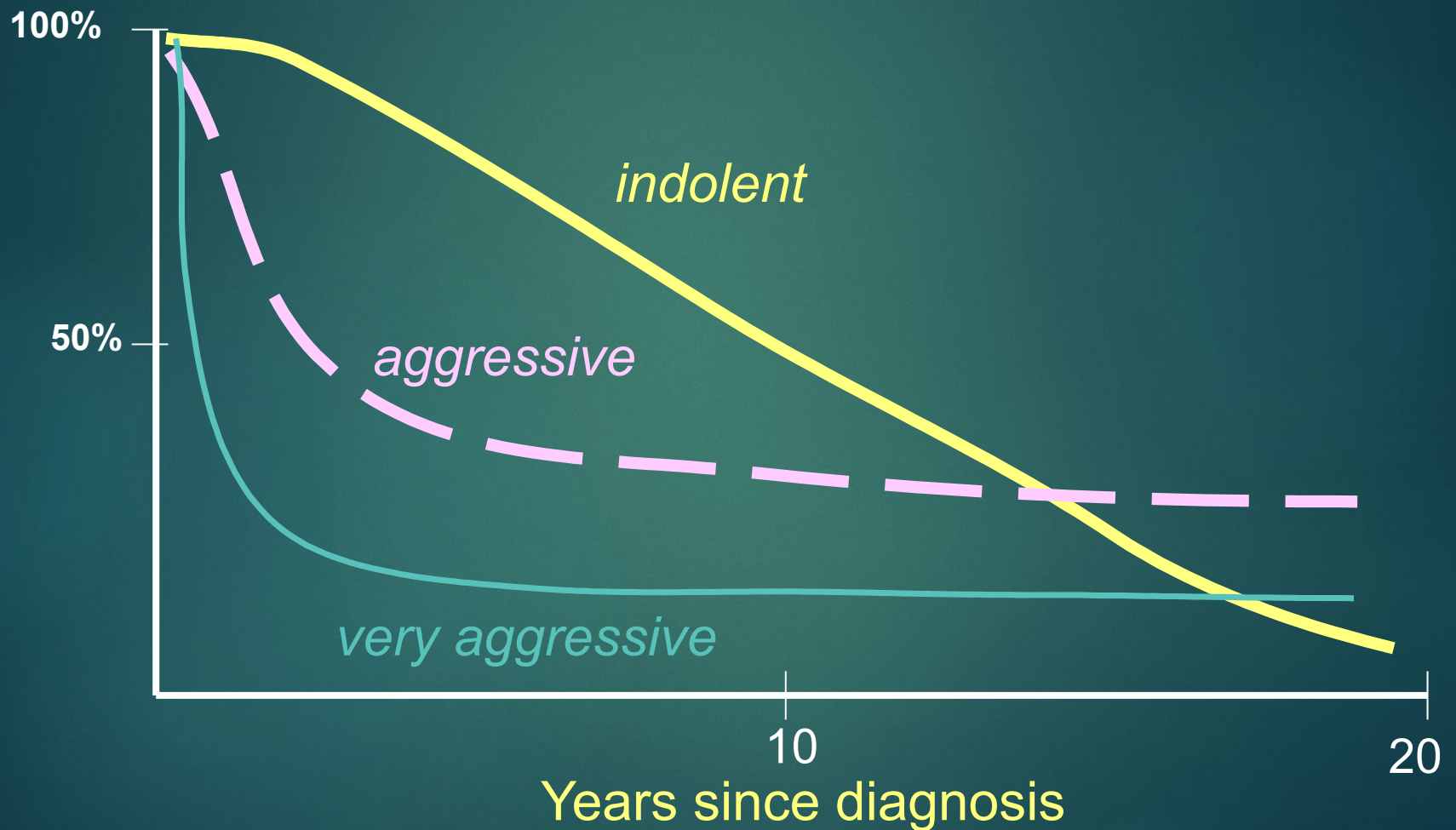
Therapy of aggressive NHL

- ▶ polychemotherapy
- ▶ golden standard : CHOP

Drug	Dose	Route	Day
Cyclophosphamide	750 mg/m ²	i.v.	1
Doxorubicin (hydroxydaunorubicine)	50 mg/ m ²	i.v.	1
Vincristine (oncovin)	1.4 mg/ m ² *	i.v.	1
Predniso(lo)ne	100 mg	p.o.	1-5

* max. dose per cycle: 2 mg

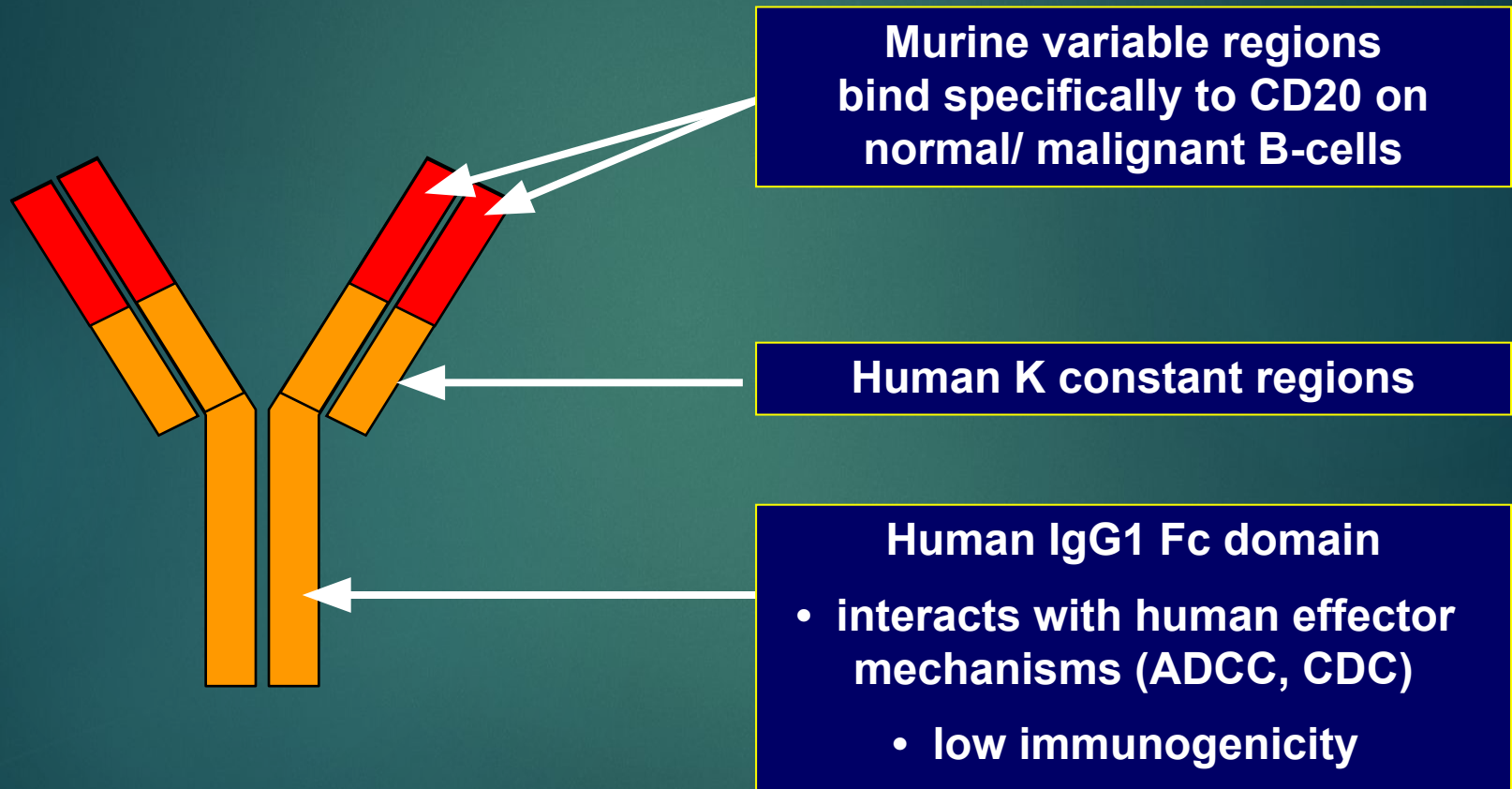
Survival of NHL patients (till 2004)





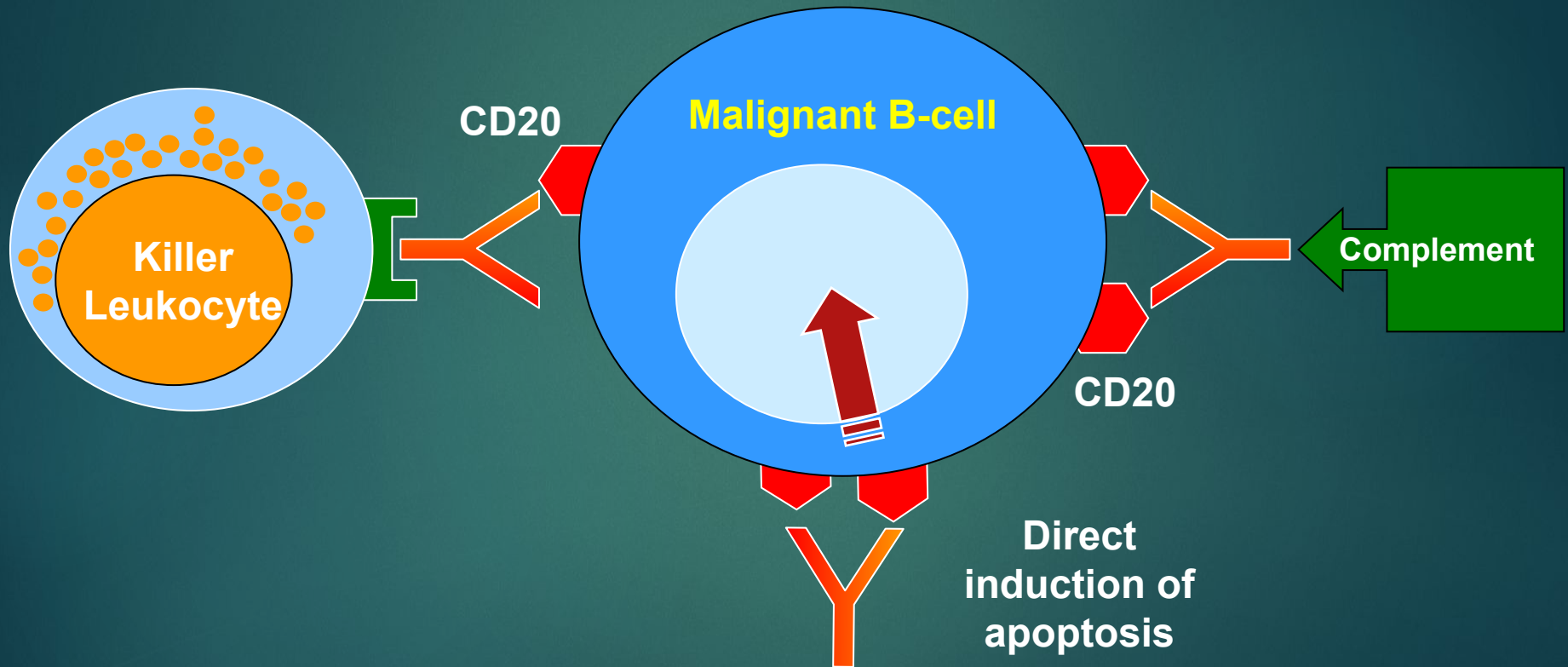
The results of the treatment of patients with NHL have been improved impressively by the use of antibodies directed against the lymphoma cells

Rituximab (mabthera®) : a mouse/ human chimeric anti- CD20 monoclonal antibody



Anti-CD20 (Rituximab= Mabthera®)

mechanism of action



Adapted from Male D, et al., *Advanced Immunology* 1996: 1.1–1.16

New developments in the treatment of lymphoma

- ▶ New monoclonal antibodies (HumaxCD20, CD22)
- ▶ **Radio-immunotherapy**
- ▶ New agents (bortezomib, lenalidomide, bendamustine, apoptosis-inducers, small molecules)
- ▶ New combinations
- ▶ Allogeneic SCT (RIST)

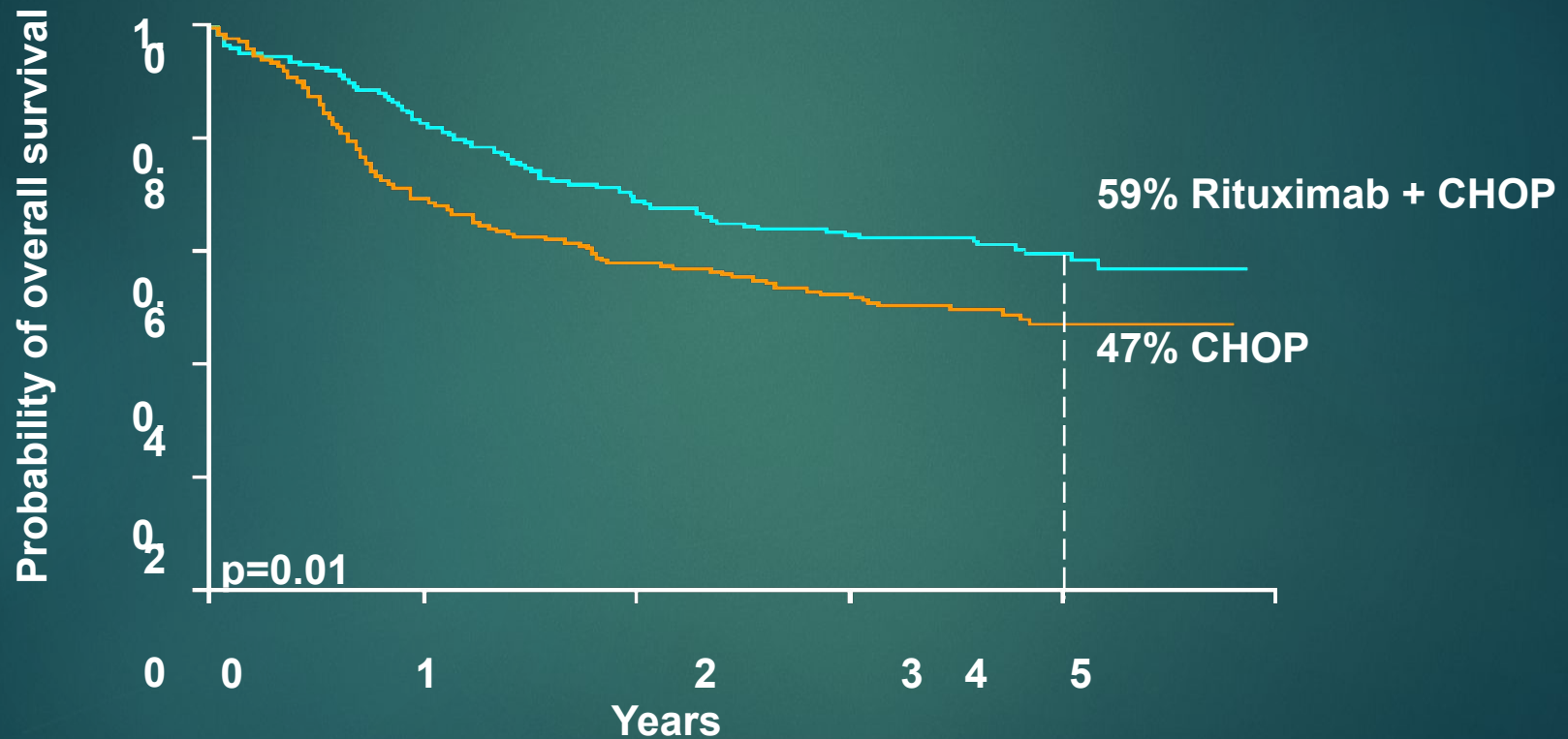
non-Hodgkin's lymphoma

Why treatment with antibodies?

- With present chemotherapy no or **insufficient cure**
- Treatment of minimal residual disease **after chemotherapy might improve prognosis**
- Antibodies are **more specific** than cytostatic drugs
- Antibodies are **less toxic**
- Antibodies have a **different mechanism of action**

DLCL in the elderly :

Rituximab improves overall survival



B Cell Neoplasm

- I. Precursor B-cell neoplasm : Precursor B-Acute Lymphoblastic Leukemia/lymphoblastic lymphoma
- II. Peripheral B-cell neoplasms
 - A. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
 - B. Lymphoplasmacytic lymphoma
 - C. Mantle cell lymphoma
 - D. Follicular lymphoma
 - E. Extranodal marginal zone B-cell lymphoma or MALT type
 - F. Nodal marginal zone B-cell lymphoma
 - G. Splenic marginal zone lymphoma
 - H. Plasmacytoma/ plasma cell myeloma
 - I. Diffuse large B-cell lymphoma, NOS
 - J. Diffuse large B cell lymphoma variants.
 - K. Burkitt's lymphoma
 - L. B cell lymphoma inclassifiable with features intermediate between DLBCL and Burkitt lymphoma
 - M. B cell lymphoma inclassifiable with features intermediate between DLBCL and classical Hodgkin lymphoma

TATALAKSANA

Pilihan terapi bergantung pada beberapa hal, antara lain: tipe limfoma (jenis histologi), stadium, sifat tumor (indolen/agresif), usia, dan keadaan umum pasien.

I. LNH INDOLEN / Low grade: (Ki-67 < 30%)

Yang termasuk dalam kelompok ini adalah:

- SLL/small lymphocytic lymphoma/CLL =chronic lymphocytic lymphoma
- MZL (marginal zone lymphoma), nodal, ektranodal dan splenic)
- Lymphoplasmacytic lymphoma
- Follicular lymphoma gr 1-2
- Mycosis Fungoides
- Primary cutaneous anaplastic large cell lymphoma)

A. LNH INDOLEN STADIUM I DAN II

Radioterapi memperpanjang disease free survival pada beberapa pasien. Standar pilihan terapi :

1. Iradiasi
2. Kemoterapi dilanjutkan dengan radiasi
3. Kemoterapi (terutama pada stadium ≥ 2 menurut kriteria

GELF)

4. Kombinasi kemoterapi dan imunoterapi
5. Observasi

B. LNH INDOLEN / low grade STADIUM II bulky,

III, IV Standar pilihan terapi :

1. Observasi (kategori 1) bila tidak terdapat indikasi untuk terapi.

Termasuk dalam indikasi untuk terapi:

- Terdapat gejala
- Mengancam fungsi organ
- Sitopenia sekunder terhadap limfoma
- *Bulky*
- Progresif
- Uji Klinik

2. Terapi yang dapat diberikan:

1. Rituximab dapat diberikan sebagai kombinasi terapi lini pertama yaitu R-CVP. Pada kondisi dimana Rituximab tidak dapat diberikan maka kemoterapi kombinasi merupakan pilihan pertama misalnya: COPP, CHOP dan FND.
2. Purine nucleoside analogs (Fludarabin) pada LNH primer
3. Alkylating agent oral (dengan/tanpa steroid), bila kemoterapi kombinasi tidak dapat diberikan/ditoleransi

(cyclofosfamid, chlorambucil)

4. Rituximab maintenance dapat dipertimbangkan
5. Kemoterapi intensif ± Total Body irradiation (TBI) diikuti dengan stem cell rescue dapat dipertimbangkan pada kasus tertentu
6. Raditerapi paliatif, diberikan pada tumor yang besar (bulky) untuk mengurangi nyeri/obstruksi.

C. LNH INDOLEN/ low grade RELAPS

Standar pilihan terapi:

1. Radiasi paliatif
2. Kemoterapi
3. Transplantasi sumsum tulang

II. LNH AGRESIF / *High grade*: (Ki-67 > 30%)

Yang termasuk dalam kelompok ini adalah:

- MCL (Mantle cell lymphoma, pleomorphic variant)
- Diffuse large B cell lymphoma, Follicular lymphoma gr III, B cell lymphoma unclassifiable with features between diffuse large B cell and Burkitt,
- T cell lymphomas

A. LNH STADIUM I DAN II

Pada kondisi *tumor non bulky* (diameter tumor <7.5cm) dengan kriteria: pasien muda risiko rendah atau rendah-

menengah (aalPI score ≤ 1) dan risiko tinggi atau menengah-tinggi (aalPI ≥ 2), bila fasilitas memungkinkan, kemoterapi kombinasi R-CHOP 6 siklus merupakan protokol standar saat ini serta dapat dipertimbangkan pemberian radioterapi (untuk konsolidasi), atau kemoterapi 3 siklus dilanjutkan dengan radioterapi.

B. LNH STADIUM I-II (BULKY), III DAN IV

- Bila memungkinkan, pemberian kemoterapi RCHOP 6 siklus $\pm$ radioterapi konsolidasi, dipertimbangkan pada stadium I dan II
- Uji klinik pada stadium III dan IV

C. LNH REFRAKTER/RELAPS

- Pasien LNH refrakter yang gagal mencapai remisi, dapat diberikan terapi salvage dengan radioterapi jika area yang terkena tidak ekstensif. Terapi pilihan bila memungkinkan adalah kemoterapi salvage diikuti dengan transplantasi sumsum tulang
- Kemoterapi *salvage* seperti R-DHAP maupun R-ICE

III. LNH “LEUKEMIA-LIKE”: Lymphoblastic, Burkitt, “double hit” lymphoma.

- *High dose chemotherapy* plus radioterapi diikuti dengan transplantasi sumsum tulang

REGIMEN TERAPI YANG DISARANKAN¹⁷

Terapi Lini Pertama

- Rituximab + CHOP (Cyclophosphamide, doxorubicine, vincristine, prednisone) (kategori 1)
- Dosed dense RCHOP 14 (Kategori 3)
- Dosed adjusted R- EPOCH (Rituximab, Etoposide, Prednison, Vincristin, Cyclophosphamide, doxorubicin) (kategori 2B)

Terapi Lini Pertama pada pasien dengan fungsi ventrikuler kiri buruk atau sangat rentan

- RCEPP—rituximab, cyclophosphamide, etoposide, prednisone, procarbazine
- RCDOP—rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone
- DA-EPOCH – etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin+ rituximab
- RCEOP – rituximab, cyclophosphamide, etoposide, vincristine, prednisone
- RGCVP – rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone

Pasien > 80 tahun dengan komorbiditas

- R-mini CHOP
- RGCVP – rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone

Terapi Lini Pertama Konsolidasi (Opsional)

- Age-adjusted IPI high risk disease: Terapi dosis tinggi dengan penyelamatan stem sel autolog
- Double-hit DLBCL: Terapi dosis tinggi dengan penyelamatan stem sel autolog

Keberadaan penyakit bersamaan dengan manifestasi pada SSP (CNS disease)

- Parenkimal: methotrexate sistemik 3 g/m² atau lebih, pada hari ke-15 dari 21 hari pemberian siklus R-CHOP yang didukung dengan pemberian *growth factors*
- Leptomeningeal : methotrexate/cytarabine intratekal, pertimbangkan pemasangan Ommaya reservoir dan/atau methotrexate sistemik
(3 – 3.5 g/m²)

REGIMEN TERAPI YANG DISARANKAN¹⁷

Terapi Lini Kedua dan Terapi Lanjutan (dengan intensi untuk high-dose therapy)

- DHAP - dexamethasone, cisplatin, cytarabine $\pm$ rituximab
- ESHAP - etoposide, methylprednisolone, cytarabine, cisplatin $\pm$ rituximab
- GDP – gemcitabine, dexametason, cisplatin $\pm$ rituximab atau gemcitabine, dexametason, carboplatin $\pm$ R
- GemOx – gemcitabine, oxaliplatin $\pm$ rituximab
- ICE - ifosfamide, carboplatin, etoposide $\pm$ rituximab
- miniBEAM – carmustine, etoposide, cytarabine, melphalan $\pm$ rituximab
- MINE - mesna, ifosfamide, mitoxantrone, etoposide $\pm$ rituximab

Terapi Lini Kedua dan Terapi Lanjutan (tanpa intensi untuk high-dose therapy)

- Bendmustine $\pm$ rituximab
- Brentuximab vedotin untuk pasien dengan CD30+ (kategori 2B)
- CEPP $\pm$ rituximab (cyclophosphamide, etoposide, prednisone, procarbazine) – PO dan IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) $\pm$ rituximab
- DA-EPOCH – etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin $\pm$ rituximab
- GDP $\pm$ rituximab atau gemcitabine, dexametason, carboplatin $\pm$ rituximab
- GemOR $\pm$ rituximab
- Lenalidomide $\pm$ rituximab (non-GCB DLBCL)
- Rituximab

DAFTAR PUSTAKA

1. Jemal a, Siegal R, Ward E, et al. Cancer facts & figures 2007. *Atlanta Am Cancer Soc* 2007; 1: 1–68.
2. Shankland KR, Armitage JO, Non-Hancock BW. Hodgkin lymphoma. *Lancet* 2012; 380: 848–857.
3. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; 329: 987–94.
4. Smedby KE, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes : a pooled analysis within the InterLymph Consortium. *Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes : a pooled analysis within the InterLymph Consortium*. 2013; 111: 4029–4038.
5. Smith MT, Skibola CF, Allan JM, et al. Causal models of leukaemia and lymphoma. *IARC Sci Publ* 2004; 373–92.
6. Swedlow S, Campo E, Harris N. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Geneva, Switzerland: WHO Press, 2008.
7. Hehn S, Grogan T, Miller T. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. *J Clin Oncol* 2004; 22: 3046–52.
8. Pappa V, Hussain H, Reznick R. Role of image-guided core-needle biopsy in the management of patients with lymphoma. *J Clin Oncol* 1996; 14: 2427–2430.
9. Freedman A, Nadler L. Differential diagnosis and sites of disease at presentation. In: Kufe D, Pollock R, Weichselbaum R (eds) *Holland-Frei Cancer Medicine*. Hamilton: BC Decker <http://www.ncbi.nlm.nih.gov/books/NBK13973/> (2003).
10. Armitage JO, Armitage JO. Staging Non-Hodgkin Lymphoma. Epub ahead of print 2009. DOI: 10.3322/canjclin.55.6.368.
11. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The lugano classification. *J Clin Oncol* 2014; 32: 3059–3067.
12. Olweny CL. Cotswolds modification of the Ann Arbor staging system for Hodgkin's disease. *J Clin Oncol* 1990; 8: 1598.
13. Tulaar A, Wahyuni L, Nuhonni S. *Pedoman Pelayanan Kedokteran Fisik dan Rehabilitasi pada Disabilitas*. Jakarta: Pedosri.
14. Wahyuni L, Tulaar A. *Pedoman Standar Pengelolaan Disabilitas Berdasarkan Kewenangan Pemberi*

15. *Pelayanan Kesehatan*. Jakarta: Pedosri, 2014.
16. Nuhonni S, Indriani. *Panduan Pelayanan Klinis Kedokteran Fisik dan Rehabilitasi: Disabilitas pada Kanker*. Jakarta: Perdosri, 2014.
17. Non-Hodgkin Lymphoma - SEER Stat Fact Sheets <http://seer.cancer.gov/statfacts/html/nhl.html>.
18. NCCN guidelines on non-Hodgkin's lymphomas. Version 3.2016.
19. August D, Huhmann M, American Society of Parenteral and Enteral Nutrition (ASPEN) Board of Directors. ASPEN clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *J Parent Ent Nutr* 2009; 33: 472– 500.
20. Argiles J. Cancer-associated malnutrition. *Eur J Oncol Nurs* 2005; 9: S39–S50.
21. Donohue C, Ryan A, Reynolds J. Cancer cachexia: mechanisms and clinical implications. *Gastroenterol Res Pr*. Epub ahead of print 2011. DOI: 10.155/2011/601434.
22. Caderholm T, Bosaeus I, Barrazoni R, et al. Diagnostic criteria for malnutrition-An ESPEN consensus statement. *Clin Nutr* 2015; 34: 335–40.
23. Arends J. ESPEN Congress Geneva 2014 LLL LIVE COURSE. In: *NUTRITIONAL SUPPORT IN CANCER Drug therapy for cancer cachexia: Pharmacologic Therapy*. 2014.
24. What is Cancer Cachexia? | Cancer Cachexia <http://www.cancercachexia.com/what-is-cancer-cachexia>.
25. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on Enteral Nutrition : Non Surgical Oncology. *Clin Nutr* 2006; 25: 245–59.
26. Cangiano C, Laviano A, Meguid M, et al. Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *J Natl Cancer Inst* 1996; 88: 550–2.
27. Rolfe R. The role of probiotic cultures in the control of gastrointestinal health. *J Nutr* 2000; 130: 396S–402S.
28. Vargo M, Riuta J, Franklin D. Rehabilitation for patients with cancer diagnosis. In: *Delisa's physical medicine and rehabilitation: principal & practice*. Philadelphia: Lippincott Williams & Wilkins, 2010, pp. 1168–70.
29. Scottish Intercollegiate Guidelines Network. SIGN Control of pain in adults with cancer. 2008; 14.
30. The British Pain Society. Cancer Pain Management. 2010; 7–8.
31. Silver J. Nonpharmacologic pain management in the

- patient with cancer. In: Stubblefield M, O'dell M (eds) *Cancer rehabilitation: principles and practice*. New York: Demos Medical Publishing, 2009, pp. 479–83.
31. Boland B, Sherry V, Polomano R. Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors | Cancer Network <http://www.cancernetwork.com/oncology-nursing/chemotherapy-induced-peripheral-neuropathy-cancer-survivors>.
 32. Hershman D, Lacchetti C, Dworkin R, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers : American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2014; 32: 1941–67.
 33. Stubblefield M, Burstein H, Burton A, et al. NCCN Task Force: Management of neuropathy in cancer. *J Natl Compr Cancer Netw* 2009; 7: 1–26.
 34. American Cancer Society. *Peripheral neuropathy caused by chemotherapy*. Atlanta, 2013.
 35. Wahyuni L, Tulaar A. Cedera medula spinalis (spinal cord injury - SCI). In: *Panduan Pelayanan Klinis Kedokteran Fisik dan Rehabilitasi*. Jakarta: Perdosri, 2012, pp. 10–4.
 36. Wahyuni L, Tulaar A. Sindroma Dekondisi. In: *Panduan Pelayanan Klinis Kedokteran Fisik dan Rehabilitasi*. 2012, pp. 226–39.
 37. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood* 2015; 123: 837–843.
 38. Selection P. Chemotherapy Alone Compared With Chemotherapy Plus. 1998; 21–26.



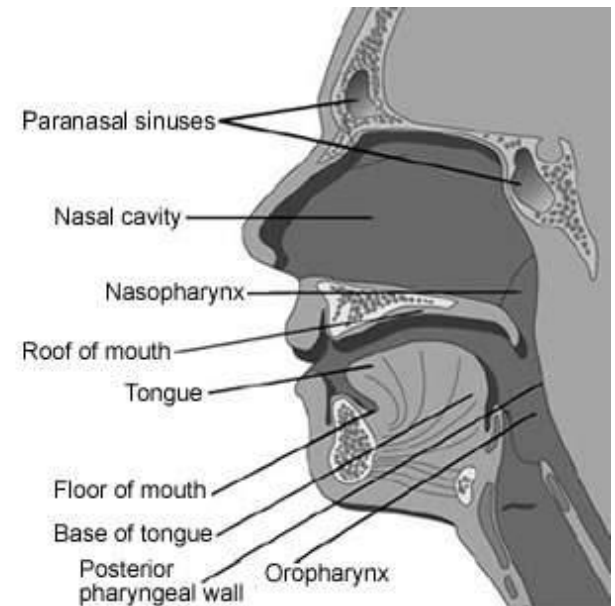
FARMAKOTERAPI KANKER NASOFARING

POKOK BAHASAN

- I. DEFINISI KANKER NASOFARING
- II. EPIDEMIOLOGI
- III. ETIOLOGI DAN PATOGENESIS
- IV. PENENTUAN STADIUM
- V. TANDA DAN GEJALA KLINIK
- VI. DIAGNOSIS
- VII. BIOPSI & MRI
- VIII. ALGORITMA TERAPI KNF
- IX. PENATALAKSANAAN
- X. PROGNOSIS

II. DEFINISI KANKER NASOFARING

- ▶ Nasofaring adalah suatu rongga dalam tengkorak di atas langit-langit mulut dan dibelakang hidung, tersembunyi dan sering disebut rongga buntu. Bagian depan berhubungan dengan udara luar melalui cuping hidung, bagian belakang melalui rongga mulut dan tenggorokan (orofaring).



III. EPIDEMIOLOGI

- Disebut juga “Cantonese cancer” atau “Kwantung cancer” (nama lain dari Guandong □ propinsi di Guangzhou)

Daerah geografi	Rata2 kasus/100.000/th	Prosentase rata2 kasus /th
Cina Selatan	80 (10-150)	61
Alaska & Greenland	18 (15-20)	13
Cina Utara	7 (5-9)	5
Medeteranian	7 (5-9)	5
Afrika Utara	7 (5-9)	5
Asia Tenggara	7 (5-9)	5
Amerika Utara, Eropa Barat, Jepang	1 (1-1,5)	1

IV. ETIOLOGI DAN PATOGENESIS

1. Faktor lingkungan
 - ▶ konsumsi ikan asin dan makanan yg diasinkan lainnya (N-nitrosodimethylamin)
 - ▶ Pemejanaan formaldehid, debu, asap,, hidrokarbon
 2. Faktor Genetik
 - ▶ Cina Selatan □ *haplotypes* □ *human leukocyte antigen/HLA* □ HLA-A2, HLA-B46, HLA-B58
 3. Epstein-Barr-Virus
 - ▶ virus herrpes yg bertanggung jawab atas terjadinya glandula fever
 - ▶ Antibodi tinggi (anti –EBV)
- Usia > resiko >, pria > wanita

V. PENENTUAN STADIUM

- Tergantung penyebaran, rabaan, histologi, biopsi, CT-scan, MRI
- T ☐ *primary tumor*
 - TX: Tumor primer yang tidak dapat diperkirakan.
 - T0: Tidak ada tumor primer
 - Tis: Carcinoma in situ
 - T1: Tumor terbatas pada nasofaring, atau tumor meluas ke orofaring dan / atau rongga hidung tanpa ekstensi parapharyngeal *
 - T2: Tumor dengan ekstensi parapharyngeal *
 - T3: Tumor melibatkan struktur tulang dari dasar tengkorak dan /atau sinus paranasal
 - T4: Tumor dengan ekstensi intrakranial dan / atau keterlibatan saraf kranial, hipofaring, orbit, atau dengan ekstensi ke fossa / masticator infratemporal ruang

* Catatan: Ekstensi parapharyngeal menunjukkan posterolateral infiltrasi tumor.

UA. REGIONAL LYMPH NODES (N)

- ▶ Distribusi dan dampak prognostik regional kelenjar getah bening menyebar dari kanker nasofaring, khususnya dari tipe tidak berdiferensiasi, berbeda dari mereka kanker mukosa kepala dan leher lainnya dan membenarkan penggunaan skema klasifikasi N yang berbeda.
- ▶ NX: Daerah lymph nodes tidak dapat diperkirakan.
- ▶ N0: Tidak ada metastase pada daerah *lymph node*.
- ▶ N1: Metastasis unilateral di nodus limfa serviks, 6 cm atau kurang dalam dimensi terbesar, di atas fossa supraklavikula, dan / atau unilateral atau bilateral, kelenjar getah bening retrofaringeal, 6 cm atau kurang, dalam dimensi terbesar *
- ▶ N2: Metastasis bilateral pada nodus limfa serviks, 6 cm atau kurang dalam dimensi terbesar, di atas supraklavikula fossa *
- ▶ N3: Metastasis di kelenjar getah bening * > 6 cm dan / atau ke fossa supraklavikula *
 - ▶ N3a: >6 cm
 - ▶ N3b: Penyebaran ke *supraclavicular fossa*. **

VB. REGIONAL LYMPH NODES (N)

- ▶ Notes : * *Mildline nodes* dikategorikan sebagai *ipsilateral nodes*
- ▶ Notes : ** Zona supraklavikula atau fossa relevan dengan stadium karsinoma nasofaring dan merupakan daerah segitiga awalnya dijelaskan oleh Ho. Didefinisikan oleh tiga poin:
 - (1) margin superior dari ujung sternum klavikula,
 - (2) margin superior dari ujung lateral klavikula,
 - (3) titik di mana leher bertemu bahu (Gambar 4.2).

Perhatikan bahwa ini akan mencakup bagian kaudal tingkat IV dan VB.

Semua kasus dengan kelenjar getah bening (seluruhnya atau sebagian) di fossa dianggap N3b.

VC. METASTASIS ORGAN JAUH (M)

- ▶ M0: Tidak ada metastasis organ jauh.
- ▶ M1: Metastasis organ jauh

ANATOMIC STAGE/PROGNOSTIC GROUPS

Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Penggolongan stadium menurut AJCC (American Joint Committee on Cancer) Edisi Ke 7

Penggolongan menurut WHO

- Pelaporan diagnosis karsinoma nasofaring berdasarkan kriteria WHO yaitu:
 - 1. Karsinoma Sel Skuamosa Berkeratin (WHO Tipe 1) (squamous cell carcinoma)
 - 2. Karsinoma Tidak Berkeratin:
 - a. Berdiferensiasi (WHO Tipe 2) (transitional cell carcinoma)
 - b. Tidak Berdiferensiasi (WHO Tipe 3) (lymphoepithelial carcinoma)
 - 3. Karsinoma Basaloid Skuamosa

TABLE 4.1. Classification of nasopharyngeal carcinoma

<i>WHO classification</i>	<i>Former terminology</i>
Keratinizing squamous cell carcinoma	WHO Type I (squamous cell carcinoma)
Nonkeratinizing carcinoma	
Differentiated	WHO Type II (transitional cell carcinoma)
Undifferentiated	WHO Type III (lymphoepithelial carcinoma)
Basaloid squamous cell carcinoma	No synonym exists (recently described)

VI. TANDA DAN GEJALA KLINIK

- ▶ Hidung tersumbat, dapat dicurigai bila pilek lebih dari 1 bulan, terutama pada usia lebih dari 40 th sedang pada pemeriksaan hidung tidak tampak kelainan, pilek keluar ingus kental bau busuk ada titik atau garis darah, pada penderita usia lebih 40 th sering mimisan.
- ▶ Gangguan pendengaran (biasanya hanya pada satu telinga), tipe hantaran 15-20%. Telinga seperti ada air berdengung, *gemrebeg* atau tinitus. Gejala ini relatif jarang.
- ▶ Benjolan di leher (suatu tanda penyebaran kanker kelenjar di leher). Para ahli menyatakan bahwa tumor leher yang terletak setengah bagian atas leher, harus dicurigai mempunyai induk tumor di nasofaring.

- ▶ Sakit kepala
- ▶ Masalah menelan
- ▶ Penglihatan ganda
- ▶ Perdarahan hidung (mimisan)
- ▶ Pasien-pasien ras Cina biasanya terserang pada usia 30th, sementara ras Kaukasian pada usia 50th. Laki-laki mempunyai kemungkinan dua kali terkena KNF dibanding perempuan.

TANDA DAN GEJALA KLINIK

VII. DIAGNOSIS

- ▶ Endoscopi
- ▶ Laboratorium ☐ anti EBV-IgA tinggi
- ▶ CT-scan
- ▶ MRI
- ▶ PET

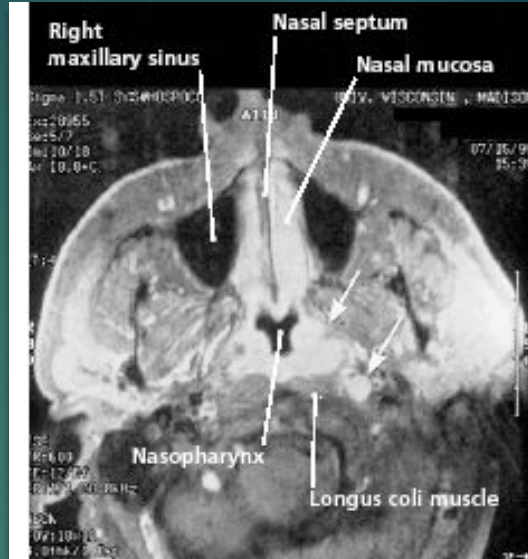
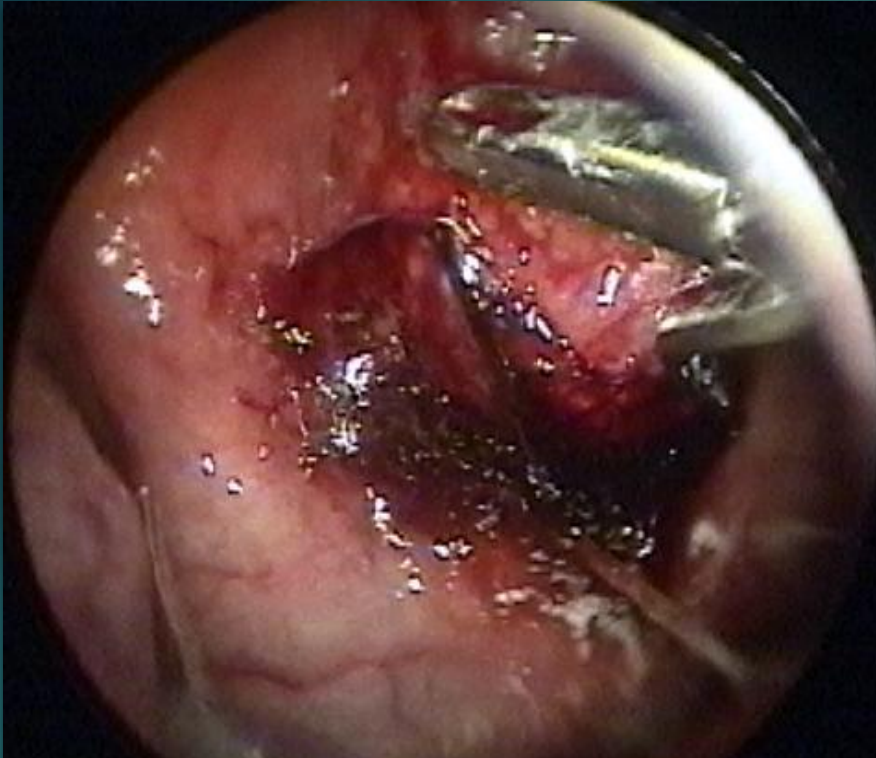
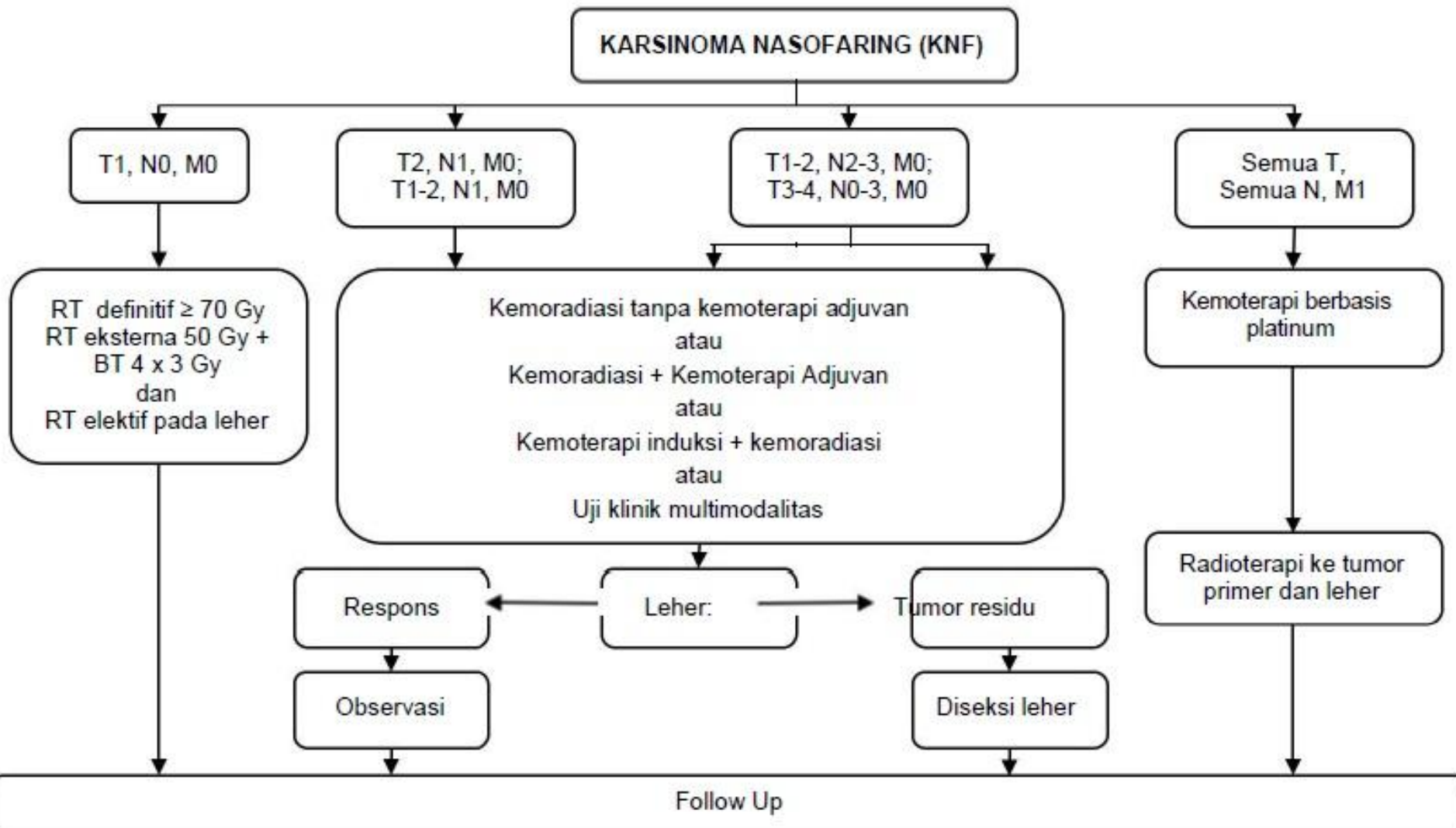


FIGURE 1. Sagittal magnetic resonance image in a patient with newly diagnosed squamous cell carcinoma of the nasopharynx. Arrows denote the primary tumor and a lateral retropharyngeal node metastasis. The patient was treated with high-dose radiation therapy and has been free of disease for two years.

VIII. BIOPSY & MRI

IX. ALGORITMA TERAPI KNF

Lampiran 2. Algoritma Penatalaksanaan KNF



X. PENATALAKSANAAN

Table 2 Summary of treatment recommendations for Cancer of the nasopharynx (NPC)

Early stage	Stage I	Radiation alone
Intermediate stage	Stage II	Concurrent chemoradiotherapy (I, B)
Advanced stage	Stage III, IVA, IVB	Concurrent chemoradiotherapy +/- adjuvant chemotherapy (I, A)
Problematic radiation therapy (RT) planning (e.g. tumor abutting chiasm)	Stage IVA, IVB	Induction chemotherapy followed by concurrent chemoradiotherapy (II, B)

XA. Prinsip Kemoterapi

- ▶ Adapun regimen kemoterapi yang dapat diberikan adalah :
- ▶ 1. Cisplatin Mingguan-Radioterapi
- ▶ 2. Docetaxel-Cisplatin-5-Fluorouracil
- ▶ 3. 5-Fluorouracil-Cisplatin
- ▶ 4. Methotrexate
- ▶ 6. Paclitaxel-Cisplatin
- ▶ 7. Capecitabine
- ▶ 8. Cisplatin-Radioterapi + Ajuvan
Cisplatin-Fluorouracil
- ▶ 9. Gemcitabine-Cisplatin

XB. Obat-obatan Simptomatik

- ▶ 1. Keluhan yang biasa timbul saat sedang diradiasi terutama adalah akibat reaksi akut pada mukosa mulut, berupa nyeri untuk mengunyah dan menelan.
- ▶ Tx : Keluhan ini dapat dikurangi dengan obat kumur yang mengandung tanda septik dan adstringent, (diberikan 3 – 4 sehari). Bila ada tandatanda moniliasis, dapat diberikan antimikotik missal nystatin.
- ▶ 3. Pemberian obat-obat yang mengandung anestesi lokal dapat mengurangi keluhan nyeri menelan.
- ▶ 4. Sedangkan untuk keluhan umum, misalnya nausea, anoreksia dan sebagainya dapat diberikan terapi simptomatik.
- ▶ 5. Radioterapi juga diberikan pada kasus metastasis untuk tulang, paru, hati, dan otak.

XI. PROGNOSIS

- ▶ Tergantung terapi dan stadium
- ▶ Stadium I □ > 90%
- ▶ Stadium IV □ 50% □ banyak faktor

XII. DAFTAR PUSTAKA

- ▶ American Society of Health –System Pharmacist, 2005, *Drug Infomation*, Bethesda, MD, Wiconsin Avenue
- ▶ Chan ATC ea. Nasopharyngeal cancer: EHNS-ESMO-ESTRO clinical pratice guidelines for diagnosis, treatment and follow-up. *Ann. of Oncol.* 2012; 23(Supplement 7).
- ▶ Fischer. D.S. 1993., *The Cancer Chemotherapy Handbook.*, ed 4th. USA.
- ▶ Komite Penanggulangan Kanker Nasional. Panduan Penatalaksanaan Kanker Nasofaring. Kementerian Kesehatan Republik Indonesia. 2015.
- ▶ Kosmidis.P.A.,2005., *Handbook Of Oncological Emergencies.*, Scodland .
- ▶ Pazdur. R.MD. 2001., *Cancer Management: A Multidisciplinary Approach.*, ed 5th. New York.
- ▶ Skarin A.T.1997 *Oncology Pocket Guide to Chemotherapy*, Third Edition. Mosby-Wolfe. New York.
- ▶ Solimando.D.A.,2003., *Drug Information Handbook For Oncology*, ed.3th. lexi – com. Ohio.
- ▶ Van de Velde.1999., *Oncology.*, Panitia Kanker RSUP Sarjito. Jogjakarta.
- ▶ <http://cancerweb.ncl.ac.uk>
- ▶ www.aafp.org/afp
- ▶ www.cancercare.on.ca/ccopgi/
- ▶ [www. Spinwrap.ucsd.edu](http://www.Spinwrap.ucsd.edu)
- ▶ Effective Health Care volume 8 no 5 2004

TUGAS



Membuat paper berisi:

- ▶ Kasus
- ▶ Analisis kasus menggunakan metode SOAP
- ▶ Pembahasan : pemilihan terapi, KIE, monitoring
- ▶ Literatur yang mendukung/daftar pustaka (EBM dan referensi ilmiah lain)
- ▶ Sertakan minimal satu EBM (mahasiswa direkomendasikan untuk tidak asal memilih EBM namun harus menyertakan alasan yang kuat mengapa EBM tersebut layak untuk digunakan sebagai acuan dalam pemilihan tata laksana terapi)

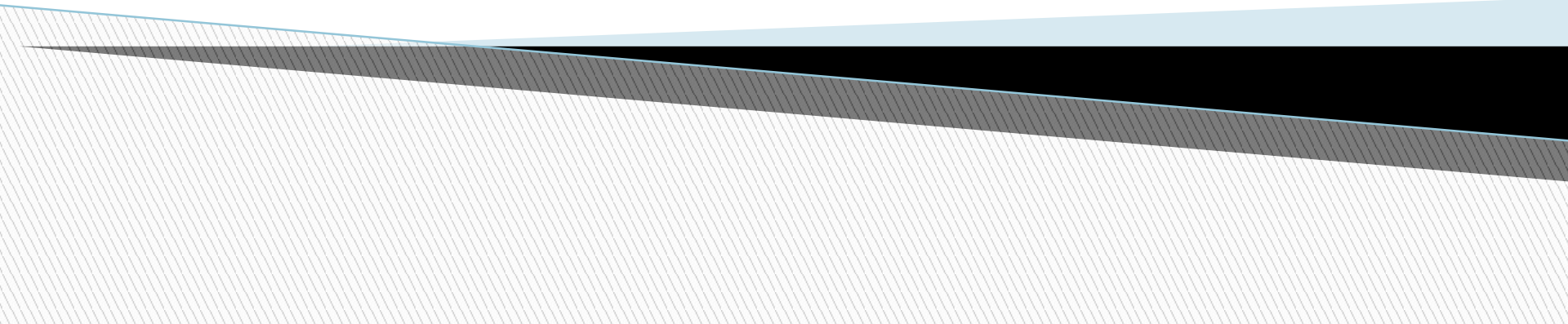
Aspek Penilaian

Aspek Penilaian	Persentase
Penyusunan Subjektif & Objektif	5 %
Assessment	50 %
Care Plan	25 %
Presentasi/Diskusi Kasus	20 %

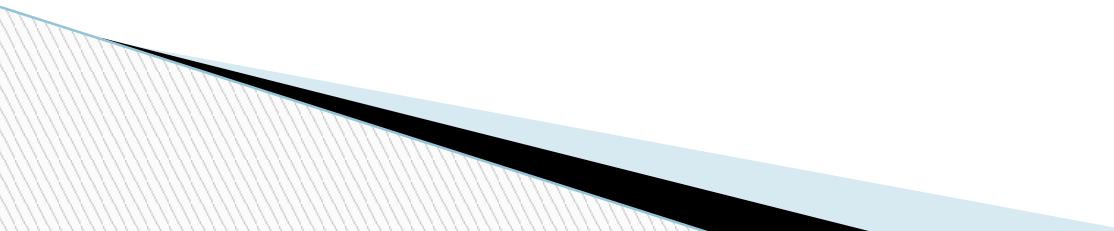
Penilaian Skor Akhir Tugas

Rentang Skor Total (Skala 100)	Rentang Nilai (skala 4)	
	Angka	Huruf
≥ 85	4.00	A
80 – 84	3.70	A-
75 – 79	3.30	B+
70 – 74	3.00	B
65 – 69	2.70	C+
60 – 64	2.00	C
55 – 59	1.00	D
< 55	0.00	E

LUNG CANCER



EPIDEMIOLOGI

- Kanker yang tersering pada pria dan wanita
 - Di Eropa paling sering pada pria
 - Di Indonesia pada wanita kanker ke 5, pada pria no 2 setelah nasofaring cancer
 - 32% dari kanker pada pria meninggal dan 25% dari seluruh wanita yang terkena kanker meninggal
- 

Estimated New Cases*

			Males	Females			
Prostate	241,740	29%			Breast	226,870	29%
Lung & bronchus	116,470	14%			Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%			Colon & rectum	70,040	9%
Urinary bladder	55,600	7%			Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%			Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%			Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%			Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%			Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%			Ovary	22,280	3%
Pancreas	22,090	3%			Pancreas	21,830	3%
All Sites	848,170	100%			All Sites	790,740	100%

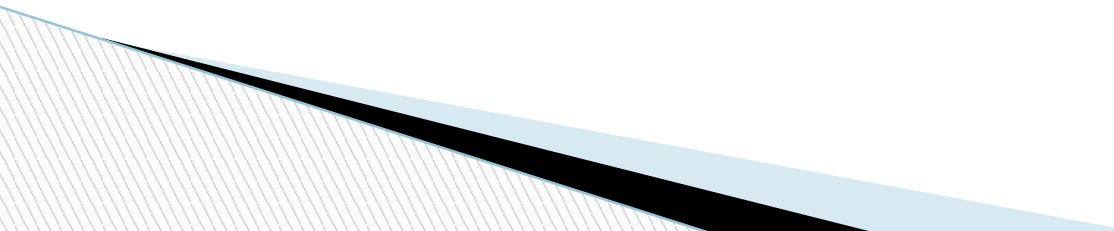
Estimated Deaths

			Males	Females			
Lung & bronchus	87,750	29%			Lung & bronchus	72,590	26%
Prostate	28,170	9%			Breast	39,510	14%
Colon & rectum	26,470	9%			Colon & rectum	25,220	9%
Pancreas	18,850	6%			Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%			Ovary	15,500	6%
Leukemia	13,500	4%			Leukemia	10,040	4%
Esophagus	12,040	4%			Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%			Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%			Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%			Brain & other nervous system	5,980	2%
All Sites	301,820	100%			All Sites	275,370	100%

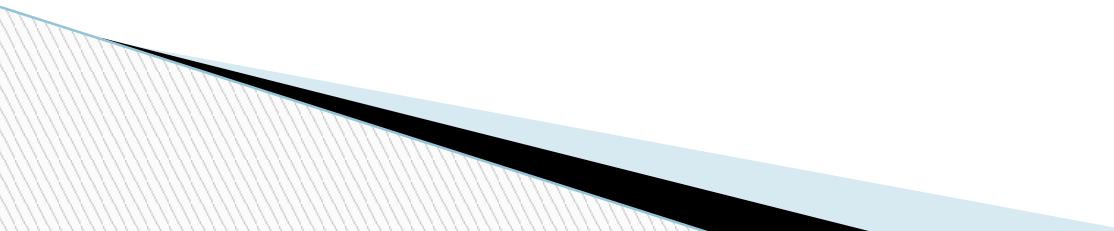
ETIOLOGI

- ▣ Asap rokok
- ▣ Pekerjaan dan lingkungan ▣ sering terpapar asbestos, chloromethyl ethers, berbagai jenis logam berat, polycyclic aromatic hydrocarbons

FAKTOR RESIKO

- Merokok
 - Menjadi *second hand smoke*
 - Keluarga memiliki riwayat penyakit tersebut
 - Memiliki gangguan pada paru (punya penyakit paru)
- 

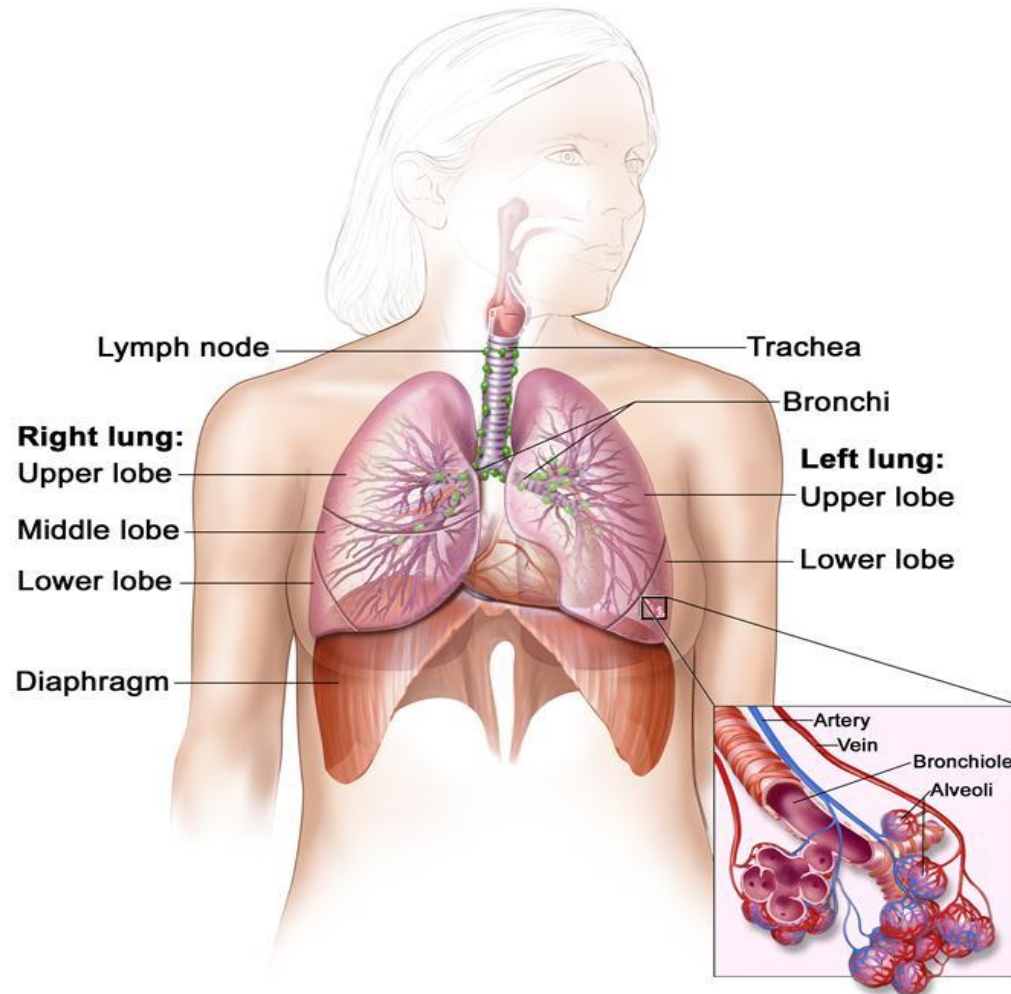
GEJALA DAN TANDA

- Batuk
 - Darah pada mukus paru
 - Napas pendek
 - Mengi
 - Nyeri pada dada
 - Sakit saat menelan
 - Suara serak
- 

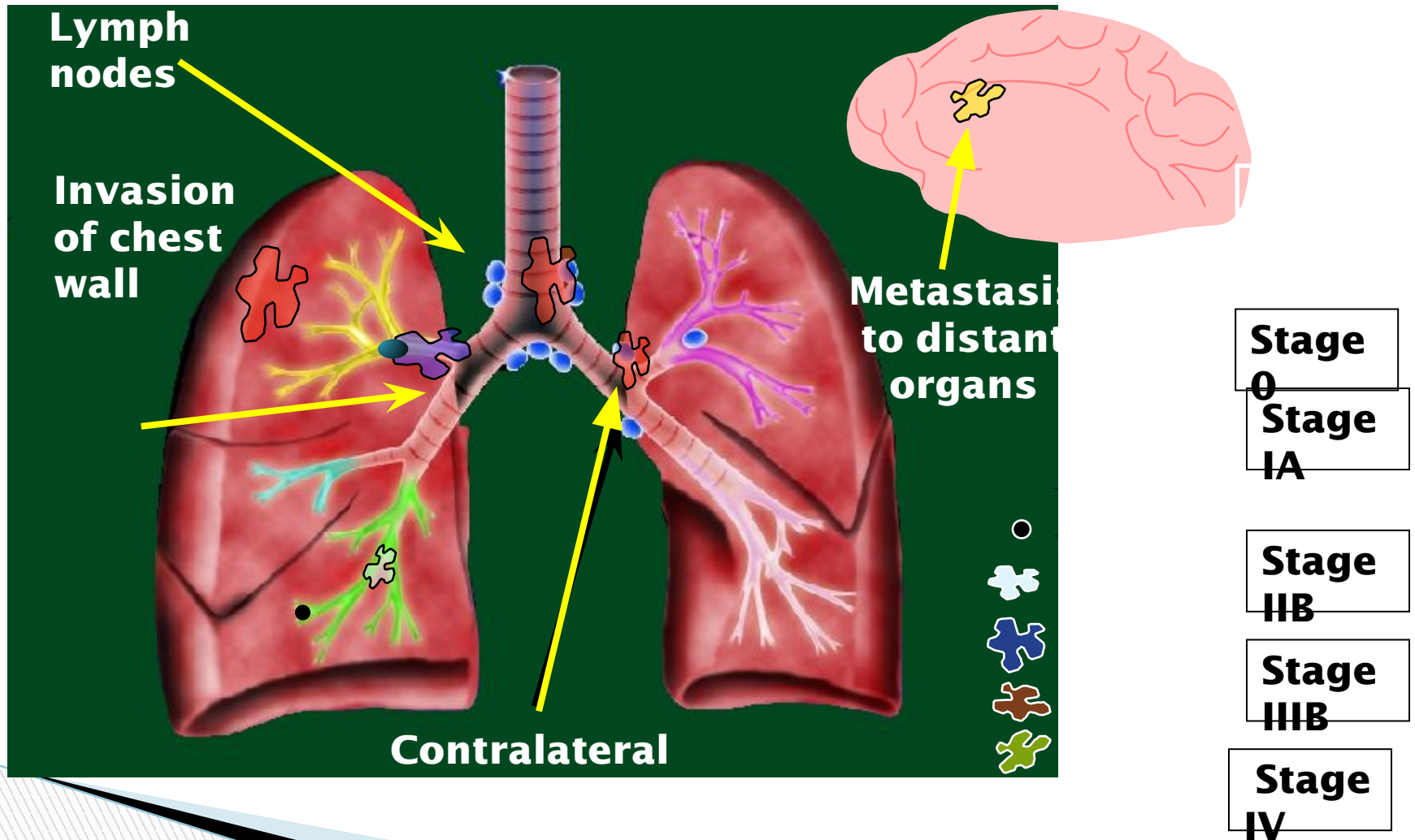
TIPE

1. Non Small Cell Lung Cancer
(NSCLC = 75% of lung cancer)
2. Small Cell Lung Cancer
(SCLC = 25% of lung cancer)

Anatomi Paru



NSCLC stages



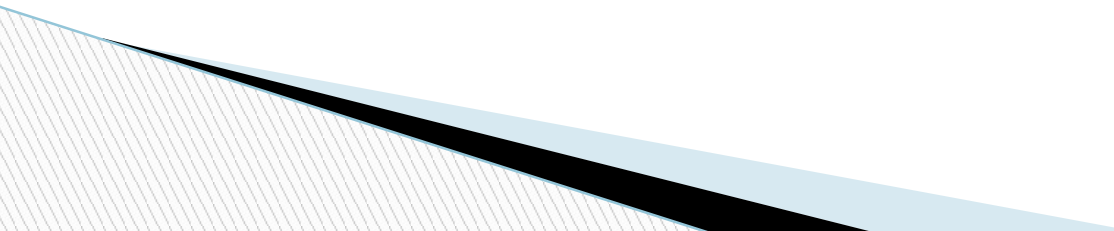
STADIUM LUNG CANCER

- Stadium kanker paru didasarkan pada 3 parameter yakni :
 - tumour (T)
 - lymph nodes (N)
 - metastasis involment (M)

Stadium awal □ 0 dan I

Stadium lanjut □ II dan III

Stadium akhir □ IV



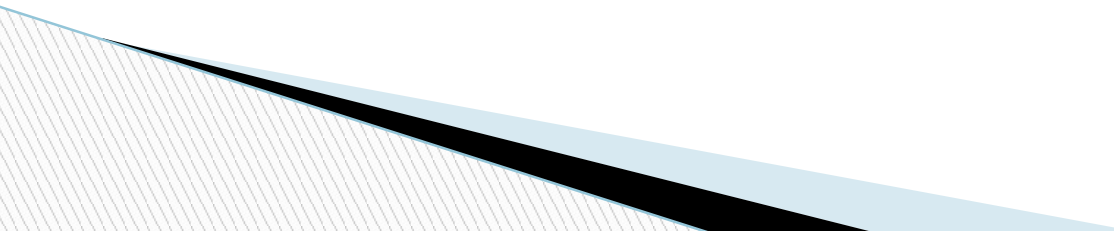
- Stadium awal □ terlokalisir dan ukuran kecil
 - Stadium IA □ mengenai 2 cabang bronkeolus
 - Stadium II B □ percabangan pada bronkus
 - Stadium III □ mengenai bronkus, atau terletak pada pinggir paru
 - Stadium IV □ di ekstra paru
- 

TABLE 126–3. Tumor (T), Node (N), Metastasis (M) Staging for Lung Cancer

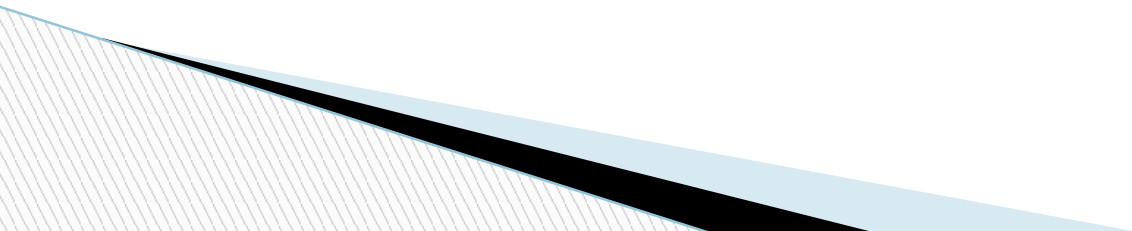
T _x	Positive malignant cell; no lesion seen
T ₁	≤3 cm surrounded by lung or visceral pleura
T ₂	>3 cm or involvement of main bronchus 2 cm or more distal to the carina, or invasion of visceral pleura, or associated atelectasis or obstructive pneumonitis extending to hilar region
T ₃	Direct invasion of chest wall, diaphragm, mediastinal pleura, or parietal pericardium; or tumor in main bronchus less than 2 cm distal to the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T ₄	Invasion of mediastinum, heart, great vessel, trachea, esophagus, vertebral body, or carina; or tumor with a malignant pleural effusion
N ₀	No regional lymph node involvement
N ₁	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph node(s), including direct extension
N ₂	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N ₃	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M ₀	No distant metastases
M ₁	Distant metastases

Stage Groupings

Stage IA	T ₁	N ₀	M ₀
Stage IB	T ₂	N ₀	M ₀
Stage IIA	T ₁	N ₁	M ₀
Stage IIB	T ₂	N ₁	M ₀
	T ₃	N ₀	M ₀
Stage IIIA	T ₁ –T ₃	N ₂	M ₀
	T ₃	N ₁	M ₀
Stage IIIB	Any T	N ₃	M ₀
	T ₄	Any N	M ₀
Stage IV	Any T	Any N	M ₁

From AJCC.³⁴

TATA LAKSANA TERAPI

- Surgery
 - Radiasi
 - Kemoterapi
- 

How Do You Treat...

Crabgrass

--

Cut It or Tear it
Out

Cancer

--

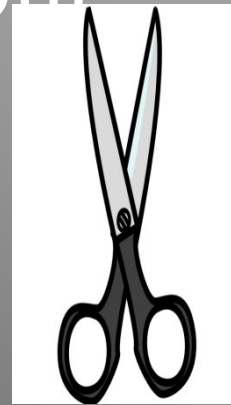
Surgery

How Do You Treat...

Crabgrass

--

Cut It or Tear it
Out



Cancer

--

Surgery

How Do You Treat...

Crabgrass

--

Burn It

Cancer

--

Radiation Therapy

How Do You Treat...

Crabgrass

--

Burn It



Cancer

--

Radiation Therapy

How Do You Treat...

Crabgrass

--

Poison It

Cancer

--

Chemotherapy

How Do You Treat...

Crabgrass

--

Poison It

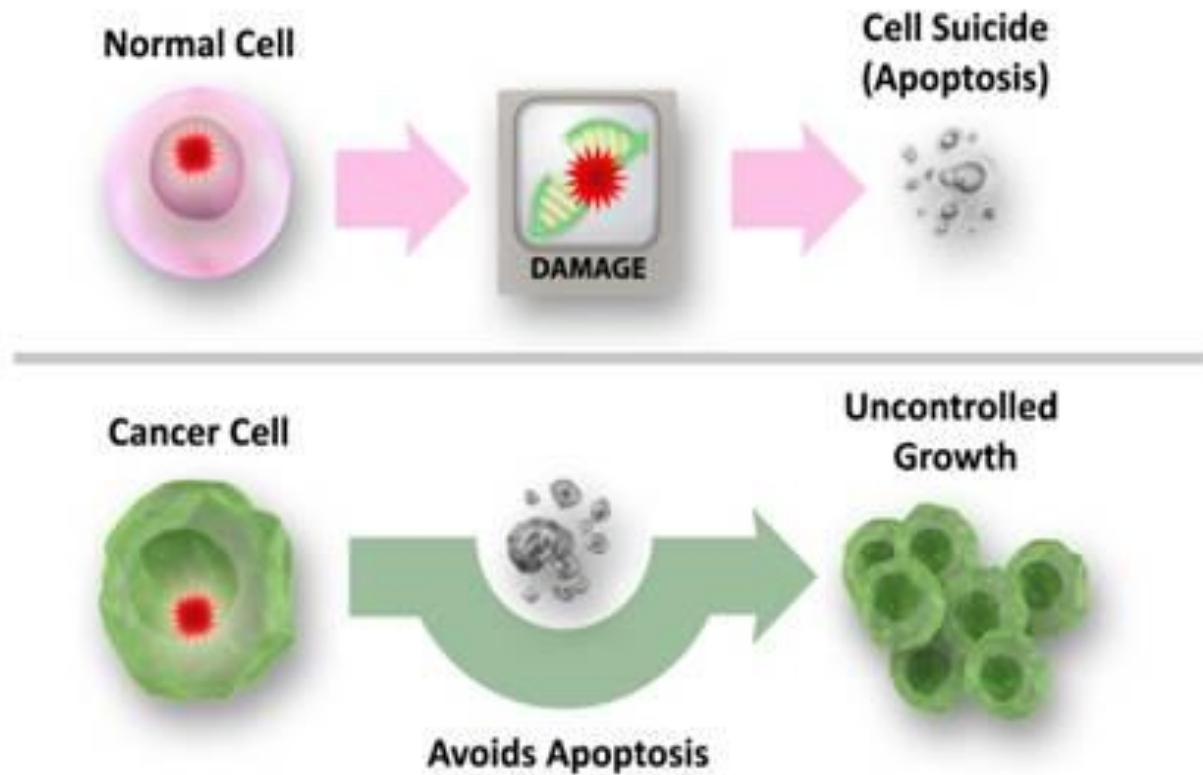


Chemotherapy

Cancer

--

Apoptosis (Programmed Cell Death)



OPERASI

- Digunakan untuk kanker stadium awal, yakni I atau II

RADIOTERAPI

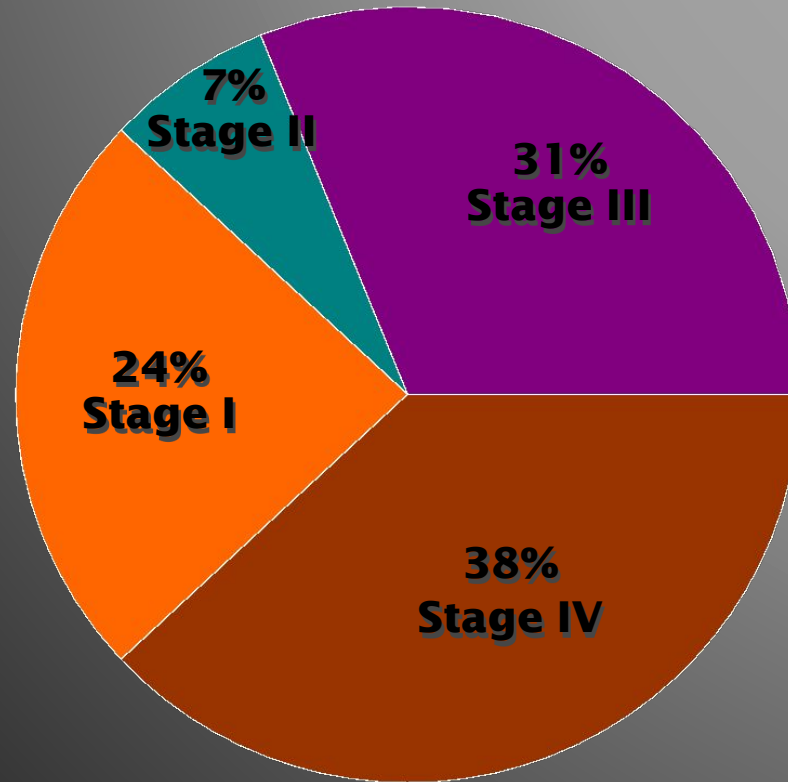
- kuratif terapi untuk pengobatan tumor yang kecil dan terlokalisasi
- Post operasi (terapi adjuvant) untuk mencegah kekambuhan pada lokal lesi atau sebagai terapi paliatif untuk stadium yang lebih lanjut (mengontrol nyeri pada bone metastase, atau gejala yang mengganggu)

TABLE 126-4. Combination Regimens Using Newer Agents for Non-Small Cell Lung Cancer

Reference	Evaluate/Total Patients and Stage	Regimen	Overall Response Rate (%)	Median Survival Duration	Median 1-Year Survival (%)	Time to Disease Progression
Paclitaxel + cisplatin versus etoposide + cisplatin						
Bonomi et al ¹²	574/599 888 109 IV 465	Etoposide 100 mg/m ² IV days 1, 2, and 3; cisplatin 75 mg/m ² IV day 1; cycle: every 21 days	12%	7.6 mo	31.8%	2.8 mo
		Paclitaxel 250 mg/m ² over 24 hours IV day 1; cisplatin 75 mg/m ² IV day 2; filgrastim 5 mcg/kg SC from day 3 until ANC $\geq 10,000/\text{mm}^3$; cycle: every 21 days	27.2%	10 mo	40.3%	5 mo
		Paclitaxel 115 mg/m ² over 24 hours IV day 1; cisplatin 75 mg/m ² IV day 2; cycle: every 21 days	25.3%	9.5 mo	37.4%	4.4 mo
Cisplatin (C) + paclitaxel (P) or gemcitabine (G) or docetaxel (D) versus carboplatin (Cb) + paclitaxel						
ECCO total	1155/1,207	CP (reference arm for trial); cisplatin 75 mg/m ² IV day 1; paclitaxel 175 mg/m ² over 24 hours IV day 1; cycle: every 21 days	21%	7.8 mo	31%	3.4 mo
1594, phase III	(1083 PS 0-1) (63 PS 2)					
Schiller et al ¹³	98 888 968 IV	GC; gemcitabine 1000 mg/m ² IV days 1, 8, 15; cisplatin 100 mg/m ² IV day 1; cycle: every 28 days	22%	8.1 mo	36%	4.2 mo ^a
		DC; docetaxel 75 mg/m ² IV day 1; cisplatin 75 mg/m ² IV day 1; cycle: every 21 days	17%	7.4 mo	31%	3.7 mo
		PCh; paclitaxel 225 mg/m ² over 3 hours IV day 1; carboplatin AUC 6 IV day 1; cycle: every 21 days	17%	8.1 mo	34%	3.1 mo
Paclitaxel + carboplatin versus vinorelbine (V) + cisplatin						
SWOG	408/444	PCh; paclitaxel 225 mg/m ² over 3 hours IV day 1; carboplatin AUC 6 IV day 1; cycle: every 21 days	PR 27%	8.0 mo	36%	NR
Phase III	chemo-naïve (PS 0-1); 12% HR; n = 207					
Kelly et al ¹⁴	11% HR; n = 201	VC; vinorelbine 25 mg/m ² IV weekly; cisplatin 100 mg/m ² IV day 1; cycle: every 28 days	PR 27%	8.0 mo	33%	NR
Cisplatin (C) + vinorelbine or vindesine (Vind) versus vinorelbine						
LeChevalier et al ¹⁵	192/206 chemo-naïve (PS ≤ 2) 23 88A 58 88B 102 IV 185/200 21 88A 49 88B 109 IV 199/206 20 88A 65 88B 97 IV	VC; vinorelbine 30 mg/m ² IV weekly; cisplatin 120 mg/m ² days 1 and 29, then every 6 weeks	30%	9.2 mo ^d	35% ^d	NR
		VindC; vindesine 3 mg/m ² every week for 6 wk then every 2 weeks thereafter; cisplatin 120 mg/m ² days 1 and 29, then every 6 weeks	19%	7.4 mo	27%	NR
		V; vinorelbine 30 mg/m ² weekly	14%	7.2 mo	30%	NR
Cisplatin + gemcitabine or etoposide						
Abratt et al ¹⁶	50/53 chemo-naïve; (PS 0 = 1, 1 = 34, 2 = 18) 14 88A 19 88B 20 IV	GC; gemcitabine 1000 mg/m ² IV weekly on days 1, 8, 15; cisplatin 100 mg/m ² IV day 15; cycle: every 28 days	52% (CR 4%) (PR 48%)	13 mo	61%	NR
Cardinal et al¹⁷						
	135/135 chemo-naïve (PS 0-1) 67 88B 68 IV	GC; gemcitabine 1250 mg/m ² IV weekly on days 1 and 8; cisplatin 100 mg/m ² IV day 1; cycle: every 21 days	40.6% ^a (p = .02)	8.7 mo	NR	TTP ^b 8.7 mo ^a (p = .01) 7.2 mo
		EC; etoposide 100 mg/m ² IV days 1, 2, 3; cisplatin 100 mg/m ² IV day 1; cycle: every 21 days	21.9%	7.2 mo	NR	
Irinotecan + cisplatin						
DeVore et al ¹⁸	52 chemo-naïve (PS 0 = 12, 1 = 32, 2 = 8) 11 88B 44 IV	IC; irinotecan 60 mg/m ² IV days 1, 8, 15; required ≥ 40 mg/m ² in 60% of patients; cisplatin 80 mg/m ² IV day 1; cycle: every 28 days	28.8%	9.9 mo	37%	NR
Masuda et al¹²						
	378/398 chemo-naïve; (PS 0-1, 51%; PS 2, 7%) 37% 88B 63% IV	IC; irinotecan 60 mg/m ² IV days 1, 8, 15; cisplatin 80 mg/m ² IV day 1; cycle: every 28 days	43%	50.3 wk	47.5%	
		G/Vind; cisplatin 80 mg/m ² IV day 1; vindesine 3 mg/m ² IV days 1, 8, 15; cycle: every 28 days	31%	47.7 wk	37.9%	
		I(CP)-11; irinotecan 100 mg/m ² IV days 1, 8, 15	21%	46.1 wk	40.7%	

Current Problems of NSCLC –

1. Majority of patients were diagnosed at non-curative stages



Current Problems of NSCLC –

2. High Treatment Failure in Curative Setting

5 Years Survival Rate

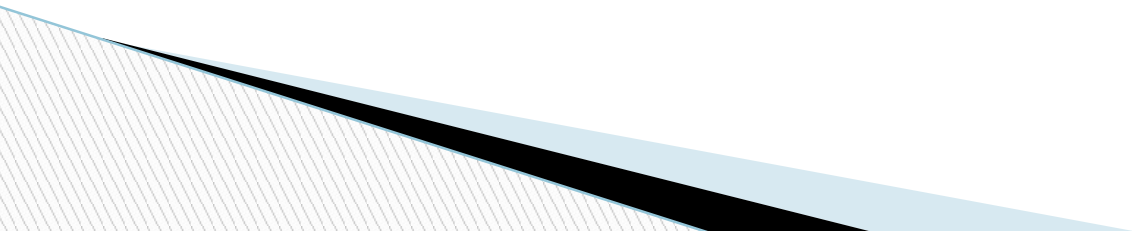
Stage	NSCLC	Br C	Cr C
I	61%	98%	75%
II	24-34%	76-88%	70%
IIIA	13%	49-56%	40%

Current Problem of NSCLC –

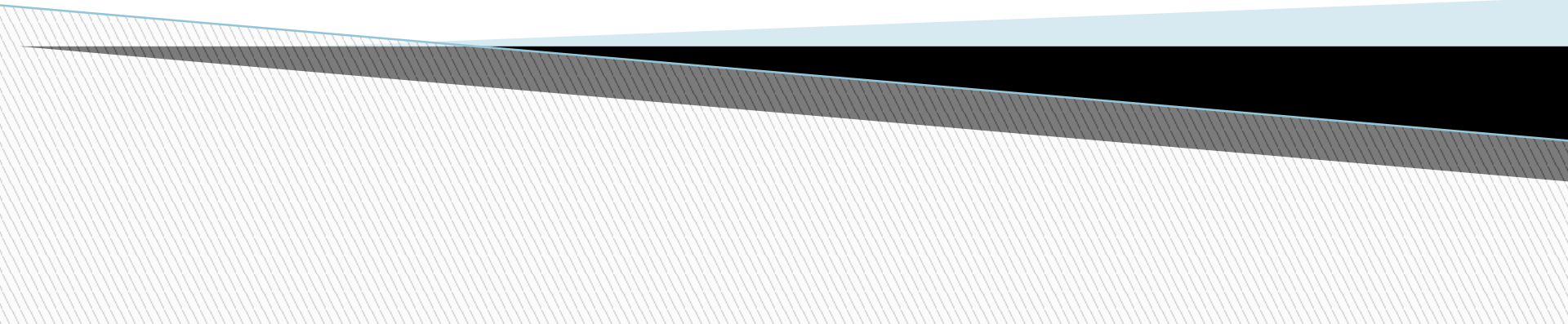
3. Outcome of Advanced Stage Disease is Very Poor

- With-out treatment no one survive at 2 years
- Treatment with doublet CT (platinum-based) produce 1 year survival rate of 30%
- Response not durable

Potential Strategies to Improve NSCLC Outcomes

- ▣ Screening program
 - ▣ Adjuvant/neo-adjuvant chemotherapy
 - ▣ Targeted Therapies
- 

Screening Program **for** **Lung Cancer**



Spiral CT for Early Lung Cancer Detection

▣ ELCAP (Lancet 1999;354:99)

- Low dose spiral CT in 1000 asymptomatic smokers
- Results:
 - 2.7% lung cancers diagnosed by spiral CT vs. 0.7% by CT rontgen
 - 85% cancers were stage I vs. 22% stage >I

▣ I-ELCAP (NEJM 2006;355:1763-71)

- Low dose spiral CT 31,567 asymptomatic screened “at-risk” individuals (inc. second hand smoke exposed)
- Results
 - 85% stage I, estimated 10-yr survival 88%

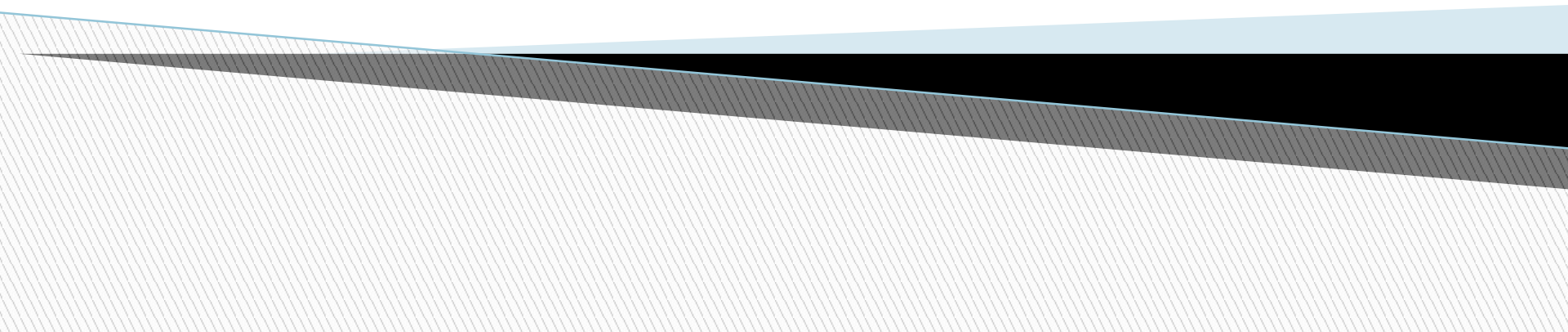
Imaging Tools for Lung Cancer

Imaging study	Resolution (mm)	Sensitivity (%)	Specificity (%)
Chest X-ray	6-10	48	90
Conventional chest CT scan	3-6	71	58
Low dose spiral chest CT scan	1-3	91	50
Chest MRI	5	70	NR
PET scan	4-6	85	98

Screening in Lung Cancer

- Screening for lung cancer by any tool in any risk population is not (yet) indicated
- Patients at risk, including ex-smokers, should contact their physician when signs or symptoms occur

Chemotherapy for Advanced NSCLC



Chemotherapy for Advanced NSCLC

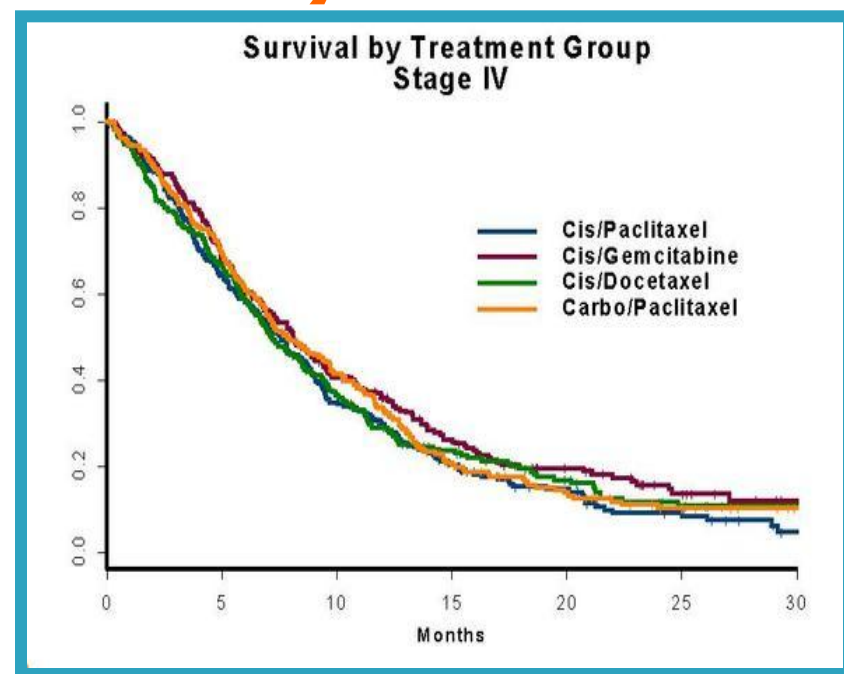
Cx for Stage IV NSCLC

- Chemotherapy improved survival in selected population compared to best supportive care
- Platinum-based regimens
- Good performance status
- Age < 70 years old

(BMJ.

1995;311:899-909)

ECOG 1594 Study



(N Engl J Med. 2002;346:92-98)

Advanced NSCLC Therapy

State of the Art

- Chemotherapy > BSC
- 2 drugs > 1 drug regimens
- 3 drugs $\approx$ 2 drug regimens
 - more toxic & more expensive
- Second-line therapy “works”
- Quality of life is improved
 - 1st & 2nd line CT improve Q of L

Targeted Therapies for NSCLC

- Gefetinib
- . Erlotinib
- . Bevacizumab

Bevacizumab

- Monoclonal antibody against vascular endothelial growth factor (VEGF), which stimulates angiogenesis (growth of new blood vessels into tumor)
- Deprives tumors of the blood supply they need for growth and invasion
- Effective against cancers of colon, lung, breast, kidney, and brain

Bevacizumab

- blocks angiogenesis by preventing activation through VEGF
- Binds all VEGF isoforms with high affinity and specificity
- Blocks binding of VEGF to all of its receptors
- Prevents activation of all VEGF receptors
- Prevents activation of downstream signaling pathways
- Prevents endothelial cell proliferation and migration

Bevacizumab Blocks Angiogenesis

**Recombinant
humanized
monoclonal
antibody to
VEGF-A**

TUMOR

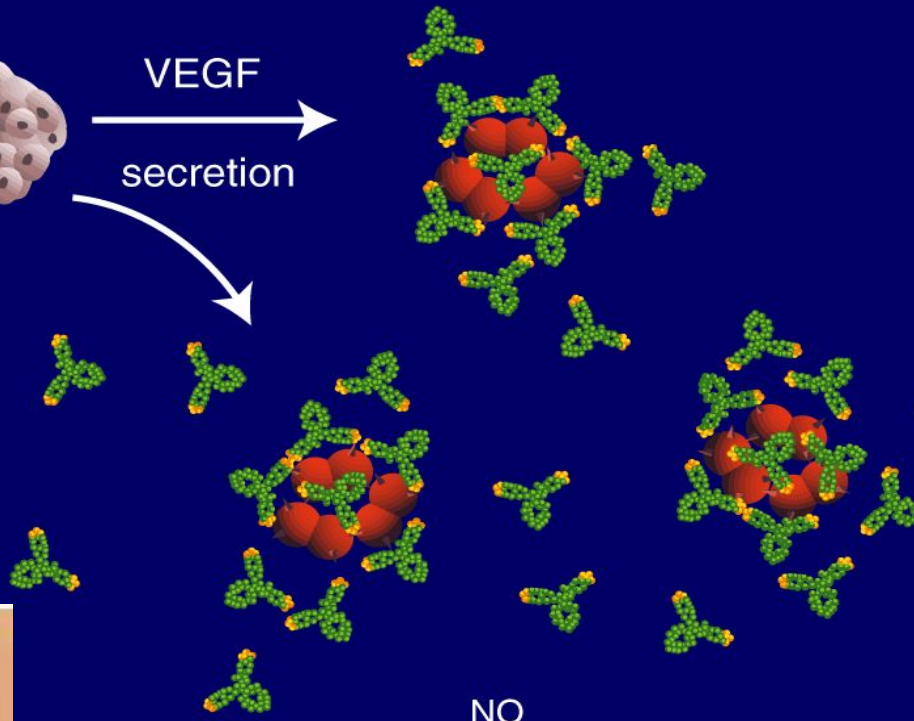
VEGF

secretion

AVASTIN™ - VEGF
complexes

NO
BINDING

NO ANGIOGENESIS



TRIBUTE: Chemotherapy + Erlotinib Treatment in NSCLC

- Erlotinib (E) plus chemotherapy (C) (carboplatin and paclitaxel) did not prolong survival compared with chemotherapy alone
 - 1-year survival: E + C 46.9% vs C 43.8%
 - Patients who had never smoked experienced survival improvements when treated with erlotinib plus chemotherapy

Median Survival, mos	Erlotinib + Chemotherapy	Chemotherapy	<i>P</i> Value
All patients (N = 1079)	10.6	10.5	.95
Never smoked (n = 105)	22.5	10.1	.01

ECOG 4599: Phase III Trial of Bevacizumab in NSCLC

Treatment-naïve patients
with confirmed stage IIIB or
IV cancer; adequate
hematologic, hepatic, and
renal function

(N = 878)

PC
Paclitaxel 200 mg/m²
Carboplatin AUC = 6 mg/mL/min
(once every 3 weeks) x 6 cycles
(n = 433*)

PCB
PC (once every 3 weeks) x 6 cycles +
Bevacizumab 15 mg/kg (once every
3 weeks) until disease progression
(n = 417*)

*Eligible patients included in analysis.

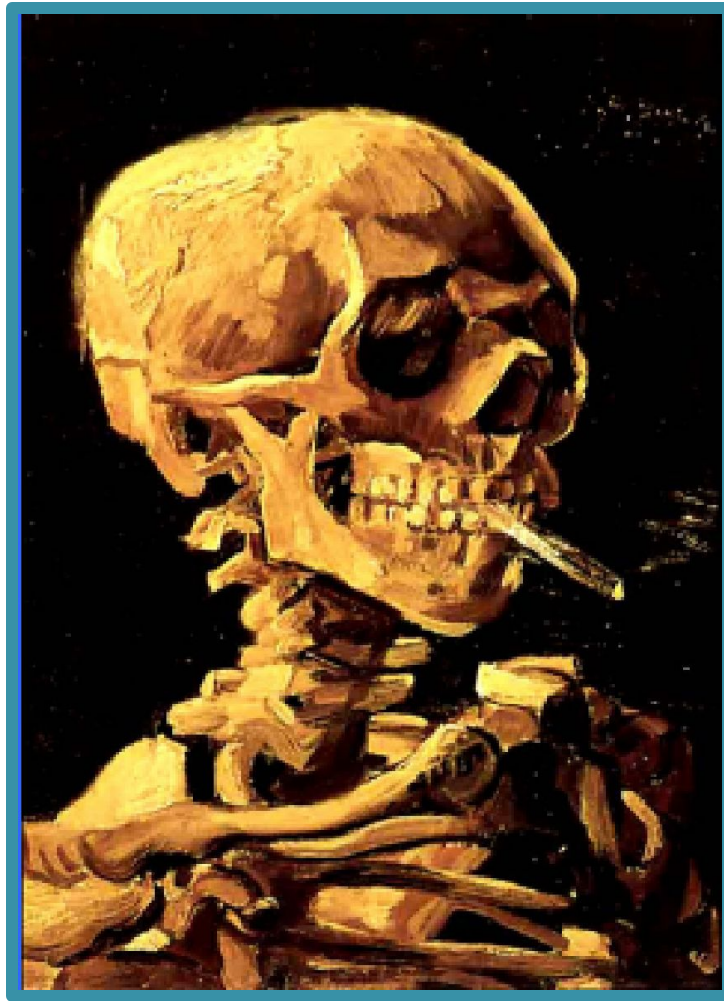
ECOG 4599: Improved Survival Associated With PCB Treatment

- Median overall survival significantly improved in PCB arm (12.3 months compared with 10.3 months in PC arm) (HR for death: 0.79; 95% CI: 0.67-0.92; $P = .003$)
 - 12-month survival
 - PCB: 51%
 - PC: 44%
 - 24-month survival
 - PCB: 22%
 - PC: 15%
- Progression-free survival also significantly improved in PCB arm (6.2 months compared with 4.5 months in PC arm) (HR for disease progression: 0.66; 95% CI: 0.57-0.77; $P < .001$)

Pencegahan

- Hentikan dan cegah rokok
- Jauhi perokok aktif
- Life style yang sehat

Thank You for Your Attention



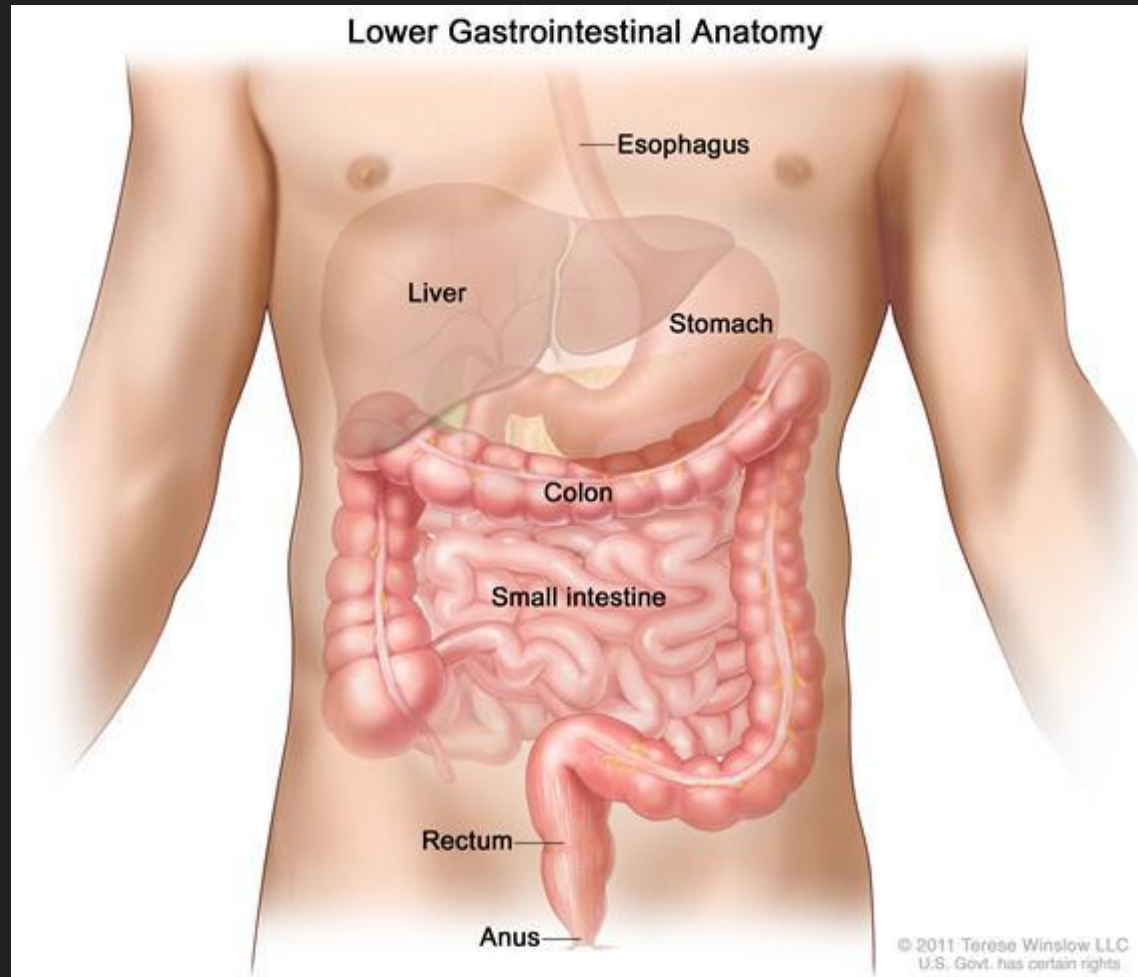
LET'S STOP SMOKING

KANKER KOLOREKTAL

PENDAHULUAN

- Kanker Colorectal, juga disebut kanker kolon atau kanker usus besar, yaitu kanker yang tumbuh dan berkembang di usus besar, dubur dan usus buntu.
- Kanker colorectal melibatkan kolon, rektum dan anal
- Dijadikan satu pembahasan karena beberapa persamaan □ terapi berbeda tergantung lokasi
- Merupakan kanker yang paling banyak terjadi pada dewasa baik laki-laki maupun perempuan
- Merupakan penyebab kematian tertinggi ketiga di Amerika

Anatomi sistem pencernaan



EPIDEMIOLOGI

- Di dunia kanker kolorektal menduduki peringkat ketiga pada tingkat insiden dan mortalitas
- Pada tahun 2002 terdapat lebih dari 1 juta insiden kanker kolorektal dengan tingkat mortalitas lebih dari 50%. 9,5 % pria & 9,3% wanita penderita kanker adalah kanker kolorektal
- Angka insiden tertinggi □ Eropa □ Amerika □ Australia □ Selandia Baru
- Terendah □ India □ Amerika Selatan □ Arab Israel

EPIDEMIOLOGI INDONESIA

- Insidensi □ tinggi, mortalitas □ tinggi
- Pria = wanita □ dewasa muda
- 75% di rektosigmoid
- Pria □ kanker paru □ kanker kolorektal
- Wanita □ kanker payudara □ kanker rahim □ kanker kolorektal

ETIOLOGI DAN FAKTOR RESIKO

- I. Faktor Resiko Yang tidak dapat diubah
 - A. Usia : meningkat pada usia > 50 th, 9 dari 10 penderita terdiagnosa pada usia > 50th
 - B. Riwayat polip kolorektal atau kanker kolorektal : riwayat adenomatous polyps atau kanker kolorektal yg belum tuntas
 - C. Riwayat IBD □ dysplasia
 - D. Riwayat keluarga : kanker kolorektal □ 1 dari 5 penderita kanker kolorektal mempunyai riwayat keluarga menderita kanker kolorektal.
 - E. Sindrome genetik □ mutasi sel yang diturunkan □ FAP (*familial adenomatous polypopsis*) : mutasi gen APC (*adenomatous polyposis coli*), 1% dari kanker kolorektal, HNPCC (*hereditary non-polypopsis colorectal cancer*)

ETIOLOGI DAN FAKTOR RESIKO (con't)

- HNPCC : Lynch Syndrome □ 3-5% kanker kolorektal
- Turcot syndrome □ 2 tipe (mirip FAP dan mirip HNPCC)
- Peutz-Jeghers syndrome
- MUTYH-berhubungan dg polyposis

G. Latar belakang ras dan etnik

Ras Afrika-Amerika □ insiden >>, Yahudi >> dari seluruh ras di dunia (mutasi DNA I1307K APC)

H. DM tipe 2 □ kesamaan faktor resiko : BB>>

2. Faktor Gaya Hidup □ diet, BB, OR

FAKTOR GAYA HIDUP

1. Tipe diet tertentu □ konsumsi daging merah dan daging olahan menaikkan resiko, diet tinggi serat, rendah lemak dan cukup Ca menurunkan resiko
2. Kurang aktivitas fisik
3. Obesitas
4. Merokok
5. Alkohol
6. Kerja shift malam □ sekurang-kurangnya 3 malam/bulan berturut-turut atau selama 15 tahun

Treatment kanker sebelumnya

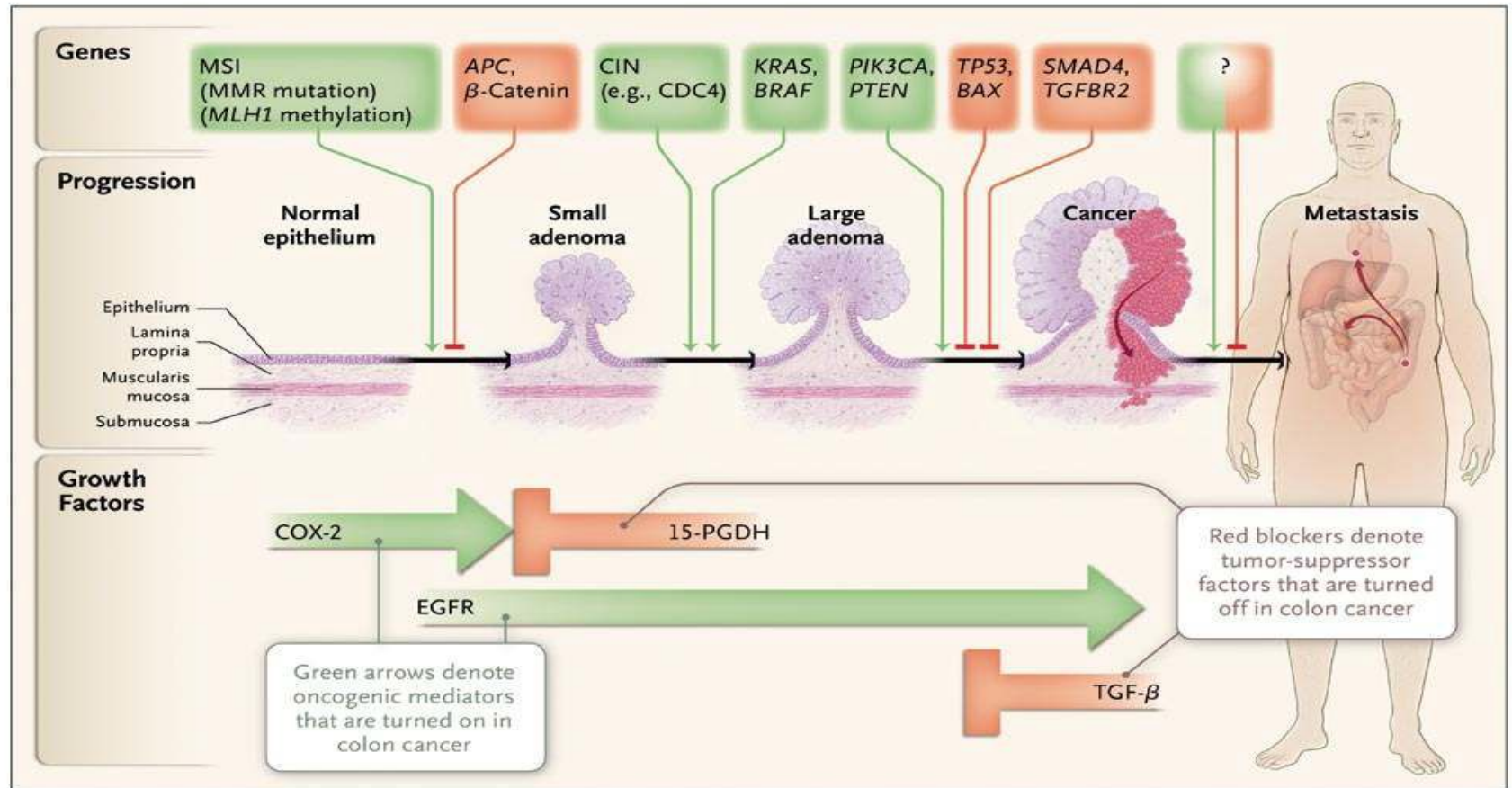
FAKTOR GAYA HIDUP

TABLE 127-1. Lifestyle Factors Associated with Colorectal Cancer Risk

Factor	Comments
Aspirin and non-aspirin NSAID use	Regular use associated with risk reduction, perhaps as much as 50%
Postmenopausal hormone use	Exogenous hormone intake decreases risk 19%–34%
Alcohol intake	Heavy use increases colorectal risk two- to threefold
Physical inactivity and obesity	Elevated BMI and physical inactivity associated with increased risk
Tobacco use	Use of tobacco products estimated to contribute to up to 12% of colorectal cancer deaths annually
Diabetes	Hyperinsulinemia may promote colorectal cancer development
Western diet	High fat, red meat consumption, and low fiber intake possibly associated with increased risk

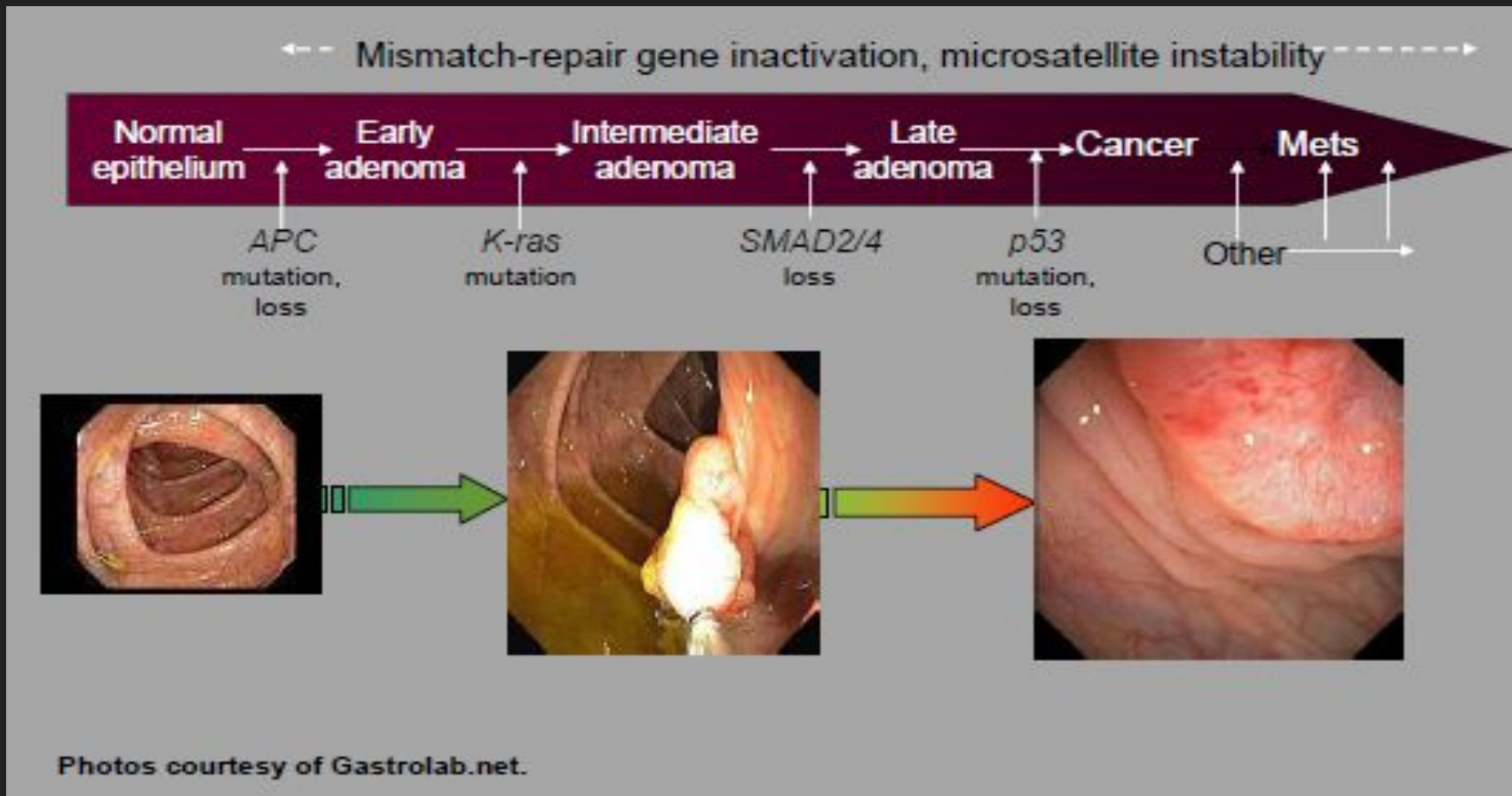
BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.
From Potter.⁶

PATOFISIOLOGI



- Dalam perkembangan kanker usus besar, perubahan genetik menargetkan gen yang diidentifikasi (di bagian atas diagram)
- Ketidakstabilan jalur mikrosatelit (MSI) yang diprakarsai oleh mutasi gen *mismatch repair* (MMR) atau penyimpangan metilasi MLH1 dan selanjutnya terkait dengan mutasi hilir di TGFBR2 dan BAX. Penyimpangan metilasi MLH1 dan mutasi BRAF masing-masing terkait dengan jalur seratedadenoma
- Tanda tanya menunjukkan bahwa perubahan genetik atau epigenetik spesifik untuk perkembangan metastasis belum diidentifikasi.
- Jalur faktor pertumbuhan utama yang diubah selama neoplasia usus (ditampilkan di bagian bawah diagram). CIN menandakan ketidakstabilan kromosom, EGFR reseptor faktor pertumbuhan epidermal, 15-PGDH 15-prostaglandin dehidrogenase, dan TGF- β mengubah faktor pertumbuhan β .

PATOFISIOLOGI



PATOFISIOLOGI

- Terjadinya kanker kolorektal □ multistep yang melibatkan perubahan genetik dan fenotip (hipometilasi DNA, mutasi APC, ketidaknormalan β -catenin, k-RAS, aktivasi onkogen B-raf, penghapusan tumor supresi pada kromosom 18q (mutasi SMAD-4) , kerusakan sinyal *tumor growth factor- β* dan rusaknya fungsi p53

PENCEGAHAN

- l. Screening □ terutama untuk riwayat keluarga dg kanker kolorektal

Kriteria Amsterdam

- a. Setidaknya ada 3 kerabat menderita kanker kolorektal
- b. Hubungan : orang tua-saudara-anak
- c. Kejadian pada 2 generasi
- d. Ada yang menderita kanker kolorektal pada usia < 50th

Bethesda

- e. Lebih muda dari 50th, menderita kanker yg berhubungan dg HNPCC
- f. Lebih muda dari 50th, menderita kanker kolorektal yg berhubungan dg HNPCC
- g. Usia berapa saja, menderita kanker yg berhubungan dg HNPCC

STRATEGI PENCEGAHAN

TABLE 127-3. Prevention Strategies for Colorectal Cancer

Prevention Strategy	Proposed Mechanism of Protective Effect
High-fiber diet supplementation ^a	Decreases fecal bile acids; decreases bowel transit time; direct binding to fecal mutagens; dilution of fecal material
Dietary fat reduction ^a	Decreases fecal bile acids; reduces consumption of heterocyclic amines and other carcinogens that are produced through meat preparation and processing techniques
Nonsteroidal anti-inflammatory agents	Inhibit COX-2; induce apoptosis via 15-LOX-1
Folic acid	Increases levels of intracellular folate
Calcium	Direct binding to bile and fatty acids; inhibits epithelial cell proliferation
Estrogens	Decrease synthesis of secondary bile acids; decrease production of IGF-1; direct antiproliferative effects on colorectal epithelium
Ursodeoxycholic acid	Modulates bile acid composition; inhibits cell proliferation
Aminosalicylates ^b	Inhibit cellular proliferation and induce apoptosis
Eflornithine	Inhibits cellular proliferation through alterations in polyamine metabolism
Oltipraz	Detoxifies activated carcinogens via glutathione S transferase inhibition

^aTo date, findings from randomized trials have failed to demonstrate a protective effect of low-fat high-fiber fruit and vegetable dietary intake in reducing risk of recurrence of colorectal adenomas or colorectal cancer.

^bIn individuals with pre-existing ulcerative colitis or inflammatory bowel disease.

COX-2, cyclooxygenase-2; 15-LOX-1, 15-lipoxygenase-1; IGF-1, insulin-like growth factor 1.

From Järne et al,³⁰ Redaelli et al,³¹ and Steele.³²

SCREENING

Flexible sigmoidoscopy	Fairly quick and safe Usually doesn't require full bowel preparation Sedation usually not used Does not require a specialist Done every 5 years	Views only about a third of the colon Can miss small polyps Can't remove all polyps May be some discomfort Very small risk of bleeding, infection, or bowel tear Colonoscopy will be needed if abnormal
Colonoscopy	Can usually view entire colon Can biopsy and remove polyps Done every 10 years Can diagnose other diseases	Can miss small polyps Full bowel preparation needed More expensive on a one-time basis than other forms of testing Sedation of some kind is usually needed Will need someone to drive you home You may miss a day of work Small risk of bleeding, bowel tears, or infection
Double-contrast barium enema (DCBE)	Can usually view entire colon Relatively safe Done every 5 years No sedation needed	Can miss small polyps Full bowel preparation needed Some false positive test results Cannot remove polyps during testing Colonoscopy will be needed if abnormal
CT colonography (virtual colonoscopy)	Fairly quick and safe Can usually view entire colon Done every 5 years No sedation needed	Can miss small polyps Full bowel preparation needed Some false positive test results Cannot remove polyps during testing Colonoscopy will be needed if abnormal Still fairly new -- may be insurance issues
Fecal occult blood test (FOBT)	No direct risk to the colon No bowel preparation Sampling done at home Inexpensive	May miss many polyps and some cancers May produce false-positive test results May have pre-test dietary limitations Should be done every year Colonoscopy will be needed if abnormal
Fecal immunochemical test (FIT)	No direct risk to the colon No bowel preparation No pre-test dietary restrictions Sampling done at home Fairly inexpensive	May miss many polyps and some cancers May produce false-positive test results Should be done every year Colonoscopy will be needed if abnormal

GEJALA DAN TANDA

- Gejala

- Perubahan kebiasaan buang air besar (kenaikan frekuensi/diare, konstipasi, berkurangnya feses lebih dari beberapa hari)
- Perdarahan rektal, feses gelap, atau darah di feses
- Nausea, vomiting, abdominal discomfort
- Kram perut
- Lemah dan fatigue

- Tanda

- Hepatomegali dan jaundice
- Edema lengan (keterlibatan limpa, tromboplebitis, fistula, turunnya BB, lower back pain, dll)

LABORATORIUM TEST

- Tes darah : CBC (cek anemia), enzim hati, tumor marker (CEA)
- Biopsi □ uji lab sampel (bisa juga dari hasil colonoscopy), uji MSI
- CT scan
- Ultrasound
- MRI
- X-ray
- PET (positron emission tomography)
- Angiography

STAGE

TABLE 127–8. Colon Cancer Stage by TNM Classification

Stage	T	N	M	Dukes ^a	MAC ^a
0	T _{is}	N ₀	M ₀	—	—
I	T ₁	N ₀	M ₀	A	A
	T ₂	N ₀	M ₀	A	B1
IIA	T ₃	N ₀	M ₀	B	B2
IIB	T ₄	N ₀	M ₀	B	B3
IIIA	T ₁ –T ₂	N ₁	M ₀	C	C1
IIIB	T ₃ –T ₄	N ₁	M ₀	C	C2/C3
IIIC	Any T	N ₂	M ₀	C	C1/C2/C3
IV	Any T	Any N	M ₁	—	D

^aDukes B is a composite of better (T₃ N₀ M₀) and worse (T₄ N₀ M₀) prognostic groups, as is Dukes C (any T N₁ M₀ and any T N₂ M₀). MAC is the modified Astler-Collier classification.

Used with the permission of the American Joint Committee on Cancer (AJCC), from AJCC Cancer Staging Manual.⁴⁷

STAGE

- Stage 0, TisN0M0 : stage awal : carcinoma insitu, intramucosal carcinoma
- Stage I : T1-T2N0M0 : kanker tumbuh dari mukosa muscularis ke submukosa (T1) atau ke muscularis propria (T2)
- Stage IIA : T3N0M0 : kanker tumbuh ke lapisan terluar kolon atau rektum tapi belum sampai ke organ lain
- Stage IIB : T4aN0M0 : kanker keluar kolon atau rektum tetapi belum menyebar ke organ lain
- Stage IIC : T4bN0M0 : kanker keluar kolon atau rektum menyebar ke organ dekat

STAGE IIIA

- T1-T2, N1, M0: Kanker telah berkembang dari mukosa ke submukosa (T1) dan mungkin juga telah tumbuh ke propria muskularis (T2). Penyebaran sampai ke kelenjar getah bening node 1 -3 di dekatnya (N1a/N1b) atau ke daerah lemak di dekat kelenjar getah bening tetapi bukan merupakan node sendiri (N1c). Belum menyebar ke tempat jauh.
- T1, N2A, M0: Kanker telah berkembang dari mukosa ke submukosa (T1) menyebar ke kelenjar getah bening 4 -6 (N2A). Belum menyebar ke tempat jauh.

STAGE IIIB

- T3-T4a, N1, M0: Kanker telah tumbuh pada lapisan terluar dari usus besar atau rektum (T3) atau melalui peritoneum visceral (T4a) tetapi belum mencapai organ terdekat. Menyebar ke kelenjar getah bening 1-3 (N1a/N1b) atau ke daerah lemak di dekat kelenjar getah bening tetapi bukan node sendiri (N1c). Belum menyebar ke tempat jauh.
- T2-T3, N2A, M0: Kanker telah tumbuh menjadi propria muskularis (T2) atau ke lapisan terluar dari usus besar atau rektum (T3). Menyebar ke kelenjar getah bening 4-6 (N2A). Belum menyebar ke tempat yang jauh.
- T1-T2, N2B, M0: Kanker telah berkembang dari mukosa ke submukosa (T1) atau mungkin juga telah tumbuh menjadi propria muskularis (T2). Menyebar ke kelenjar getah bening 7 atau lebih di dekatnya (N2B). Belum menyebar ke tempat yang jauh.

STAGE IIIC

- T4a, N2A, M0: Kanker telah tumbuh melalui dinding usus besar atau rektum (termasuk visceral peritoneum) tetapi belum mencapai organ terdekat (T4a). menyebar ke kelenjar getah bening sekitar 4-6 (N2A). Belum menyebar ke tempat yang jauh.
- T3-T4a, N2B, M0: Kanker telah tumbuh menjadi lapisan terluar dari usus besar atau rektum (T3) atau melalui peritoneum visceral (T4a) tetapi belum mencapai organ terdekat. Menyebar ke 7 atau lebih kelenjar getah bening (N2B). Belum menyebar ke tempat yang jauh.
- T4b, N1-N2, M0: Kanker telah tumbuh melalui dinding usus besar atau rektum dan melekat atau telah tumbuh menjadi jaringan atau organ (T4b) terdekat lainnya. Menyebar ke setidaknya salah satu kelenjar getah bening terdekat atau ke daerah lemak di dekat kelenjar getah bening (N1 atau N2). Tidak menyebar ke tempat yang jauh.

STAGE IVA & STAGE IVB

- **Stage IVA** : Setiap T, Setiap N, M1a: Kanker mungkin atau telah tumbuh melalui dinding usus besar atau rektum, dan mungkin telah menyebar ke kelenjar getah bening di dekatnya. Menyebar ke 1 organ jauh (seperti hati atau paru-paru) atau set kelenjar getah bening (M1a).
- **Stage IVB** : Setiap T, Setiap N, M1b: Kanker mungkin telah tumbuh melalui dinding usus besar atau rektum, dan mungkin telah menyebar ke kelenjar getah bening di dekatnya. Menyebar ke lebih dari 1 organ jauh (seperti hati atau paru-paru) atau set kelenjar getah bening, atau telah menyebar ke bagian yang jauh dari peritoneum (selaput rongga perut) (M1b).

PROGNOSIS KANKER KOLON & KANKER REKTAL

Stage	5-year Survival Rate
I	74%
IIA	67%
IIB	59%
IIC	37%
IIIA	73%*
IIIB	46%*
IIIC	28%
IV	6%

Stage	5-year Survival Rate
I	74%
IIA	65%
IIB	52%
IIC	32%
IIIA	74%*
IIIB	45%*
IIIC	33%
IV	6%

TATA LAKSANA TERAPI

- Tujuan terapi tergantung stage □ stage I, II, III : mencegah eradikasi dan metastase, stage IV : mengurangi gejala & komplikasi, menaikkan survival
- Strategi terapi
 1. Pembedahan : pembedahan kolon (kolektomi terbuka, kolektomi dg laparoskopi, polipktomi dan eksisi lokal), pembedahan rektal
 2. Terapi radiasi
 3. Kemoterapi
 4. Terapi target

NCCN GUIDELINE VERSION 3.2013 COLON CANCER

Pathologic Stage	Adjuvant Therapy	Surveillance
Tis; T1, N0, M0	None	Koloskopi pada tahun pertama • Jika adenoma berkembang, diulang dalam 1th • Jika tidak berkembang, diulang setelah 3 th, evaluasi tiap 5th
T2, N0, M0	None	
T3, N0, M0 (no high features)	Clinical trial or Observation or consider capecitabine or 5-FU/leucovorin	• Riwayat & pemeriksaan fisik tiap 3-6 bl dalam 2th, kmd tiap 6 bl dalam 5th • CEA □ s.d.a • CTscan untuk high risk • Colonoscopy • PET
T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0	Capecitabine or 5-FU/leucovorin or FOLFOX or CapeOx or FLOX or clinical trial or Observation	

NCCN GUIDELINE VERSION 3.2013 COLON CANCER

Pathologic Stage	Adjuvant Therapy	Surveillance
T1-3, N1-2, M0 atau T4, N1-2, M0	FOLFOX atau CapeOx (untuk ke-2 kategori), pilihan lain : FLOX (kategoeri 1, atau capecitabin atau 5-FU/leucovorin	•Pemeriksaan fisik setiap 3-6 bl dalam 2th, kmd 6 bl/5th •CEA •Ctscan dada, abdomen, pelvic •Colonoscopy pd 1th kecuali jk tdk ada kolonoskopi sebelumnya karena lesi, kolonoskopi dlm 3-6 bl •Adenoma berkembang, diulang 1 th •Tidak berkembang, diulang 3 th kmd 5th

PATHOLOGIC STAGE^a

ADJUVANT THERAPY^{m,n,y}

SURVEILLANCE^t

T1-3, N1-2, M0
or T4, N1-2, M0

FOLFOX^{o,p,r} or CapeOx^{o,p,r}
(both category 1 and preferred)
Other options include:
FLOX (category 1)^{o,p,r,s}
or
Capecitabine^{o,p}
or
5-FU/leucovorin^{o,p}

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA^w every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT^h annually for up to 5 y
- Colonoscopy^b in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
 - If advanced adenoma, repeat in 1 y
 - If no advanced adenoma,^u repeat in 3 y, then every 5 y^v
- PET-CT scan is not routinely recommended
- See [Principles of Survivorship \(COL-G\)](#)

If
Recurrence,
[See Workup \(COL-9\)](#)

^aAll patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the [NCCN Guidelines for Colorectal Cancer Screening](#).

^bSee [Principles of Pathologic Review \(COL-A\)](#) - Pathological stage.

^cCT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

^dThere are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

^eBevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for stage II or III patients outside the setting of a clinical trial.

^fSee [Principles of Adjuvant Therapy \(COL-E\)](#).

^gConsider RT for T4 with penetration to a fixed structure. See [Principles of Radiation Therapy \(COL-F\)](#).

^hA benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

ⁱGrade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.

^jDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519.

^kVillous polyp, polyp >1 cm, or high-grade dysplasia.

^lRex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-71.

^mIf patient is a potential candidate for further intervention.

ⁿTesting for mismatch repair (MMR) proteins should be considered for all patients <50 years of age.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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COL-4

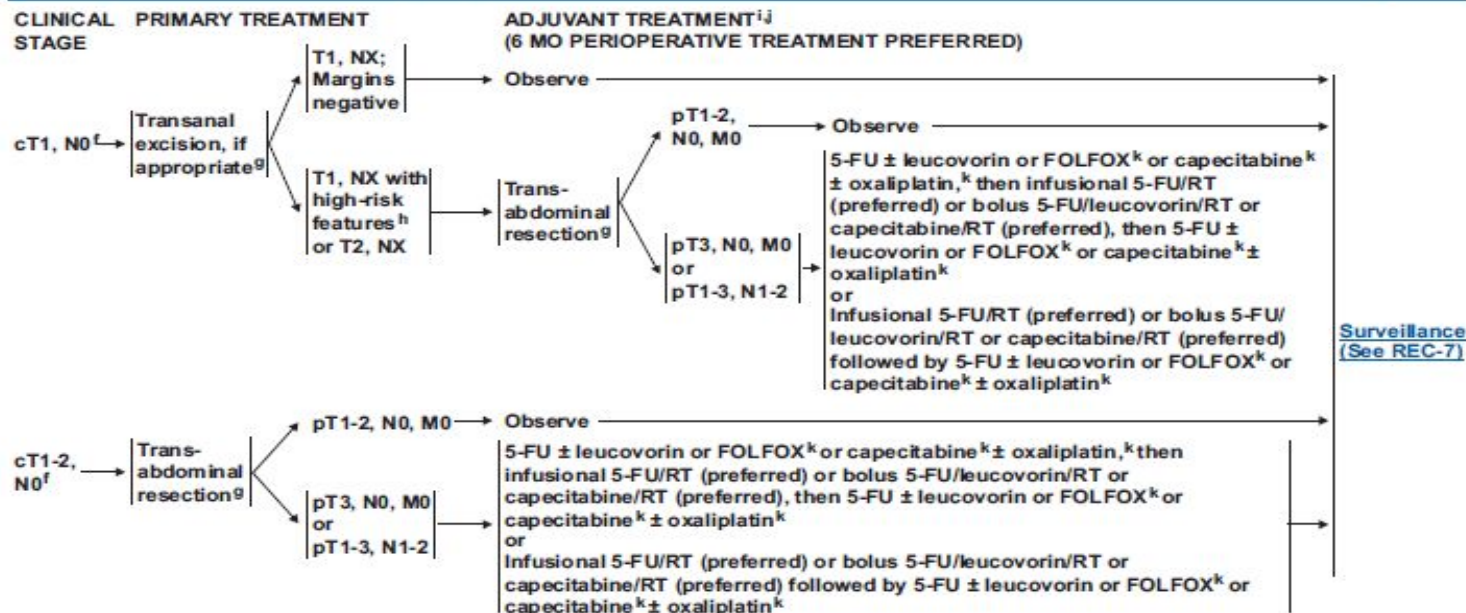
TERAPI KANKER REKTAL



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NCCN Guidelines Version 4.2013 Rectal Cancer

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^fT1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

^gSee Principles of Surgery (REC-B).

^hHigh-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.

ⁱSee Principles of Adjuvant Therapy (REC-C).

^jSee Principles of Radiation Therapy (REC-D).

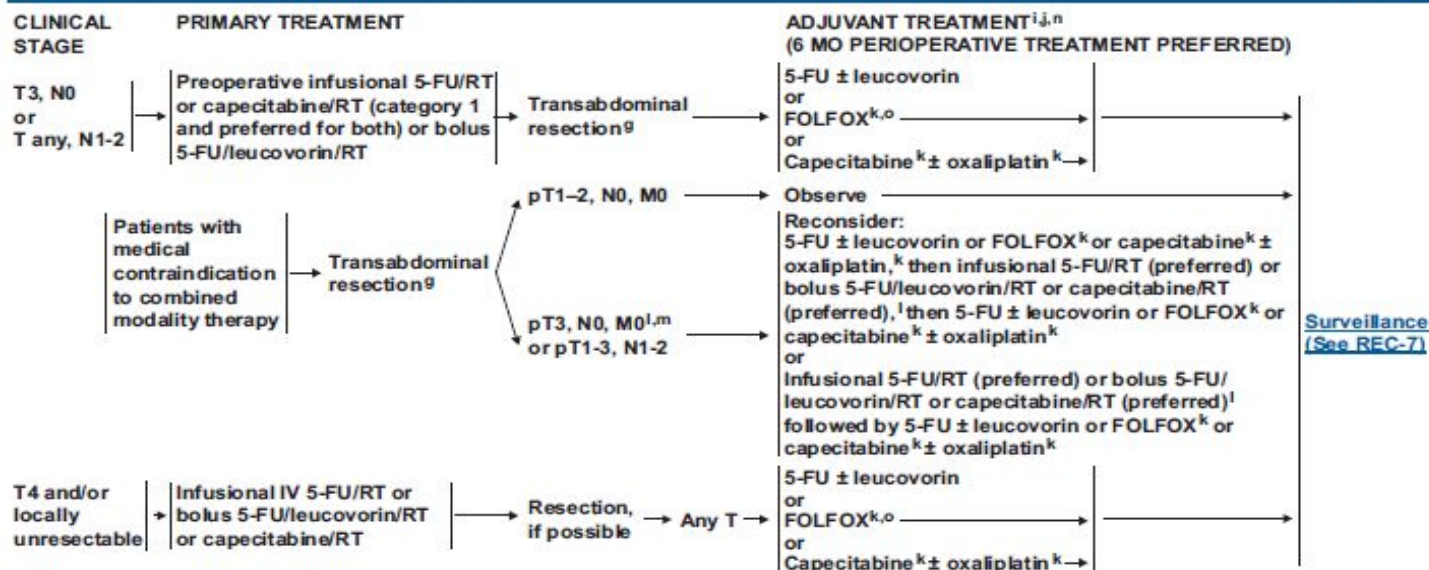
^kThe use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.

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REC-3



^g See Principles of Surgery (REC-B).

ⁱ See Principles of Adjuvant Therapy (REC-C).

^j See Principles of Radiation Therapy (REC-D).

^k The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.

^l The use of agents other than fluoropyrimidines (eg, oxaliplatin) are not recommended concurrently with RT.

^m For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.

ⁿ Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

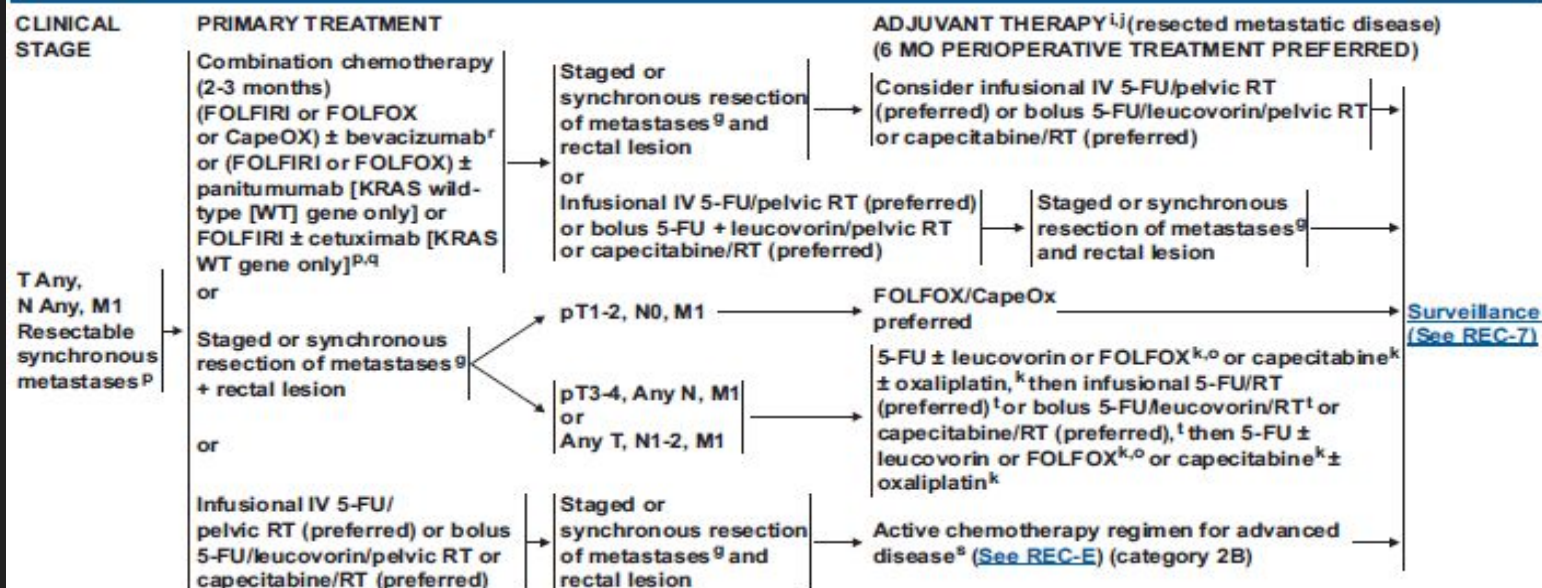
^o An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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REC-4

^g See Principles of Surgery (REC-B).ⁱ See Principles of Adjuvant Therapy (REC-C).^j See Principles of Radiation Therapy (REC-D).^k The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.^o An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.^p Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing).^q See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.^r There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.^t The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.^u FOLFOXIRI is not recommended in this setting.^v RT is only recommended for patients at increased risk for pelvic recurrence.

Note: All recommendations are category 2A unless otherwise indicated.

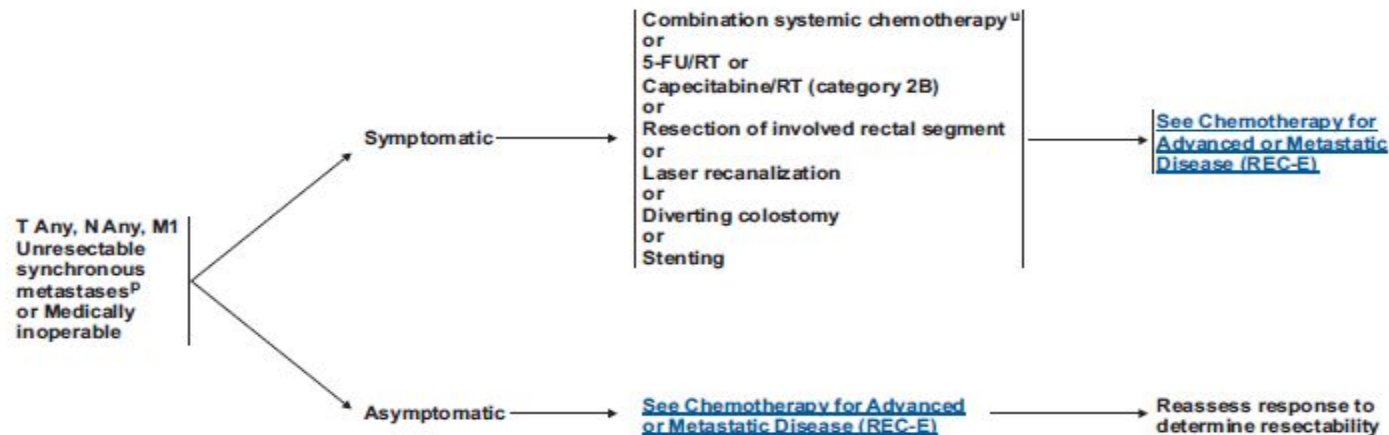
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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REC-5

CLINICAL STAGE

PRIMARY TREATMENT



^PDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). [See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS and BRAF Mutation Testing.

^U[See Chemotherapy for Advanced or Metastatic Disease \(REC-E\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TERAPI METASTASE

First Line	Second Line	Third Line
FOLFOX ± bevacizumab FOLFOX ± cetuximab* CapeOx ± bevacizumab CapeOx ± cetuximab* FOLFIRI + bevacizumab FOLFIRI ± cetuximab* 5-FU/leucovorin + bevacizumab FOLFOXIRI (2B)	FOLFIRI Irinotecan FOLFIRI + cetuximab* (2B) Irinotecan + cetuximab*† FOLFOX CapeOx	Irinotecan + cetuximab*† FOLFOX CapeOx Irinotecan → Irinotecan + cetuximab*† Clinical trial BSC

*Patients with wild-type *KRAS* only.

†In patients who cannot tolerate combination, consider either single-agent cetuximab (wild-type *KRAS* only) or single-agent panitumumab (wild-type *KRAS* only); cetuximab and panitumumab should not be used in combination.

NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. V1.2010.

METASTASE

- Ditambah terapi biologi □ bevacizumab, panitumumab, cetuximab
- Bevacizumab □ merupakan rekombinan antibodi monoklonal yang menghambat *vascular endothelial growth factor* (VEGF)
- Cetuximab □ merupakan rekombinan antibodi monoklonal yang menghambat epidermal growth factor receptor (EGFR)
- Irinotecan □ Topoisomerase-activated agent, menghambat aktivitas ikatan DNA pada topoisomerase 1 □ DNA single-strand rusak, KI : gangguan hati dg bilirubin > 2mg/dl atau transaminase > 3 x nilai normal (tanpa metastase), > 5x nilai normal (dg metastase), ES : diare

OBAT-OBAT KEMO

- FOLFOX : fluorouracil, leucovorin, oxaliplatin
- FOLFIRI : fluorouracil, leucovorin, irinotecan
- CapeOx : capecitabin, oxaliplatin
- 5-FU/leucovorin : fluorouracil, leucovorin
- FOLFOXIRI : fluorouracil, leucovorin, oxaliplatin, irinotecan

FLUOROURACIL

- Termasuk antineoplastik golongan antimetabolit
- Mekanisme : fluorinated antipirimidin analog uracil
- ES utama : mucositis, diare (memburuk jika digunakan bersama leucovorin □ hati2 utk lansia), emetogen ringan
- IO : warfarin
- Penggunaan kombinasi dg leucovorin □ menaikkan kemampuan ikatan metabolit aktif fluorouracil ke thymidilate synthase □ menaikkan aktivitas sitotoksik

FLUOROURACIL + LEUCOVORIN

TABLE 127-11. Treatment Toxicities in Intergroup Trial 0089

Toxicity	Percentage of Grade III Toxicity or Worse			
	5-FU/LD-LV	5-FU/HD-LV	5-FU/LEV	5-FU/LV/LEV
Leukopenia	11.9	2.8	9	14.9
Neutropenia	24.1	3.9	18.8	35.1
Stomatitis	18.2	1.4	3.6	22.6
Diarrhea	21.1	3.0	11.4	17.9

5-FU, fluorouracil; HD-LV, high-dose leucovorin; LD-LV, low-dose leucovorin; LEV = levamisole.

Reproduced with permission from Macdonald.⁵⁸

CAPECITABIN

- Sejenis dg 5-FU □ diubah menjadi 5-FU dalam 3 step
- ES : diare (memerlukan terapi elektrolit)
- IO : warfarin □ menaikkan efek antikoagulan □ resiko perdarahan
- Dosis untuk disfungsi ginjal : kurangi dosis sampai 25% untul Clcr 30-50ml/mnt. Hindari penggunaan bila Clcr < 30ml/mnt

OXALIPLATIN

- Antineoplastik golongan *alkylating agent* □ platinum agent
- Mekanisme : menghambat sintesa DNA dg membentuk inter dan intrastrand DNA *cross-links*
- ES : neuropati perifer > 50% pasien, akut (< 14 hari), persistent (> 14hari), emetogenik sedang, resiko anafilaksi
- Hindari dingin
- Kurangi dosis pada gagal ginjal
- Kombinasi digunakan untuk metastase □ respons rate tinggi



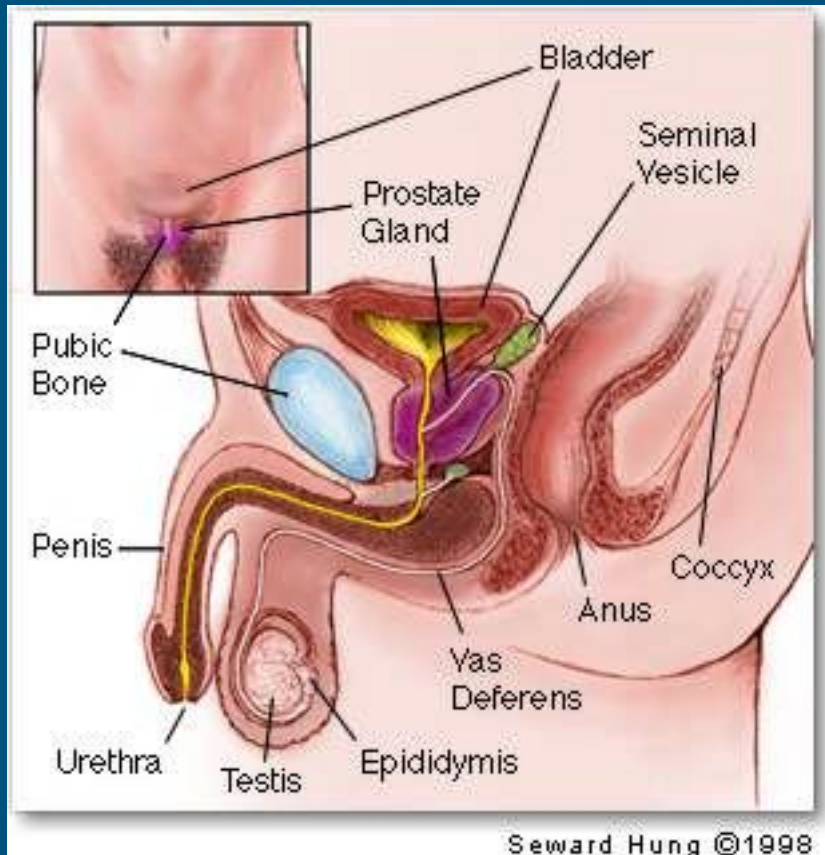
FARMAKOTERAPI KANKER PROSTAT



PENDAHULUAN

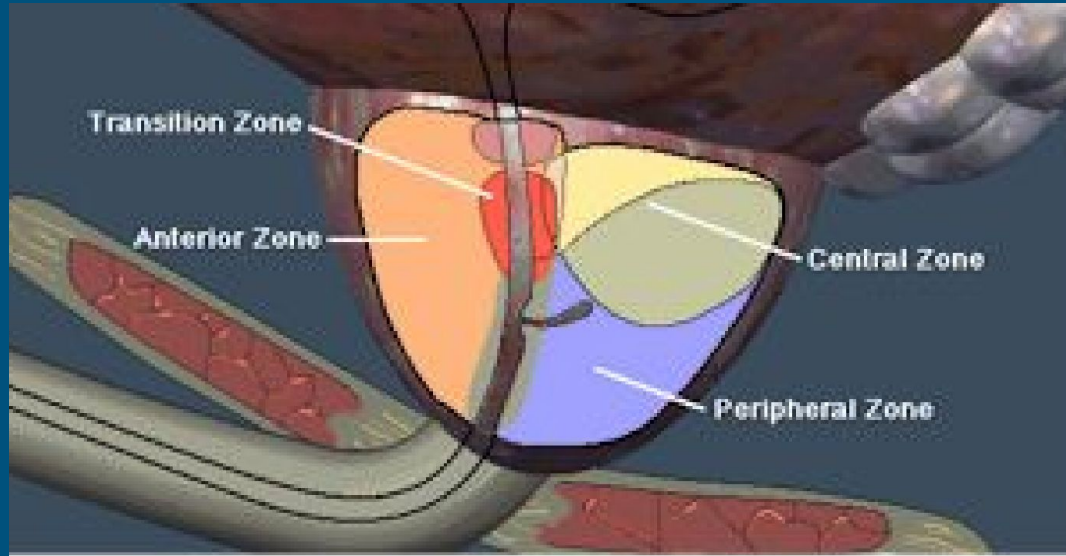
- Kanker yang paling umum terjadi pada kaum pria
- Perkiraan 232.090 kasus baru pada tahun 2005
- 1 dari 5 orang terdiagnosis pada pria
- Afrika Amerika memiliki tingkat kejadian 34% lebih tinggi dan tingkat kematian 2 kali lebih tinggi daripada kulit putih Amerika
- Pria Asia memiliki tingkat kejadian terendah
- Perkiraan 30.350 kematian pada tahun 2005 di Amerika Serikat

KELENJAR PROSTAT



- Kelenjar seks pria
- Seukuran kenari
- Membantu kontrol aliran urin
- Menghasilkan komponen cairan mani
- Menghasilkan Prostate Specific Antigen (PSA) dan Asam Fosfatase

EMPAT AREA PROSTAT



- Transition Zone
- Anterior Zone
- Peripheral Zone
- Central Zone

FAKTOR RESIKO PENINGKATAN KANKER PROSTAT

- Usia □ > 70% kasus terdiagnosa pada usia > 65 th
- Gaya hidup □ tinggi lemak dan tinggi daging, kurang vit D, vit E, likopen, β -karoten
- Hormon □ > 80% tergantung hormon, Afrika-Amerika kenaikan 15% testosteron, Jepang penurunan aktivitas 5- α reduktase, ekspresi polimorfi pada reseptor androgen
- Ras □ Afrika-Amerika insiden > tinggi
- Genetik □ riwayat keluarga, mutasi gen p53, *Rb*, E-cadherin, α -catenin, reseptor androgen, KAI1, ketidakstabilan mikrosatelit, hilangnya heterozigot di 1, 2q, 12q, 15q, 16p dan 16q

PATOFISIOLOGI

- Inaktivasi gen E-cadherin melalui hipermetilasi, prognostic marker dimana E-cadherin yg tidak normal menggambarkan tumor ganas
- Kerusakan DNA, hilangnya fungsi p53 untuk apoptosis sel □ pertumbuhan sel tidak terkontrol
- Mutasi *Rb* □ rusaknya regulasi siklus sel
- KAI1 □ *Kang ai*, gen antimetastatik pada orang Cina □ downregulasi selama perkembangan kanker
- Mutasi reseptor androgen □ lebih sering pada kanker yg telah berkembang, disebabkan oleh testikuler, steroid, antiandrogen non steroid.
- Mutasi 5- α reduktase (enzim yang mengubah testosteron menjadi DHT aktif) □ hipotesa

PATOLOGI

- Lebih dari 95% dari kanker prostat primer adalah adenocarcinoma.
- Adenokarsinoma prostat sering multifokal dan heterogen dalam pola diferensiasi. Prostatic intraepithelial neoplasia ([PIN] sel epitel atipikal noninvasif yang muncul pada asinus jinak) □ adenokarsinoma prostat.
- Sejumlah tumor langka menjelaskan beberapa persentase kasus. Ini meliputi:
 - Tumor sel kecil.
 - Intralobular karsinoma asinar.
 - Karsinoma duktal.
 - Sel karsinoma jelas.
 - Karsinoma mucinous.

GLEASON SCORING SYSTEM

- Kelas histologis adenokarsinoma prostat biasanya dilaporkan dengan sistem penilaian Gleason □ data tambahan untuk pementasan tumor dalam menentukan prognosis.
- Skor Gleason dihitung berdasarkan nilai dominan histologis, dari kelas 1 (terdeferensiasi) sampai kelas 5 (deferensiasi sangat buruk).
- Skor klasik diperoleh dengan menambahkan dua nilai pola yang paling umum, menghasilkan skor mulai dari 2 sampai 10.

TANDA DAN GEJALA

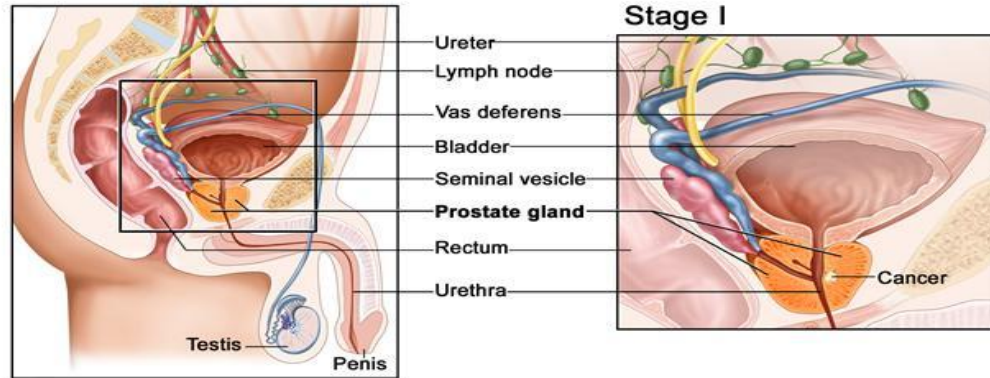
- Lokal □ tanpa gejala
- Lokal, invansif □ gangguan berkemih □ frekuensi, hesitancy (urin tidak lancar/slowly), dribbling (aliran kecil), impoten
- Penyakit yang berkembang □ sakit punggung, kompresi tulang ekor, edema anggota badan bawah, anemia, BB turun, fraktur patologi

DIAGNOSA

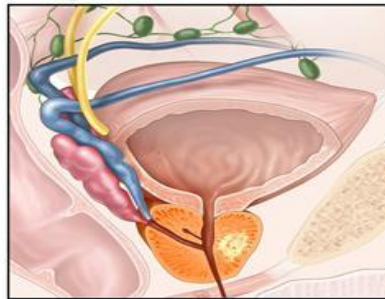
TABLE 128–3. Diagnostic and Staging Work-Up for Prostate Cancer

Initial tests	Digital rectal examination (DRE) Prostate-specific antigen (PSA) Transrectal ultrasonography (TRUS) if either DRE is positive or PSA is elevated
Staging tests	Biopsy Gleason score on biopsy specimen Bone scan Complete blood count Liver function tests Serum phosphatases (acid/alkaline) Excretory urogram Chest x-ray
Additional staging tests (depends on tumor classification, PSA, and Gleason score)	Skeletal films Lymph node evaluation Pelvic computed tomography ¹¹¹ In-labeled capromab pentetide scan Bipedal lymphangiogram Transrectal magnetic resonance imaging

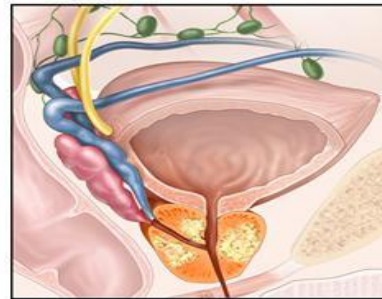
STAGING



Stage IIA



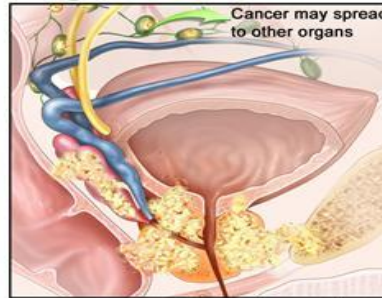
Stage IIB



Stage III



Stage IV



STAGING

TABLE 128-4. Staging and Classification Systems for Prostate Cancer

AUS ^a Stage (A-D)	AJC-UICC ^b Classification (TNM)
A (occult, nonpalpable)	T _x N _x M _x (cannot be assessed) T ₀ N ₀ M ₀ (nonpalpable) T ₀ : Focal or diffuse
A ₁ : Focal A ₂ : Diffuse	
B (confined to prostate)	T ₁ N ₀ M ₀ , T ₂ N ₀ M ₀ T ₁ (Clinically inapparent tumor not palpable or visible by imaging) T _{1a} : Tumor incidental histologic finding in 5% or less of tissue resected T _{1b} : Tumor incidental histologic finding in 5% or more of tissue resected T _{1c} : Tumor identified by needle biopsy (e.g., because of elevated PSA)
B ₁ : Single nodule in one lobe, <1.5 cm	T ₂ : (Tumor confined within the prostate ^c) T _{2a} : Tumor involves half of a lobe or less T _{2b} : Tumor involves more than half a lobe, but not both lobes T _{2c} : Tumor involves both lobes
B ₂ : Diffuse involvement of whole gland, >1.5 cm	
C (localized to periprostatic area)	T ₃ N ₀ M ₀ , T ₄ N ₀ M ₀ T ₃ : (Tumor extends through the prostatic capsule ^d) T _{3a} : Unilateral extracapsular extension T _{3b} : Bilateral extracapsular extension T _{3c} : Tumor invades the seminal vesicle(s)
C ₁ : No seminal vesicle involvement, <70 g	T ₄ : (Tumor is fixed or invades adjacent structures other than the seminal vesicles) T _{4a} : Tumor invades any of bladder neck, external sphincter, or rectum T _{4b} : Tumor invades levator muscles and/or is fixed to the pelvic wall
C ₂ : Seminal vesicle involvement, >70 g	
D (metastatic disease)	Any T, N ₁₋₄ , M ₀ , or N ₀₋₄ , M ₁ N ₁ : Metastasis in a single lymph node, 2 cm or less in greatest dimension N ₂ : Metastasis in single lymph node more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph node metastases, none more than 5 cm in greatest dimension N ₃ : Metastasis in lymph node more than 5 cm in greatest dimension M _{1a} : Nonregional lymph node(s) M _{1b} : Bone(s) M _{1c} : Other site(s)
D ₁ : Pelvic lymph nodes or ureteral obstruction	
D ₂ : Bone, distant lymph node, organ, or soft tissue metastases	

^aAmerican Urologic System.

^bAmerican Joint Committee-International Union Against Cancer.

^cNote: Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T_{1c}.

^dNote: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T₃ but as T₂.

Reproduced with permission from Montie.³⁸

PROGNOSIS

- Prognosis tergantung histologi, ukuran tumor, dan keganasan tumor lokal

TERAPI

Table 3: Treatment options for recently diagnosed localised prostate cancer^{17,22}

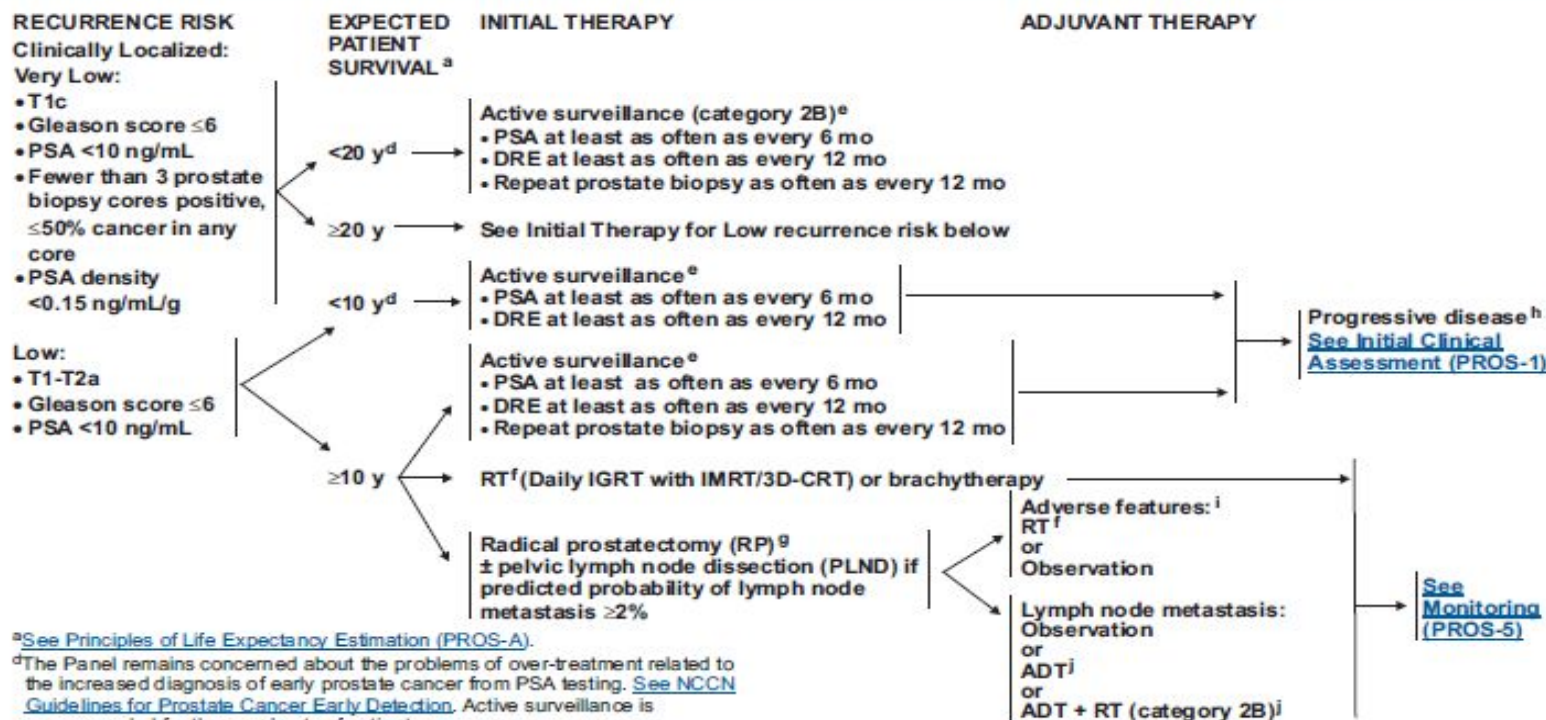
Modality	Low risk [*]	Intermediate risk [*]	High risk [*]
Active surveillance	Preferred option	Option	Not an option
Watchful waiting ^{**}	Option	Option	Option
Prostatectomy (RP)	Option	Preferred option	Preferred option ^{***}
Radiotherapy / Brachytherapy (RT)	Option	Preferred option	Preferred option ^{***}

^{*} Risk calculation based on number of positive biopsy cores, Gleason score, PSA levels

^{**} Suitable only for patients who are not candidates for curative radical therapy

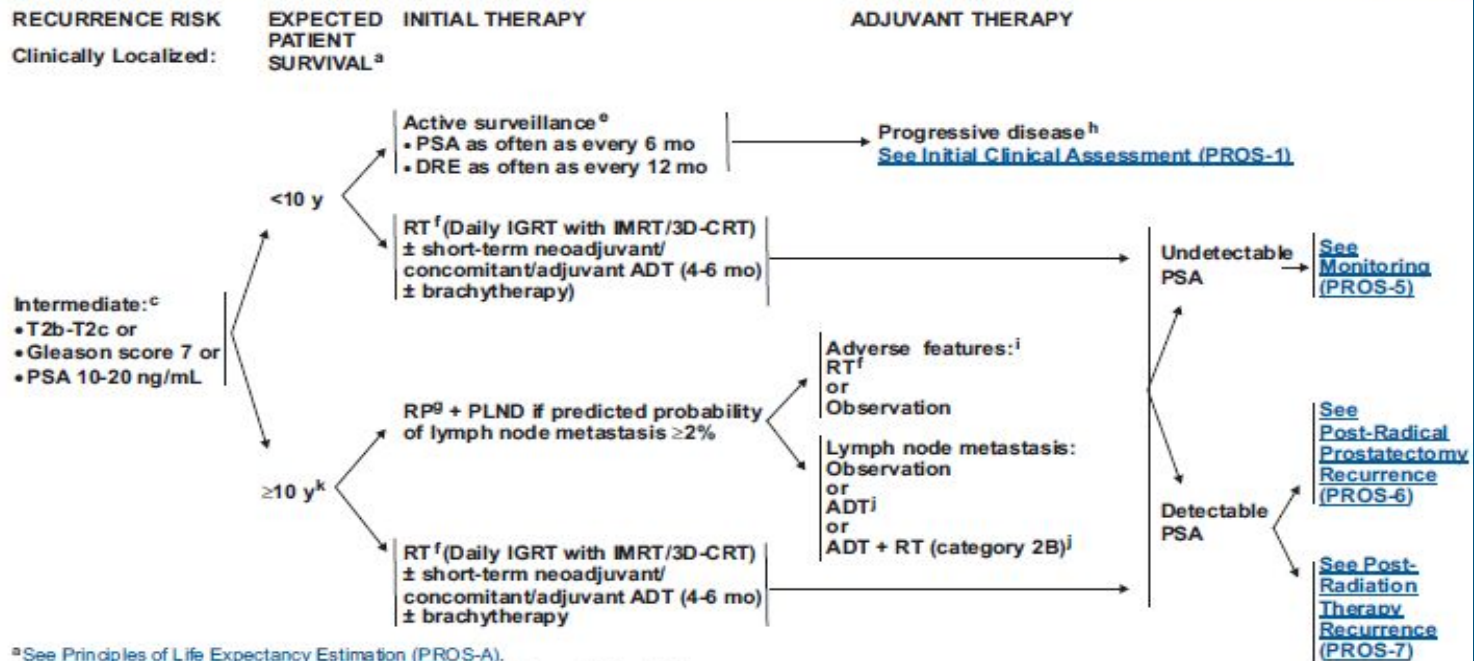
^{***} Only if there is a realistic prospect of long-term disease control; neoadjuvant androgen deprivation therapy usually co-prescribed with RT

TERAPI



Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TERAPI



^aSee Principles of Life Expectancy Estimation (PROS-A).

^cPatients with multiple adverse factors may be shifted into the next highest risk group.

^gActive surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. [See Principles of Active Surveillance \(PROS-B\)](#).

^fSee Principles of Radiation Therapy (PROS-C).

^gSee Principles of Surgery (PROS-D).

^hCriteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

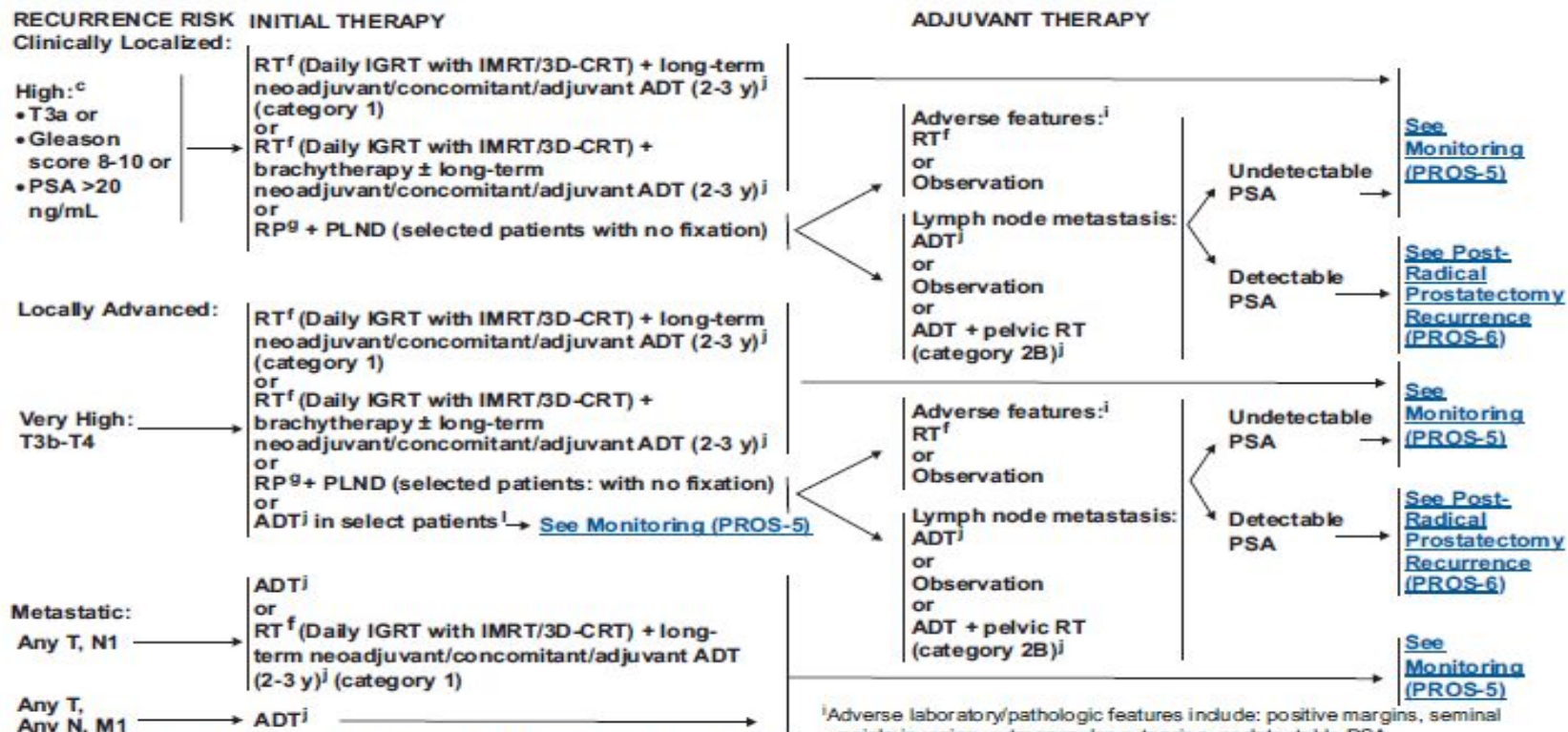
ⁱAdverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

^jSee Principles of Androgen Deprivation Therapy (PROS-E).

^kActive surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



^cPatients with multiple adverse factors may be shifted into the next highest risk group.

^fSee [Principles of Radiation Therapy \(PROS-C\)](#).

^gSee [Principles of Surgery \(PROS-D\)](#).

ⁱAdverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

^jSee [Principles of Androgen Deprivation Therapy \(PROS-E\)](#).

^lPrimary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TERAPI

- Non farmakologi □ orchiectomy : pengangkatan testis □
pertimbangkan faktor usia
- Farmakologi □ first choice : agonis LH-RH
- Second choice □ doxetacel, mitoxantrone, vinblastin,
antibiotik monoklonal

AGONIS LH-RH

Luteinizing hormone-releasing hormones

- Terapi ablasi androgen setelah pembedahan
- Contoh : leuprolid (depot, implant), goserelin (implant)
- Leuprolid asetat □ sekali sehari, depot diganti tiap bulan atau tiap 12 hari atau 16 hari
- ES : hot flashes, impoten, penurunan libido
- Sebagai terapi awal

ANTIANDROGEN

TABLE 12B-5. Antiandrogens

Antiandrogen	Usual Dose	Adverse Effects
Flutamide	750 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness Methemoglobinemia
Bicalutamide	50 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness
Nilutamide	300 mg/day for first month then 150 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (nausea or constipation) Liver function test abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis

- Monoterapi
- Kurang efektif dibanding agonis LH-RH
- Dapat digunakan dalam kombinasi hormon blokade
 - kontroversi
- Mekanisme : interfensi berbagai jalur hormon untuk eliminasi aktivitas androgen
- ESTROGEN

DOXETACEL

- Digunakan dalam kombinasi dg prednison
- Golongan antimikrotubular
- Mekanisme : menghambat depolimerase tubulin, menghambat pembelahan sel
- ES : myelosupresi, retensi cairan, edema, naiknya BB
- Sindrom retensi cairan □ dexamethason 8mg oral 2x sehari 3 hari (dimulai 1 hari sebelum doxetacel)
- Penyesuaian dosis pada gangguan hati

MITOXANTRONE

- Digunakan dalam kombinasi dg prednison
- Golongan topoisomerase
- Mekanisme : inhibitor topoisomerase II, intercalator DNA
- ES : ringan : myelosupresi, potensial : mucositis, alopecia
- Menyebabkan urin biru-hijau

ESTRAMUSTIN

- Digunakan dalam kombinasi dg vinblastin
- Golongan antimikrotubular
- Secara struktur adalah kombinasi estrogen dan alkilating, tetapi secara fungsi antimikrotubular □ interfensi mikrotubular melalui protein (MAPs)
- ES : nausea-vomiting (tgt dosis), diare, penyakit serebrovaskuler, gynecomastia
- IO : warfarin
- Monitoring ketat pada pasien dg penyakit kardiovaskuler dan serebrovaskuler
- Diminum 1-2 jam setelah makan

VINBLASTIN

- Digunakan dalam kombinasi dg estramustin
- Golongan antimikrotubular □
- ES : myelosupresi ringan, mucositis, emetogen ringan, neurotoksik
- Kurangi dosis 50% pada bilirubin total 1,5-3mg/dL, kurangi dosis 75% pada bilirubin total > 3mg/dL
- Antineoplastik lain dengan efek sedang yang bisa digunakan sebagai single terapi : siklofosamid, estramustin, 5-FU, MTX, dacarbazin, mitoxantron, doxorubicin, paclitaxel, gemcitabin, vinorelbin, cisplatin



FARMAKOTERAPI KANKER PAYUDARA

Astri Rachmawati.,
S.Farm., M.Sc., Apt

I. KANKER PAYUDARA

Apakah semua benjolan adalah kanker/ganas?



Jinak

- Benjolan lunak
- Mudah digerakkan
- Usia muda



Ganas

- Benjolan keras
- Sulit digerakkan
- Usia paling sering di atas 40 tahun

II. EPIDEMIOLOGI

- ✓ Menempati urutan kedua setelah kanker mulut rahim
- ✓ Rata-rata 10 dari 100.000 wanita di Indonesia menderita kanker payudara
- ✓ Karsinoma mammae jarang sebelum umur 25 tahun dan tidak biasa sebelum umur 30 tahun, tetapi insidensinya meningkat dengan cepat setelah umur 30 tahun dengan rata-rata medium age 60 tahun.

III. ETIOLOGI

- ▶ Genetik

Diperkirakan bahwa 5% semua kanker payudara adalah akibat predisposisi keturunan

Gen BRCA1 dan BRCA2 sangat mungkin sebagai resiko

- ▶ Virus

- ▶ Lingkungan

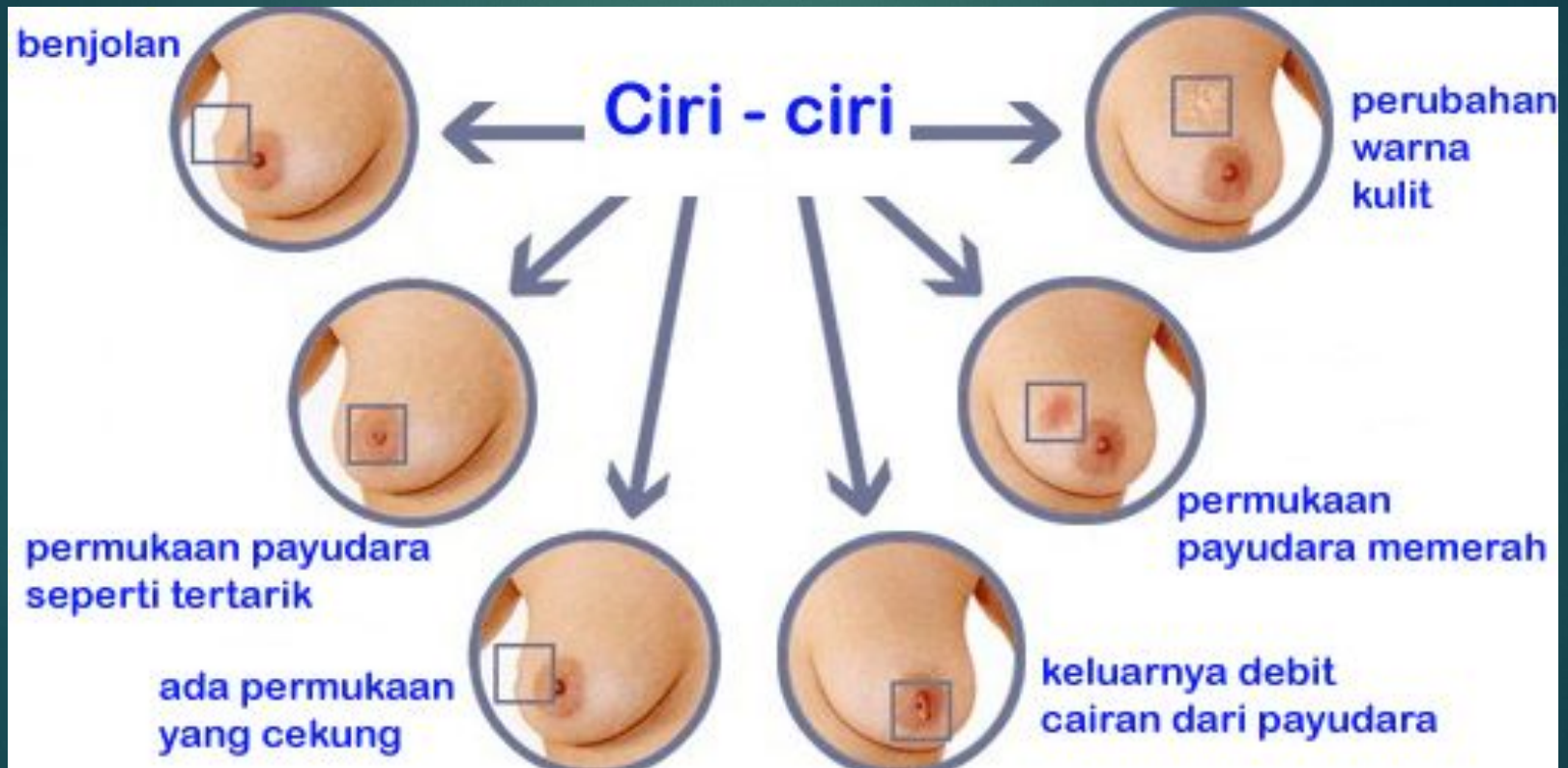
Insidensi kanker payudara berbeda-beda dalam kelompok yang secara genetis homogen dan perbedaan geografis

IV. FAKTOR RESIKO

- *Etiologi:* belum ada penyebab spesifik.



V. TANDA DAN GEJALA KLINIK



Apa saja gejalanya?



Manifestasi Klinis



1. Gejala keras di payudara (tidak nyeri, kecil-besar, melekat pada kulit)
2. Puting berubah (masuk ke dalam / retraksi, terasa sakit, mengeluarkan cairan / darah)
3. Perubahan pada kulit payudara: berkerut, iritasi seperti kulit jeruk
4. Benjolan-benjolan kecil
5. Luka di payudara yang sulit sembuh
6. Payudara terasa panas, merah & bengkak
7. Gatal di daerah sekitar puting
8. Benjolan keras terfiksasi
9. Bila benjolan itu kanker, awalnya biasanya pada 1





**Lump in breast or
underarm area**



**Change in size or
shape of breast**



**Discharge or bleeding
from the nipple**



**Change in colour or
appearance of breast
skin or areola**



**Nipple pulled
into areola**

VI. PENENTUAN STADIUM

. TAHAPAN/LUAS PENYEBARAN

TAHAPAN	LUAS PENYEBARAN	TINGKAT RATA RATA KESELAMATAN PADA MASA 5 – TAHUNAN (%)
0	Kanker non invasif	99
1	Kanker invasif kecil (kurang dr 2 cm tanpa penyebaran ke arah kelenjar getah bening aksila)	90
2	Kanker invasif (antara 2-5cm atau/dengan penyebaran pada kelenjar getah bening)	70
3 (a,b,c)	Kanker invasif besar (lebih dari 5cm dengan penyebaran pada kulit atau beberapa kelenjar getah bening)	40
4	Penyebaran yg luas atau metastasis	20



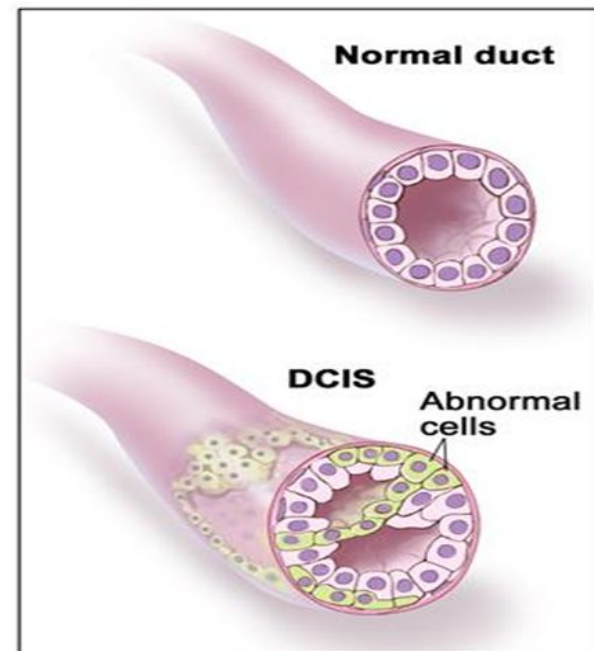
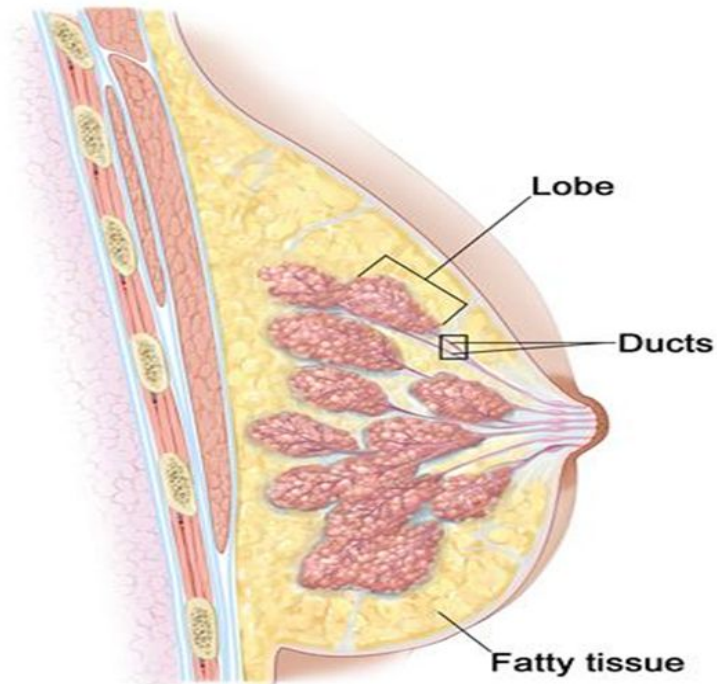
Perbandingan Penggolongan stadium Kanker Payudara menurut European Guideline VS American Guideline VS Indonesian Guideline

European Guideline 2019 VS American Guideline 2019
VS Indonesian Guideline 2019

Stage 0 (carcinoma in situ)

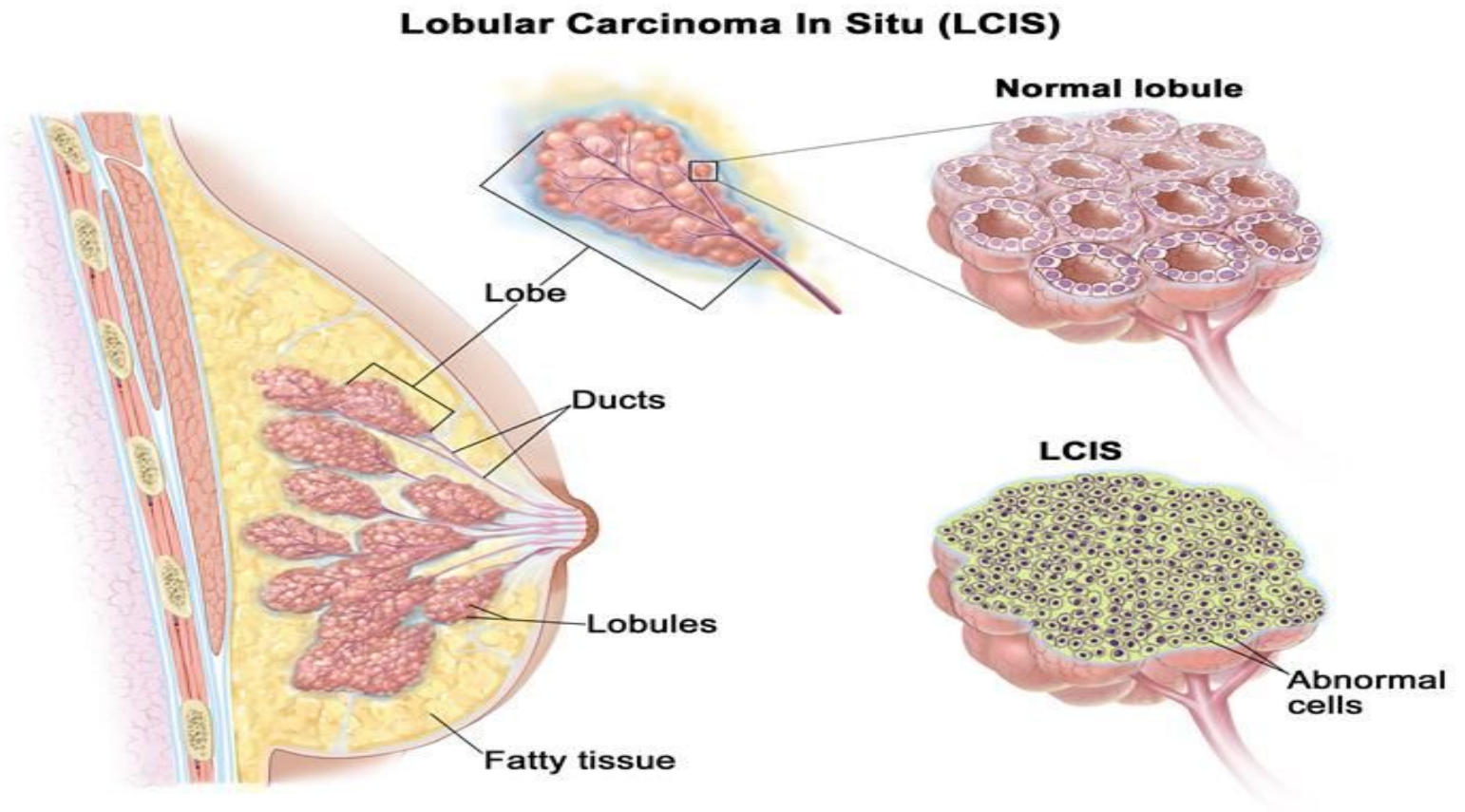
Ductal Carcinoma In situ

Ductal Carcinoma In Situ (DCIS)



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Lobular carcinoma in situ

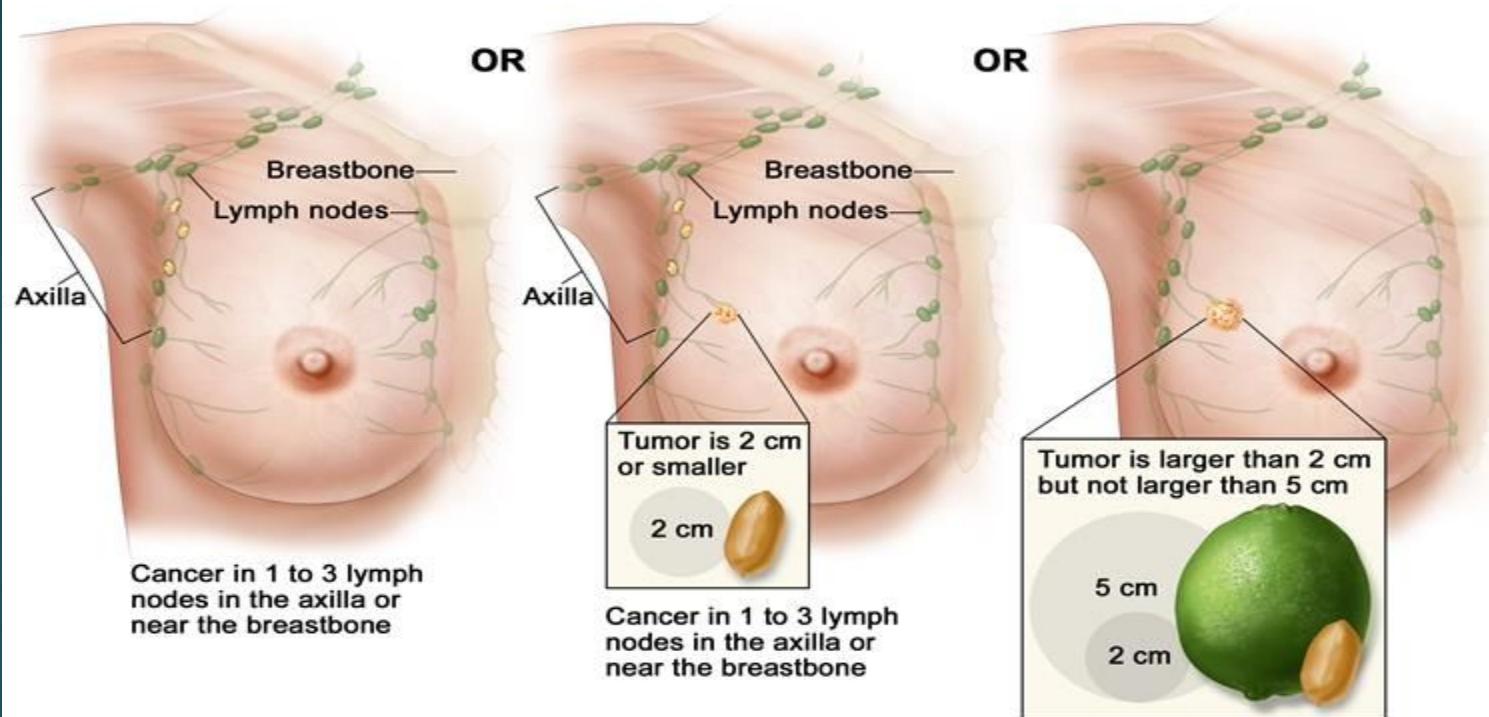


Stage IB Breast Cancer

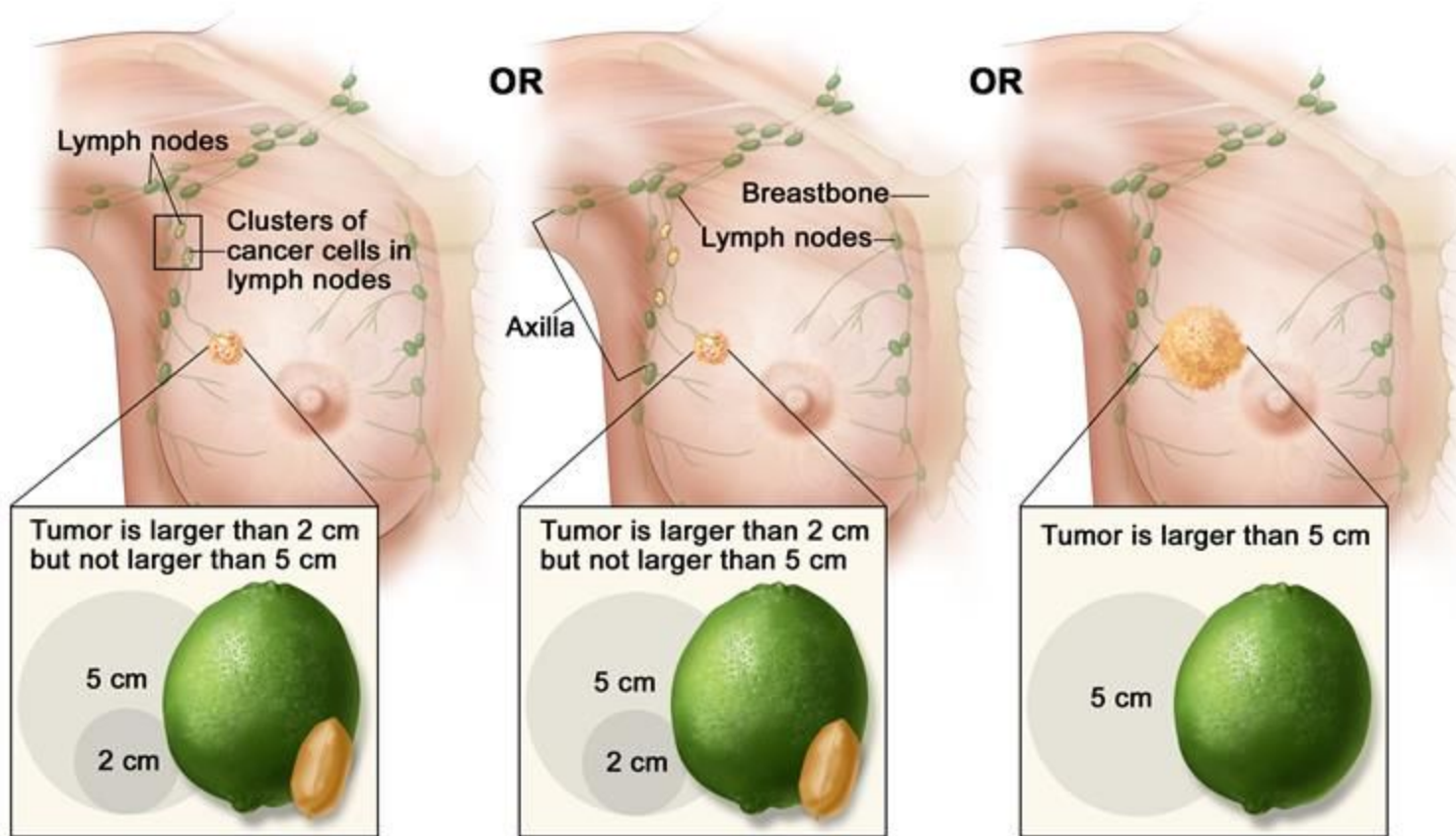


Stage II

Stage IIA Breast Cancer



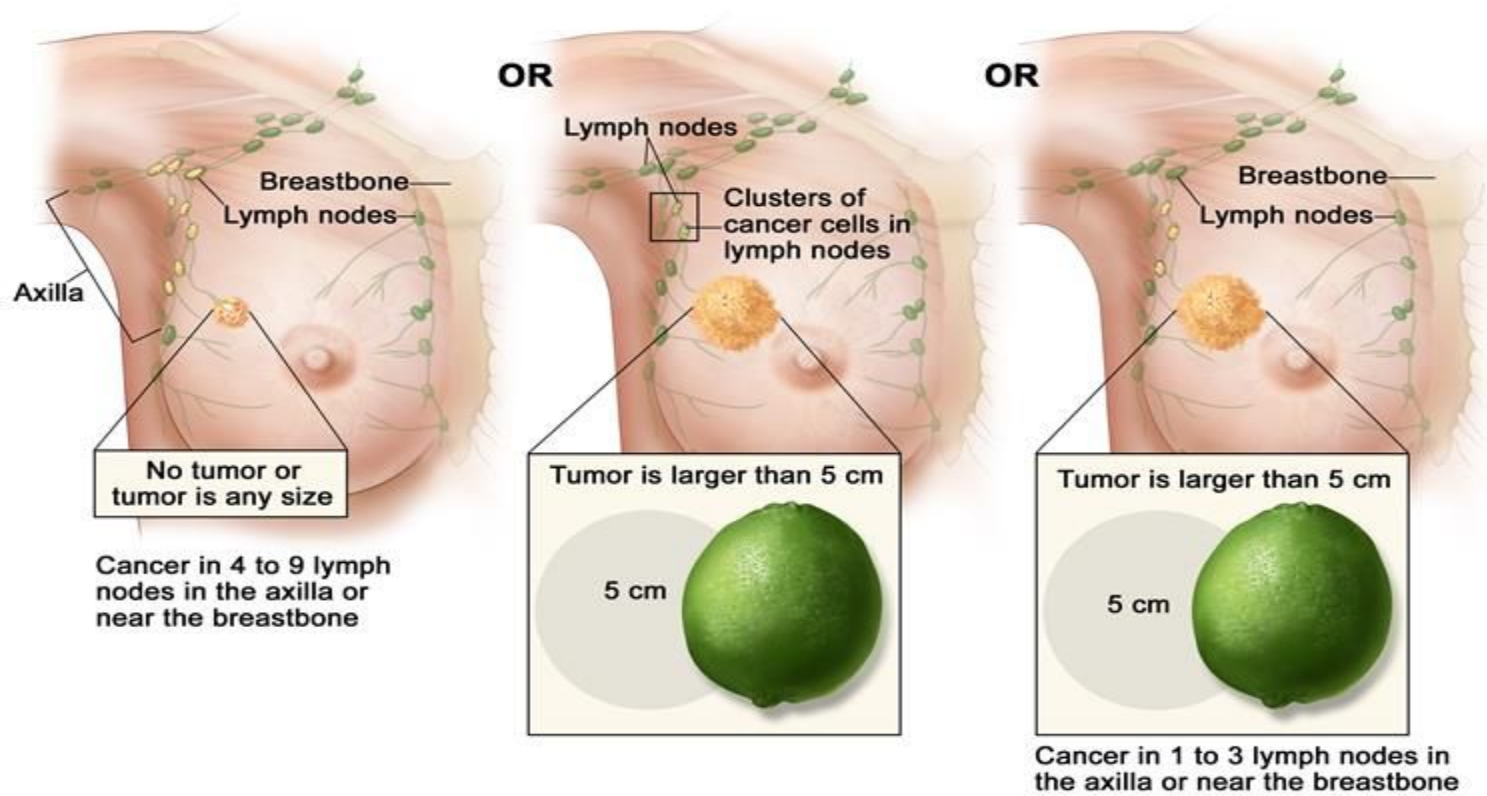
Stage IIB Breast Cancer



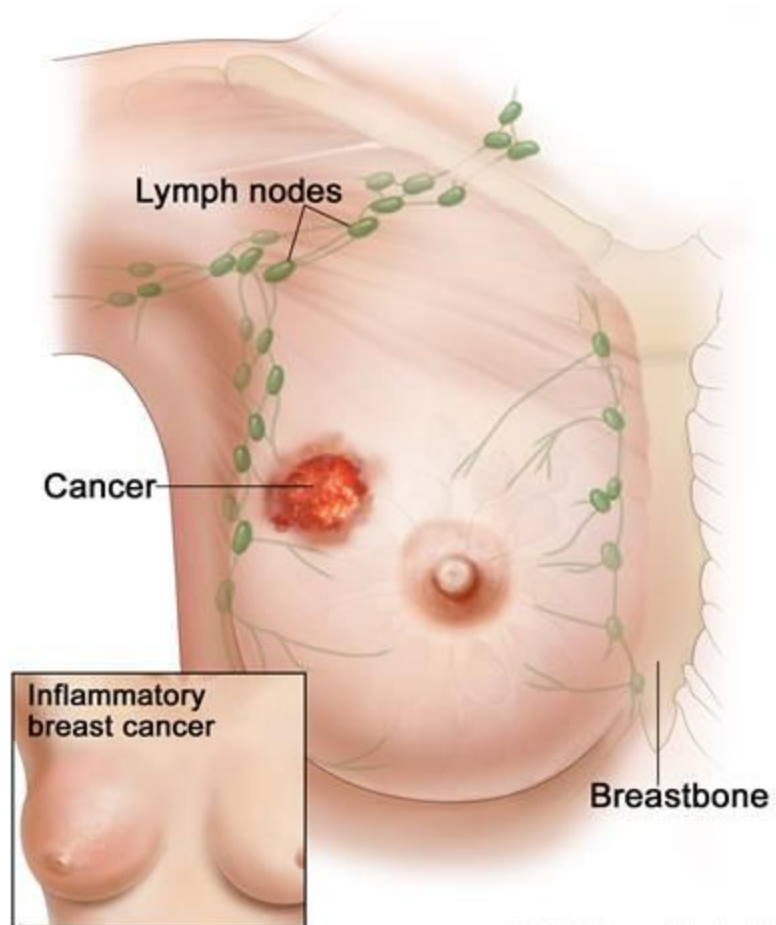
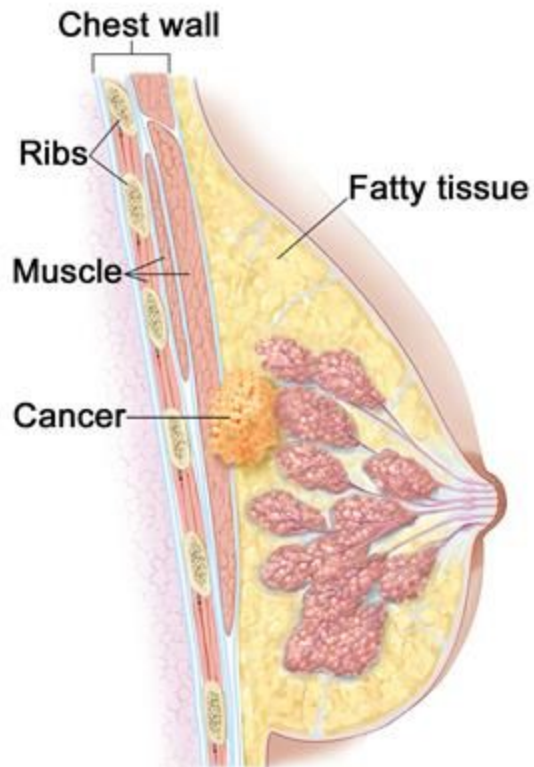
Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone

Stage III

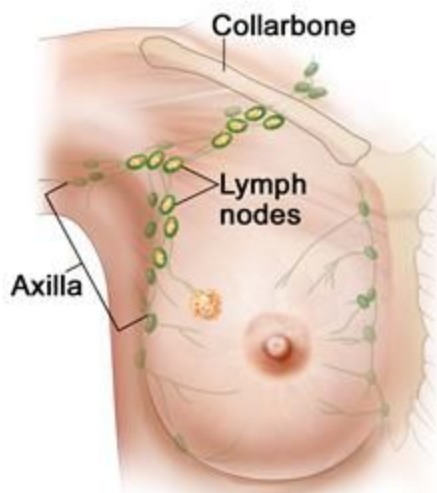
Stage IIIA Breast Cancer



Stage IIIB Breast Cancer

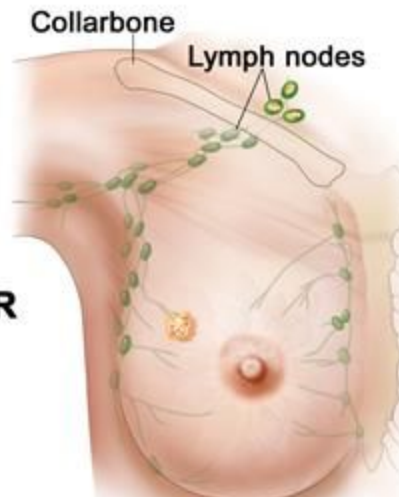


Stage IIIC Breast Cancer



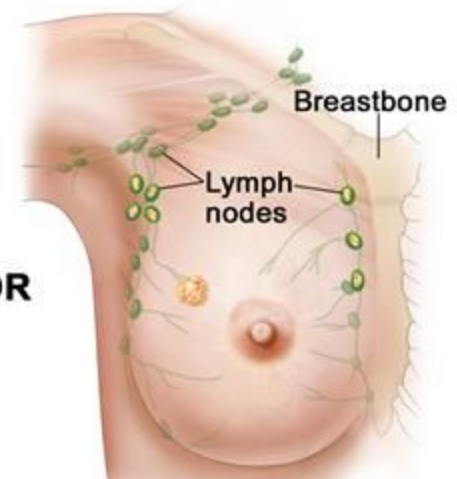
Cancer in 10 or more lymph nodes in the axilla

OR



Cancer in lymph nodes above or below the collarbone

OR



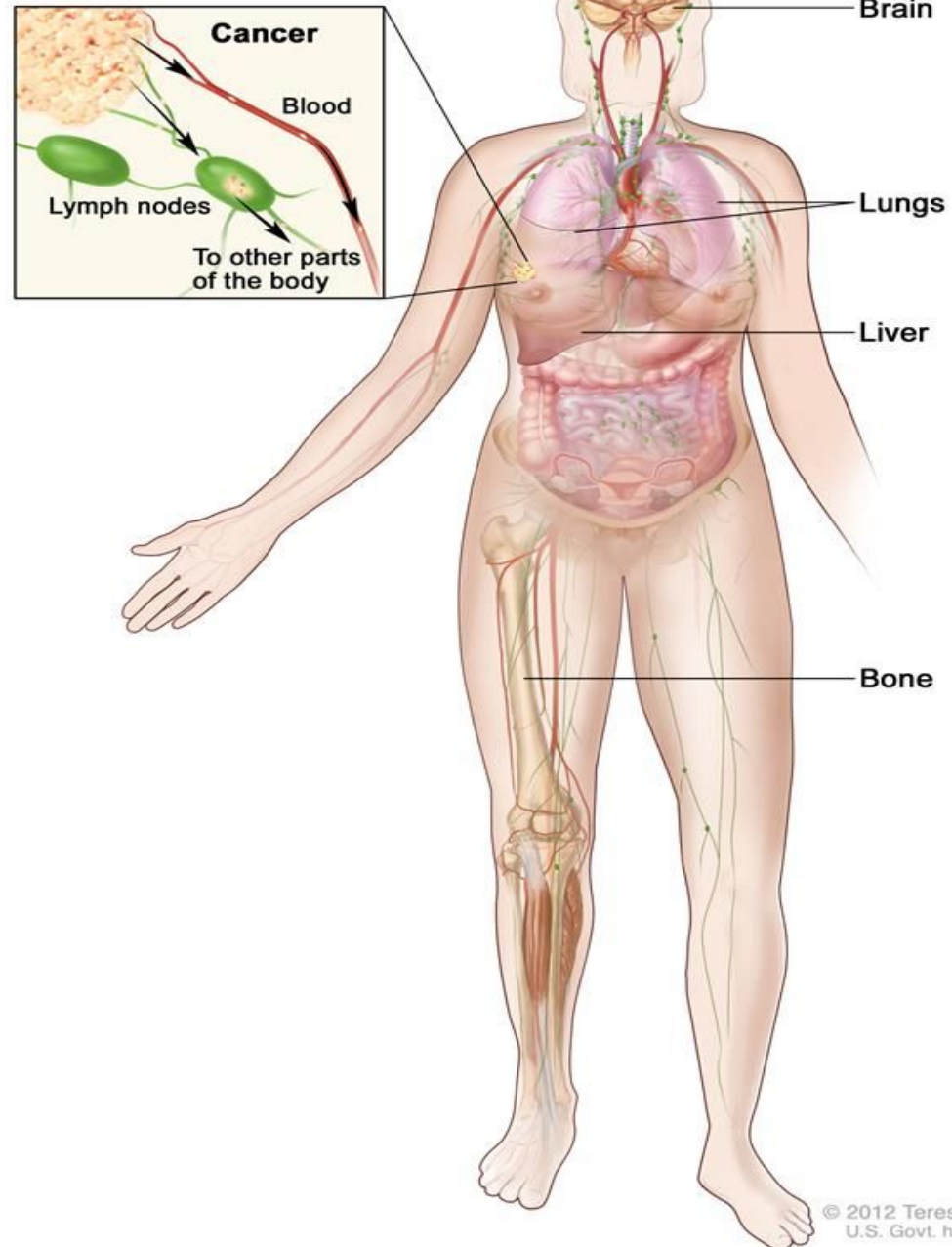
Cancer in lymph nodes in the axilla and near the breastbone

No tumor or tumor is any size

Stage IV

Stage IV Breast Cancer

Breast cancer has spread to other parts of the body:



VII. DIAGNOSIS

- ▶ Pemeriksaan Fisik > SADARI
- ▶ Mammografi
- ▶ USG
- ▶ MRI
- ▶ PETScan
- ▶ Biopsi
- ▶ Biomarker

SADARI

1. Periksa payudara Anda ketika mandi



2. Lanjutkan pemeriksaan payudara di depan cermin dengan lengan di angkat ke atas atau posisi berkacak pinggang. Periksa apakah bengkak, kemerahan atau ada perubahan di kedua payudara.



3. Tekan perlahan-lahan payudara untuk mencari benjolan, dimulai dari tengah melingkar keluar.



4. Berbaring dan ulangi pemeriksaan.

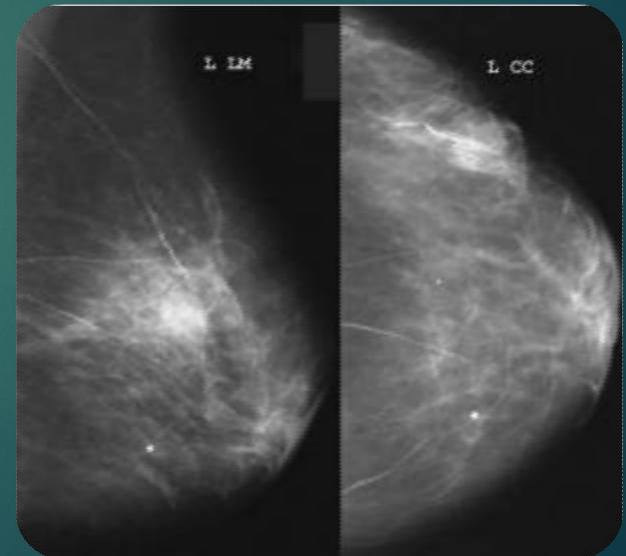
5. Lihat puting untuk melihat apakah ada cairan.



Mammografi

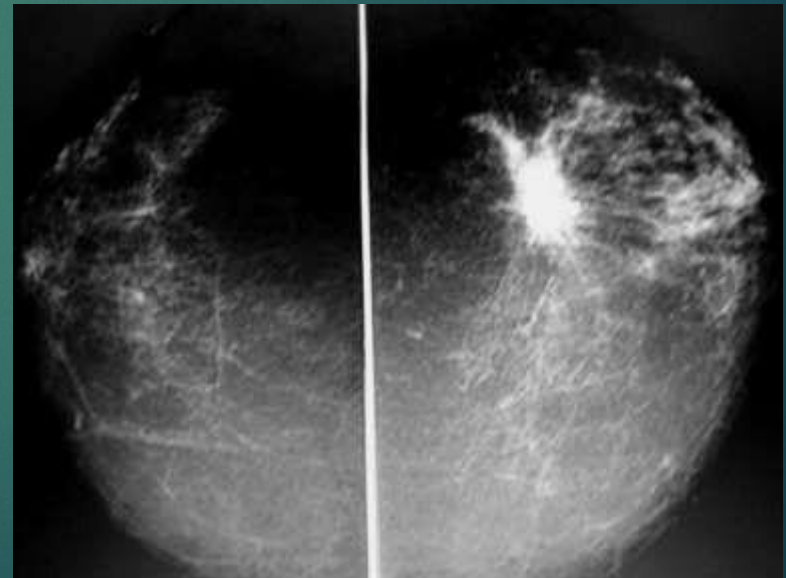


- ❑ Massa padat dengan atau tanpa gambaran seperti bintang (stellate),
- ❑ Penebalan asimetris jaringan mammae dan
- ❑ Kumpulan **mikrokalsifikasi**



● *Mammografi*

- memperlihatkan kelainan pada payudara dalam bentuk terkecil yaitu mikrokalsifikasi.
- akurasi sampai 90%.



US

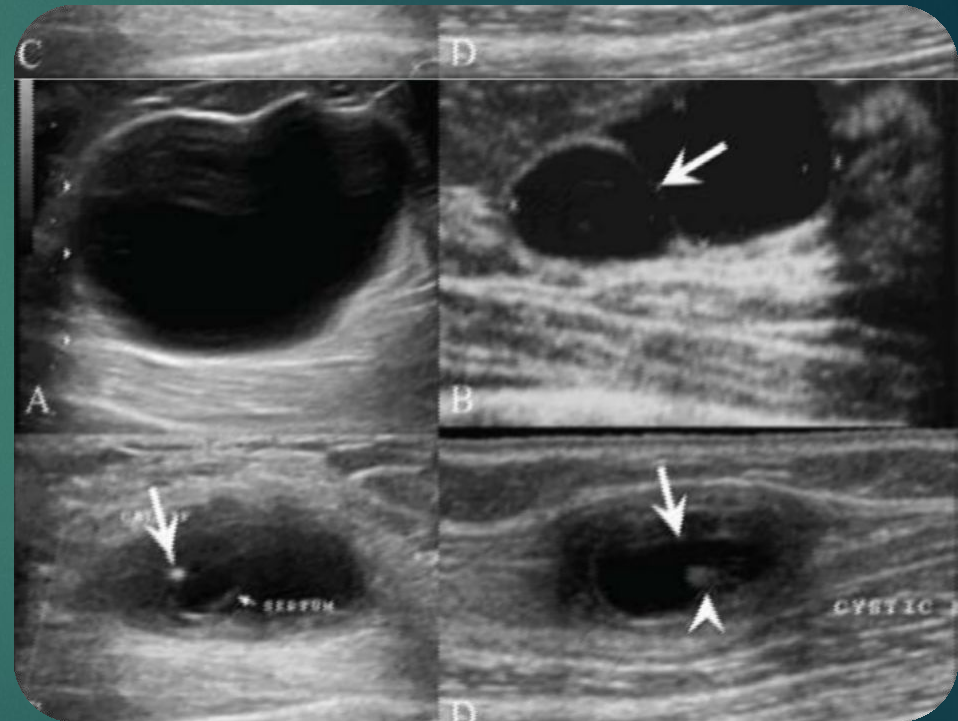
G



Kista mempunyai **gambaran** dengan batas yang tegas dengan batas yang halus dan daerah bebas echo di bagian tengahnya.

Massa payudara jinak biasanya menunjukkan kontur yang halus, berbentuk oval atau bulat, echo yang lemah di bagian sentral dengan batas yang tegas.

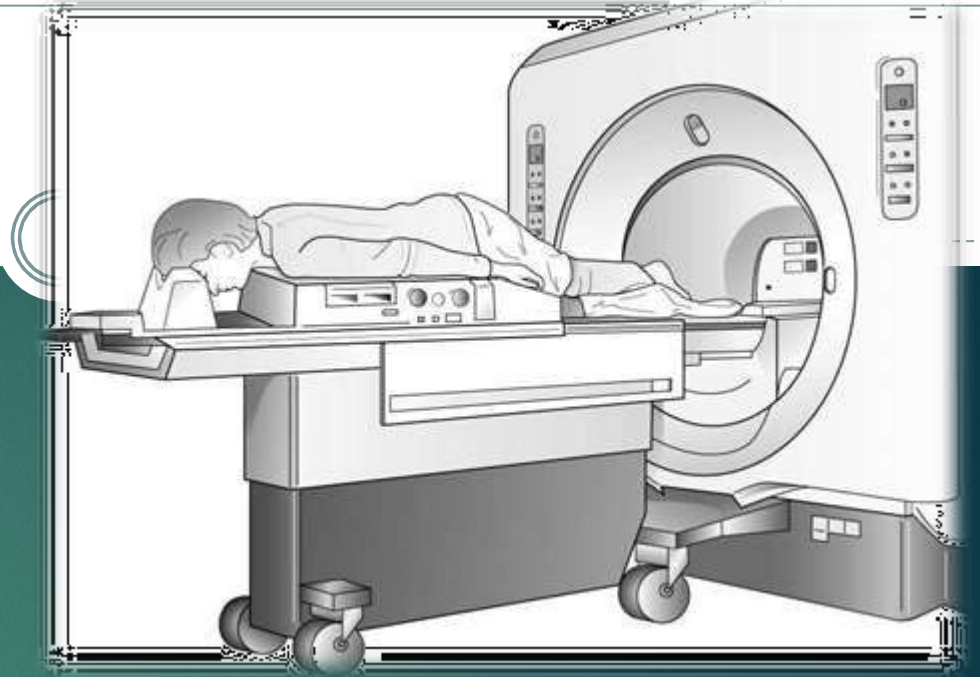
Karsinoma mammae disertai dengan dinding yang tidak beraturan, tetapi dapat juga berbatas tegas dengan peningkatan akustik.



MR

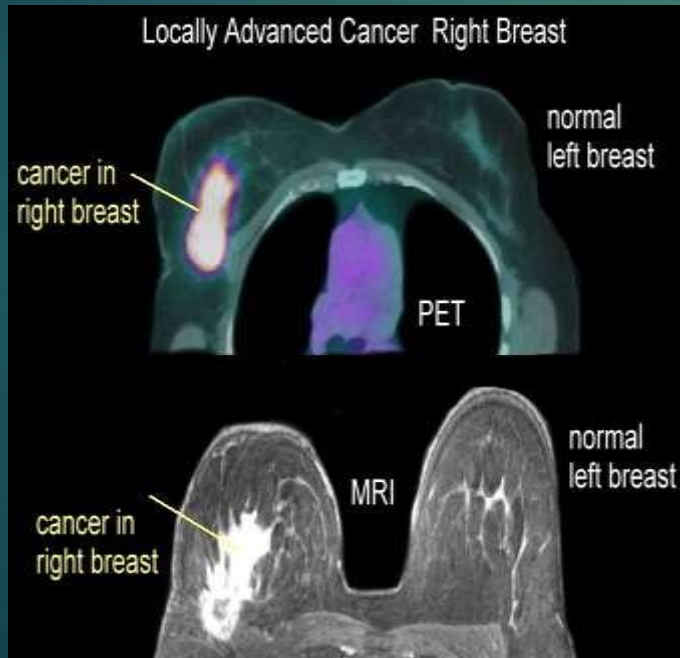


- ❑ Dapat menentukan **penyebaran dari karsinoma** terutama karsinoma lobuler atau
- ❑ Menentukan respon terhadap kemoterapi neoadjuvan.



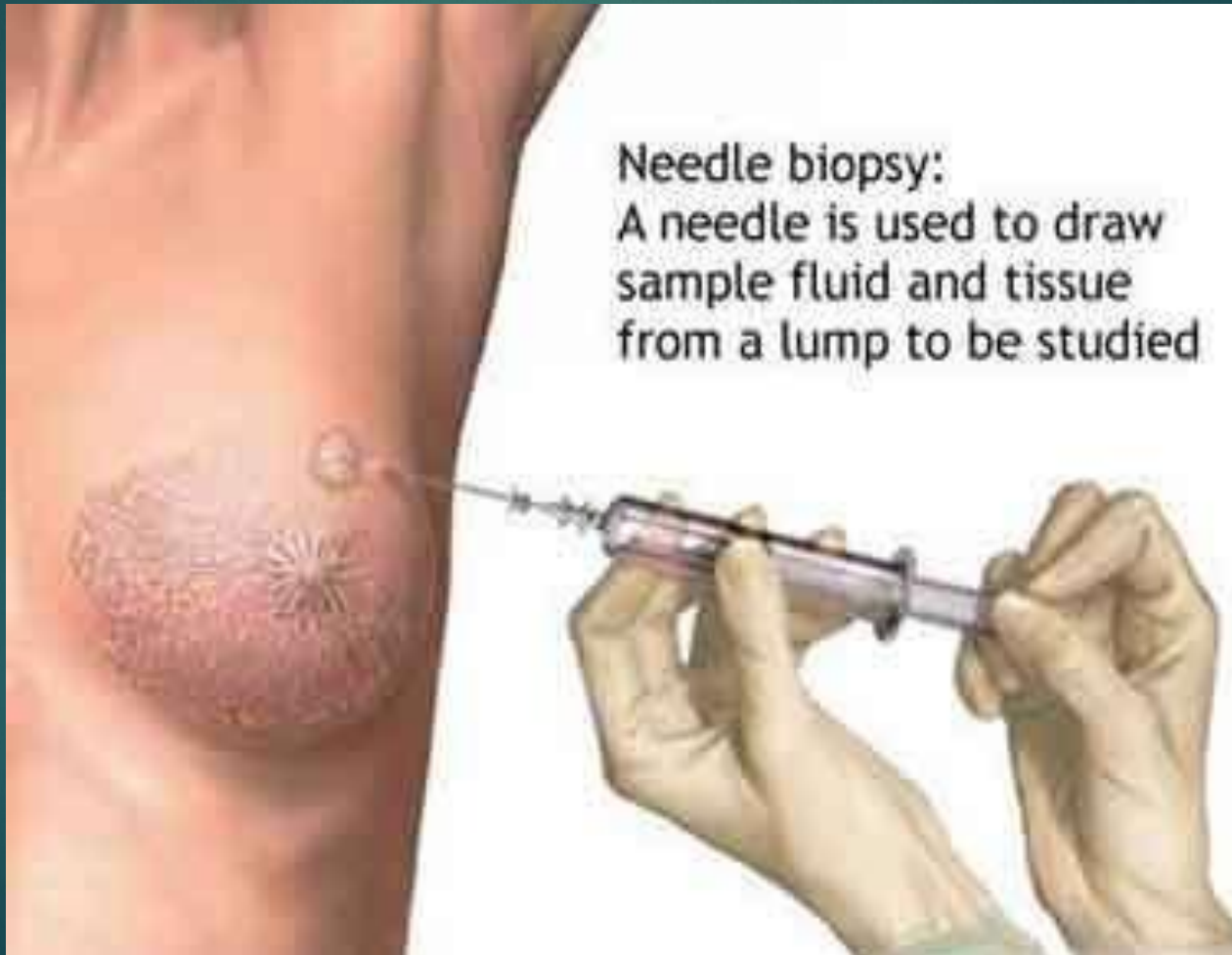
PET SCAN

- Menggambarkan **anatomi dan metabolisme sel** kanker.
- Digunakan sebagai pelengkap data dari hasil CTscan, MRI.



BIOPSI

FNAB (Fine Needle Aspiration Biopsy)



BIOMARKER



Nilai prognostik dan prediktif dari biomarker untuk karsinoma mammae antara lain :

1. Petanda proliferasi seperti *proliferating cell nuclear antigen* (PNCA), BrUdr dan Ki-67;
2. Petanda apoptosis seperti bcl-2 dan rasio bax:bcl-2;
3. Petanda angiogenesis seperti *vascular endothelial growth factor* (VEGF) dan indeks angiogenesis;
4. *Growth factors* dan *growth factor receptors* seperti *human epidermal growth receptor* (HER)-2/neu dan *epidermal growth factor receptor* (EGFr) dan p53.

VIII. PENATALAKSANAAN

- Stadium I, II, II awal (stadium operable) : sifat pengobatannya kuratif

Stadium I, II pengobatan : radikal mastektomi atau modified radikal mastektomi dengan atau tanpa radiasi dan sitostatika ajuvan

Stadium IIIA : simple mastektomi dengan radiasi dengan sitostatika ajuvan

- Stadium IIIB dan IV : sifat pengobatan : paliatif



Perbandingan Penatalaksanaan Kanker Payudara menurut European Guideline VS American Guideline VS Indonesian Guideline

European Guideline 2019 VS American Guideline 2019
VS Indonesian Guideline 2019

American Guideline 2019
(AJCC 8th Edition 2019)

Anatomic Stage Groups

19 categories

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Prognostic Stage Groups

122 categories

Pathological Prognostic Stage

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	Then the Pathological Prognostic Stage Group is...
Tis NO MO	Any	Any	Any	Any	0
T1* NO MO T0 N1mi MO T1* N1mi MO	1	Positive	Positive	Positive	IA
			Negative	Positive	IA
			Positive	Negative	IA
			Negative	Negative	IA
			Positive	Positive	IB
			Negative	Positive	IB
T2* NO MO T0 N1mi MO T1* N1mi MO	2	Positive	Positive	Positive	IIA
			Negative	Positive	IIA
			Positive	Negative	IIA
			Negative	Negative	IIA
			Positive	Positive	IIB
			Negative	Positive	IIB
T3* NO MO T0 N1mi MO T1* N1mi MO	3	Positive	Positive	Positive	IIIA
			Negative	Positive	IIIA
			Positive	Negative	IIIA
			Negative	Negative	IIIA
			Positive	Positive	IIIB
			Negative	Positive	IIIB

Pathological Prognostic Stage

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	Then the Pathological Prognostic Stage Group is...
Tis NO MO	Any	Any	Any	Any	0
T1* NO MO T0 N1mi MO T1* N1mi MO	1	Positive	Positive	Positive	IA
			Negative	Positive	IA
			Positive	Negative	IA
			Negative	Negative	IA
			Positive	Positive	IB
			Negative	Positive	IB
T2* NO MO T0 N1mi MO T1* N1mi MO	2	Positive	Positive	Positive	IIA
			Negative	Positive	IIA
			Positive	Negative	IIA
			Negative	Negative	IIA
			Positive	Positive	IIB
			Negative	Positive	IIB
T3* NO MO T0 N1mi MO T1* N1mi MO	3	Positive	Positive	Positive	IIIA
			Negative	Positive	IIIA
			Positive	Negative	IIIA
			Negative	Negative	IIIA
			Positive	Positive	IIIB
			Negative	Positive	IIIB

48. Breast

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	Then the Pathological Prognostic Stage Group is...
Tis NO MO	Any	Any	Any	Any	0
T1* NO MO T0 N1mi MO T1* N1mi MO	1	Positive	Positive	Positive	IA
			Negative	Positive	IA
			Positive	Negative	IA
			Negative	Negative	IA
			Positive	Positive	IB
			Negative	Positive	IB
T2* NO MO T0 N1mi MO T1* N1mi MO	2	Positive	Positive	Positive	IIA
			Negative	Positive	IIA
			Positive	Negative	IIA
			Negative	Negative	IIA
			Positive	Positive	IIB
			Negative	Positive	IIB
T3* NO MO T0 N1mi MO T1* N1mi MO	3	Positive	Positive	Positive	IIIA
			Negative	Positive	IIIA
			Positive	Negative	IIIA
			Negative	Negative	IIIA
			Positive	Positive	IIIB
			Negative	Positive	IIIB

*T1 includes T1m.

Pathological Prognostic Stage

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

When TNM is...	And Grade is...	And HER2 Status is...	And ER Status is...	And PR Status is...	Then the Pathological Prognostic Stage Group is...
Tis NO MO	Any	Any	Any	Any	0
T1* NO MO T0 N1mi MO T1* N1mi MO	1	Positive	Positive	Positive	IA
			Negative	Positive	IA
			Positive	Negative	IA
			Negative	Negative	IA
			Positive	Positive	IB
			Negative	Positive	IB
T2* NO MO T0 N1mi MO T1* N1mi MO	2	Positive	Positive	Positive	IIA
			Negative	Positive	IIA
			Positive	Negative	IIA
			Negative	Negative	IIA
			Positive	Positive	IIB
			Negative	Positive	IIB
T3* NO MO T0 N1mi MO T1* N1mi MO	3	Positive	Positive	Positive	IIIA
			Negative	Positive	IIIA
			Positive	Negative	IIIA
			Negative	Negative	IIIA
			Positive	Positive	IIIB
			Negative	Positive	IIIB

It will likely be challenging for medical oncologists and tumor registrars to assign stage. Phone apps are available to help assign stage.

ER/PR

- > Sekitar duapertiga dari semua kanker payudara memiliki tingkat esterogen yang signifikan dan/atau reseptor progesteron.
- Mereka dirujuk sebagai tumor reseptor esterogen positif (ER+).
- Tumor ER+ cenderung tumbuh kurang agresif dan dapat diobati dengan pengobatan menggunakan hormon.

HER2/erbB2

- HER2 adalah sebuah protein yang ditemukan pada permukaan dari sel kanker tertentu.
- Sebuah tumor dapat digambarkan sebagai HER2-positif apabila tumor tersebut memiliki lebih banyak reseptor HER2 dibanding dengan yang lain.
- Sekitar 20-25% dari semua kanker payudara memiliki tumor dengan label HER2-positif.
- Tumors HER2-positif cenderung tumbuh lebih cepat daripada jenis-jenis kanker payudara lainnya.
- Dengan mengetahui apakah sebuah kanker adalah HER2-positif dapat mempengaruhi pilihan pengobatan yang dapat diambil, karena wanita dengan tumor sejenis ini dapat diuntungkan dengan obat yang disebut trastuzumab (Herceptin®).

Biologic Types of Cancer

Features	Luminal ER positive/HER2 negative		HER2* HER2 positive	TNBC ER/HER2 negative
% of cancers	Grade 1&2: 40-55% ("luminal A")	Grade 3: 10% ("luminal B")	~20%	~15%
Common mutations	<i>PIK3CA</i> (~45%) <i>TP53</i> (~10%)	<i>PIK3CA</i> (~30%) <i>TP53</i> (~30%)	<i>PIK3CA</i> (~40%) <i>TP53</i> (~75%)	<i>PIK3CA</i> (~10%) <i>TP53</i> (~75%)
Special histologic types	Tubular, lobular, mucinous, papillary	Lobular	Some apocrine, some micropapillary	Medullary features, metaplastic**
Patients likely to have these cancers	Older women, men	<i>BRCA2</i> mutation carriers	<i>TP53</i> mutation carriers	<i>BRCA1</i> mutation carriers
Complete response to chemotherapy	<10%	10%	ER positive (~30%) ER negative (~60%)	~45%
Usual treatment	Endocrine therapy	Chemotherapy Endocrine therapy	Chemotherapy HER2 targeted therapy Endocrine if ER positive	Chemotherapy
Time to recurrence	Low rate over many years	Early peak, late recurrence possible	Early and late peaks	Early peak, late recurrences rare
Metastatic pattern	Bone (~50%) more common than viscera or brain		Viscera and brain > bone	Viscera and brain > bone

* In some classification systems, ER positive/HER2 positive cancers are called "luminal B" cancers.

** Some rare types of TNBC have a favorable prognosis – adenoid cystic carcinoma, secretory carcinoma, low grade adenosquamous carcinoma.



European Guideline 2019 (ESMO Guideline 2019)

Anatomic Stage Group

Stage 0. Non-invasive tumour confined to the breast (TisN0M0)

Stage I. Tumour is small and confined to breast tissue or with evidence of cancer in lymph nodes close to the breast

IA	The tumour is no bigger than 20 mm in diameter and is confined to the breast (T1N0M0)
IB	There is no evidence of a primary tumour (T0) or the tumour is no bigger than 20 mm in diameter (T1), but micrometastases (no bigger than 2 mm) are present in the ipsilateral level I/II axillary lymph node(s); lymph nodes are movable (N1mi); no distant metastases are present (M0)

Stage II. Tumour is in the breast or in the nearby lymph nodes, or both

IIA	- There is no evidence of a primary tumour (T0) or the tumour is no bigger than 20 mm in diameter (T1); metastases are present in the ipsilateral level I/II axillary lymph node(s) and lymph nodes are movable (N1); no distant metastases are present (M0) - The tumour is larger than 20 mm but no bigger than 50 mm in diameter (T2) and is confined to the breast (N0); no distant metastases are present (M0)
IIB	- The tumour is larger than 20 mm but no bigger than 50 mm in diameter (T2); metastases are present in the ipsilateral level I/II axillary lymph node(s) and lymph nodes are movable (N1); no distant metastases are present (M0) - The tumour is larger than 50 mm in diameter (T3) and is confined to the breast (N0); no distant metastases are present (M0)

Anatomic Stage Group

Stage III. Tumour has spread from the breast to lymph nodes close to the breast, to the skin of the breast or to the chest wall

IIIA

- There is no evidence of a primary **tumour** (T0), the **tumour** is no bigger than 20 mm in diameter (T1), the **tumour** is larger than 20 mm but no bigger than 50 mm in diameter (T2), the **tumour** is larger than 50 mm in diameter (T3); **metastases** are present in the **ipsilateral** level I/II **axillary lymph node(s)** and **lymph nodes** are fixed or matted (N2); no distant **metastases** are present (M0)
- The **tumour** is larger than 50 mm in diameter (T3); **metastases** are present in the **ipsilateral** level I/II **axillary lymph node(s)** and **lymph nodes** are movable (N1); no distant **metastases** are present (M0)

IIIB

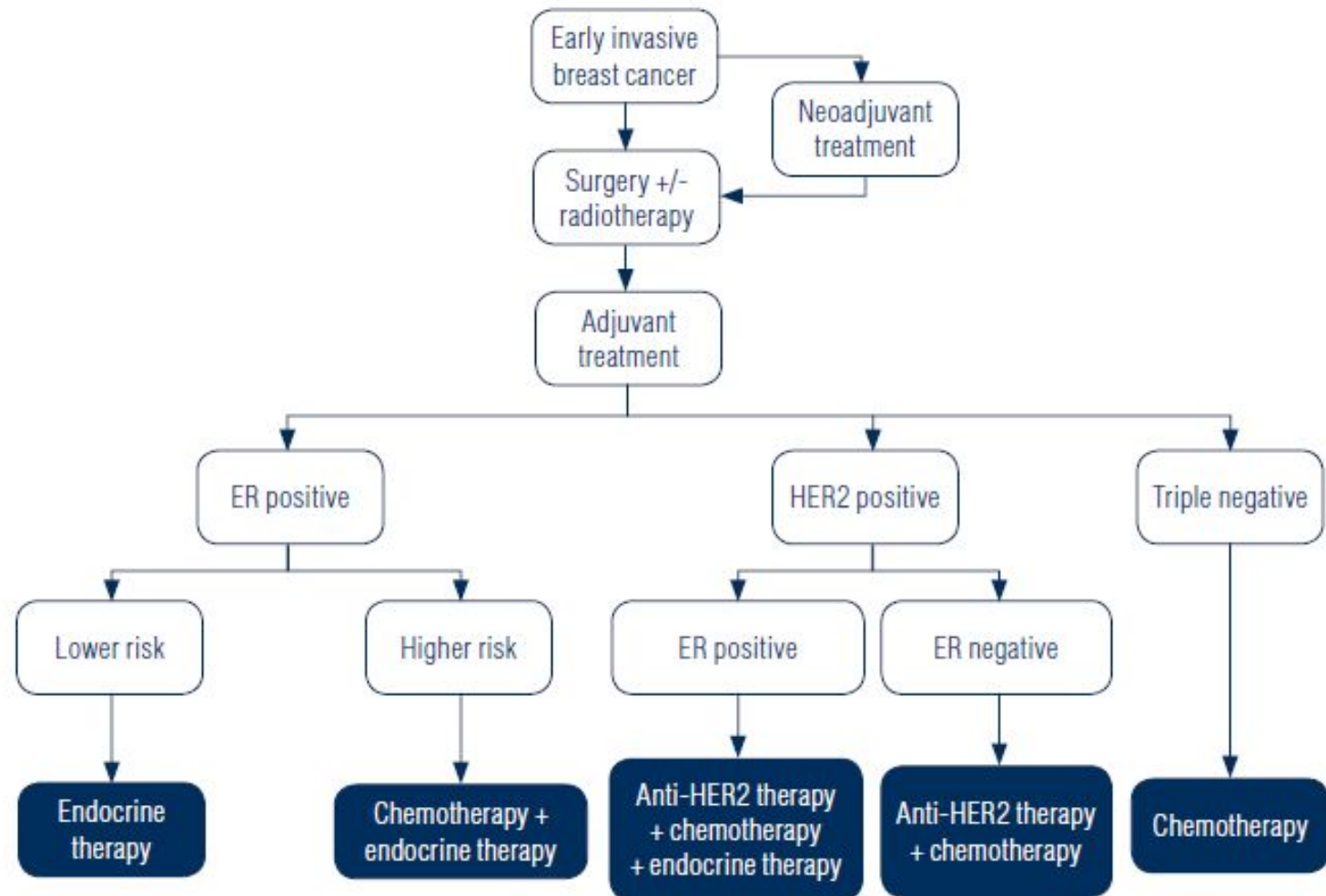
- The **tumour** (of any size) has extended to the chest wall and/or skin (T4); **lymph nodes** are not involved (N0) or **metastases** are present in the **ipsilateral** level I/II **axillary lymph node(s)** and **lymph nodes** are movable (N1) or **lymph nodes** are fixed or matted (N2); no distant **metastases** are present (M0)

IIIC

- **Tumour** of any stage (any T); **metastases** are present in the **ipsilateral** level III **axillary lymph node(s)**, in **ipsilateral** internal mammary **lymph node(s)** with clinically evident level I/II **axillary lymph node metastases**, or in **ipsilateral** supraclavicular **lymph node(s)** (N2 or N3); no distant **metastases** are present (M0)

Stage IV. The tumour has spread to other areas of the body (any T any N M1)

Biologic Types of Cancer & The Treatments



Flowchart showing **systemic** treatment approaches in early **invasive** breast cancer.

1. Operatif

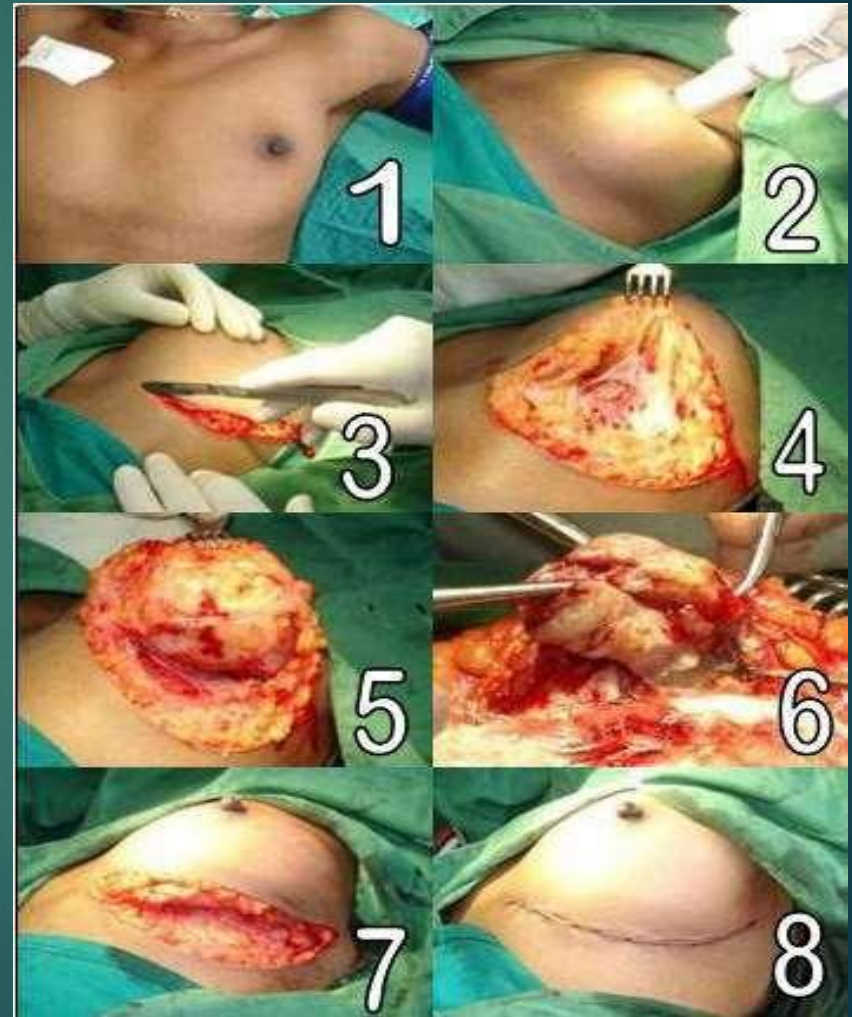
- ▶ Jenis operasi yang dapat digunakan untuk terapi kanker payudara adalah:
 - *BCS (Breast Conserving Surgery)*
 - *Lumpektomi*
 - *Mastektomi*

BCS (Breast Conserving Surgery)

- ▶ Prosedur operasi jika penderita masih ingin mempertahankan payudaranya.
- ▶ Opsi apabila :
 - tumor tidak multipel,
 - tidak terletak di sentral,
 - mamografi tidak memperlihatkan adanya tanda keganasan lain yang difus : penderita belum pernah mendapatkan terapi radiasi di dada, dapat kontrol teratur, dan tersedia sarana radio terapi yang memadai.

Lumpektomi

- Operasi ini hanya menghilangkan benjolan payudara dan beberapa jaringan normal di sekitarnya.
- Pengobatan radiasi biasanya diberikan setelah operasi jenis ini.



MASTEKTOMI



Mastektomi:

Mengangkat semua jaringan payudara, jaringan terdekat lainnya juga ikut diangkat



Radioterapi adalah pengobatan dengan sinar berenergi tinggi (seperti sinar-X) untuk membunuh sel-sel kanker ataupun menyusutkan ukuran tumornya

2. Radioterapi

3. Kemoterapi

Penggunaan obat pembunuh sel kanker. Obat ini bisa dimasukkan melalui infus vena, suntikan, dalam bentuk pil atau cairan.

1. Kemoterapi ajuvan
2. Kemoterapi neoajuvan
3. Kemoterapi untuk kanker payudara stadium lanjut



- Kemoterapi dalam penatalaksanaan kanker payudara haruslah kombinasi. Adapun kombinasi yang sering dipakai antara lain:
 - o CMF (Cyclophosphamide, Metotreksat, 5 Fluoro Uracil)
 - o CEF (Cyclophosphamide, Epirubicin, 5 Fluoro Uracil)
 - o CAF (Cyclophosphamide, Adriamycin , 5 Fluoro Uracil)
 - o Taxane + Doxorubicin
 - o Capecetabin

4. Terapi Hormon

Obat-obatan yang digunakan dalam terapi hormon:

1. Tamoxifen ® dan toremifene (Fareston ®)
2. Fulvestrant
3. Aromatase inhibitor

Terapi hormonal dapat terdiri dari :

- Ablative : bilateral ovariectomy
- Additive: Tamoxifen
- Optional: aromatase inhibitor, GnRH



Daftar Pustaka

1. Suzanna E, Sirait T, Rahayu PS, Shalmont G, Anwar E, Andalusia R et al. Registrasi kanker berbasis rumah sakit di rumah sakit kanker "Dharmais"-pusat kanker nasional, 1993-2007. Indonesian Journal of Cancer. 2012;6: 1-12.
2. Screening in Chronic Diseases
3. Baines CJ, *The Canadian National Breast Screening Study. Why? What next? And so what?* Cancer. 1995 Nov 15;76(10 Suppl):2107-12.
4. Schmidt S, et al. Breast cancer risk assessment: use of complete pedigree information and the effect of misspecified ages at diagnosis of affected relatives. Springer-Verlag 1998:102:348-356
5. Haryono, Samuel J. 2012. *Kanker payudara familial: penelusuran gena predisposisi terwaris dan perhitungan risiko*. Disertasi Fakultas Kedokteran Universitas Gadjah Mada Yogyakarta, 2012
6. Monica Morrow, Physical Examination of the Breast. In: Haris JR, Lippman ME, Morrow M, Osborne CK. Disease of the Breast. Fifth edition. Philadelphia: Lippincott Williams & Wilkins. 2014. 25-28.
7. Senkus E, Kyriakides S, Liorca P, Portmans P, Thompson A, Zackrisson S, Cordoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and Follow up. Annals of Oncology. 2013. 0. 1-17.
8. Kwon DS, Kelly CM, Ching CD. Invasive Breast Cancer. In: Feig BW, Ching CD. The MD Anderson Surgical Oncology Handbook. Lippincott William and Wilkins Fifth edition, 2012. Page 36
9. NCCN Clinical Practice Guideline in Oncology Breast Cancer version 1.2016. Patients Presenting with Breast Symptoms. NCCN, NCCN, ABC, RCP, Breast Group, Association of Breast Surgery, Breakthrough Breast Cancer, RCN. November 2010.
11. Online available from: www.nationalbreastcancer.org/clinical-breast-exam.
12. Kim, Theodore, Armando E. Giuliano, and Gary H. Lyman. Lymphatic Mapping and Sentinel Lymph Node Biopsy in Early-Stage Breast Carcinoma: A Metaanalysis. American Cancer Society, 2005. Publish online 2 December 2005 in Willer InterScience.
13. Simmons, Rache M, Sharon M. Rosenbaum Smith, and Michael P. Osborne. Methylene Blue Dye as an Alternative to Isosulfan Blue Dye for Sentinel Node Localization. 2001. Blackwell Science Inc. The Breast Journal, Volume 7, Number 3, 2001 p.181-183.
14. Brahma, Bayu, Samuel J. Haryono, Ramadhan, Lenny Sari. Methylene Blue Dye as A Single Agent in Breast Cancer Sentinel Lymph Node Biopsy: Initial Study of Cancer. Presented in 19th Asian Congress of Surgery & 1st SingHealth Surgical Congress. 2013
15. Subcategory of Breast Imaging, Breast Imaging. "Lesions Implicated with Microcalcification: A Radiology-Pathology Correlation Study". The Breast Journal 16 (1): 28–31. doi:10.1111/j.1524-4741.2009.00863.x. PMID 19929890. edit
16. American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI- RADS Atlas). Reston, Va: © American College of Radiology; 2003
17. Pennant M1, Takwoingi Y, Pennant L, et al A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for breast cancer health Technology Assess. 2010 Oct;14(50):1-103. doi: 10.3310/hta14500.
18. Goldhirsch1, E. P. Winer2, A. S. Coates3, R. D. Gelber4, M. Piccart-Gebhart5, B. Thürlimann6 and H.-J. Senn7 Panel members†Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 Ann Oncol (2013) doi: 10.1093/annonc/mdt303 First published online: August 4, 2013
19. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010 Jun;17(6):1471-4. doi: 10.1245/s10434-010-0985-4.
20. Veronesi Umberto, C Natale, L Mariani, et.al. Twenty Year Follow Up of a Randomized Study Comparing Breast-Conserving Surgery with Radical Mastectomy For Early Breast Cancer. MASSachusetts Medical Society, October 17, 2002 :. 347.
21. Fisher B, Stewart A, Bryant J, et al. Twenty Year Follow-Up a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy Plus Irradiation For The Treatment of Invasive Breast Cancer. New England Journal of Medicine, Vol 347, No.16. October 17, 2002.
22. Litiere S, Werustky G, Fentiman Ian, et.al. Breast Conserving Therapy versus Mastectomy for Stage I-II Breast Cancer: 20 Year Follow-Up of the EORTC 10801 phase 3 Randomised Trial. Lancet Oncol 2012 p. 412-419.
23. Fisher Bernard, Role of Science in the treatment of Breast Cancer When Tumor multicentricity is Present, J Natl Cancer Inst 2011; 103: 1292-1298.
24. Citron, L. Marc, Donald A. Berry, et.al. Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. Journal Clinical Oncology 21:1431-1439. 2003.
25. Dang, Chau, Monica Fornier et.al. The Safety of Dose-Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel With Transtuzumab in Her2/neu Overexpressed/Amplified Breast Cancer. Journal of Clinical Oncology, Vol. 26, No.8, March 10, 2008.
26. Jones, Stephen, Frankie Ann Holmes, Joyce O'Shaughnessy, et.al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-up

- Up of US Oncology. Research Trial 9735. Journal of Clinical Oncology, Vol. 27. No.8, March 10, 2009.
27. Citron, L. Marc, Donald A. Berry, et.al. Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/ Cancer and Leukemia Group B Trial 9741. Journal Clinical Oncology 21:1431-1439. 2003.
 28. Dang, Chau, Monica Fornier et.al. The Safety of Dose-Dense Doxorubicin and Cyclophosphamide Followed by Paclitaxel With Trastuzumab in Her2/neu Overexpressed/Amplified Breast Cancer. Journal of Clinical Oncology, Vol. 26, No.8, March 10, 2008.
 29. Jones, Stephen, Frankie Ann Holmes, Joyce O'Shaughnessy, et.al. Paclitaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology. Research Trial 9735. Journal of Clinical Oncology, Vol. 27. No.8, March 10, 2009.
 30. Bedognetti D, Sertoli RM, Pronzato P et al, Concurrent vs Sequential Adjuvant Chemotherapy and Hormone Therapy in Breast cancer :A Multicentre Randomized Phase III Trial. JNCI, Vol 103, Issue 20, October 2011, 1529-1539.
 31. Burstein, Harold J. Ann Alexis Prestrud, et.al. American Society of Clinical Oncology Clinical Practice Guideline: Update on Adjuvant Endocrine Therapy for Women with Hormone Receptor Positive Breast Cancer. Journal of Clinical Oncology, Vol. 28 No.23 August 10, 2010.
 32. Love, Richard R., Nguyen Van Dinh, Tran Tu Quy, et.al. Survival After Adjuvant Oophorectomy and Tamoxifen in Operable Breast Cancer In Premenopausal Woman. Journal of Clinical Oncology, Vol. 26. No.2 January 10, 2008.
 33. Fang, Lei, Zeinab Barekari, Bei Zhang, Zhiyong Liu, Xiaoyan Zhong. Targeted Therapy in Breast Cancer: What's New? The European Journal of Medical Sciences. Published June 27, 2011.
 34. Slamon, Dennis, Wolfgang Eiermann, Nicholas Robert, et.al. Adjuvant Trastuzumab in Her2-Positive Breast Cancer . The New England Journal of Medicine. Vol. 365. No.14, October 6, 2011.
 35. Fang, Lei, Zeinab Barekari, Bei Zhang, Zhiyong Liu, Xiaoyan Zhong. Targeted Therapy in Breast Cancer: What's New? The European Journal of Medical Sciences. Published June 27, 2011.
 36. Romera, J. Lao, T.J. Puertolas Hernandez et.al. Update On Adjuvant Hormonal Treatment of Early Breast Cancer. Springer Health Care, January 27, 2011. Vol. 28 (Suppl.6) p.1-18.
 37. Dahabreh, Issa J., Helen Linardou, Fotios Siannis, George Fountzilas, Samuel Murray. Trastuzumab in the Adjuvant treatment of Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The Oncologist 2008, Vol.13: 620-630.
 38. Gennari A, Sormani MP, Prozanto P et al, HER2 Status and Efficacy of Adjuvant Anthracyclin in Early Breast Cancer : A pooled Analysis of Randomized Trials. J Natl Cancer Inst 2008;100:144-150.
 39. Early breast cancer trialist'collaborative group. Effects of radiotherapy after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10.801 women in 17 randomised trials. Lancet Oncol 2011; 378: 1707-1716.
 40. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER et al. Twenty-year follow up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Eng J Med 2002; 347: 1233-1241.
 41. Litiere S, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, Limbergen EV et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 2012; 13(4): 412-419.
 42. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola AB et al. ESTRO consensus guideline on target volume definition for elective radiation therapy for early stage breast cancer. Radiother Oncol 2015; 114: 3-10.
 43. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutger E et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(s5): 8-30.
 44. Verma V, Vicini F, Tendulkar RD, Khan AJ, Wobb J, Bennett SE et al. The role of internal mammary node radiation as part of modern breast cancer radiotherapy: a systematic review. Int J Radiat Oncol Biol Phys 2016: article in press.
 45. Early breast cancer trialist'collaborative group. Effects of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet Oncol 2014; 383: 2127-2135.
 46. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola AB et al. ESTRO consensus guideline on target volume definition for elective radiation therapy for early stage breast cancer. Radiother Oncol 2015; 114: 3-10.
 47. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutger E et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(s5): 8-30.
 48. Verma V, Vicini F, Tendulkar RD, Khan AJ, Wobb J, Bennett SE et al. The role of internal mammary node radiation as part of modern breast cancer radiotherapy: a systematic review. Int J Radiat Oncol Biol Phys 2016: article in press.
 49. Cox BW, Spratt DE, Lovelock M et al. International spine radiosurgery consortium consensus guideline for target volume definition in spinal stereotactic radiosurgery. Int J Rad Oncol Biol Phys 2012; 83: 597-605.
 50. Lutz S, Berk L, Chang E et al. Palliative radiotherapy for bone metastases: an ASTRO evidence based guideline. Int J Rad Oncol Biol Phys 2011; 79(4): 965-976.

51. Ryu S, Pugh SL, Gertzten PC. RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1-3) spine metastases: phase 2 results. *Prac Radiat Oncol* 2014; 4: 76-81.
52. Sande TA, Ruenes R, Lund Ja et al. Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomized multicenter trial. *Radiother Oncol* 2009; 91: 261-266.
53. August DA, Huhmann MB, American Society of Parenteral and Enteral Nutrition (ASPEN) Board of Directors. ASPEN clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *J Parent Ent Nutr* 2009; 33(5): 472-500.
54. Argiles JM. Cancer-associated malnutrition. *Eur J Oncol Nurs* 2005;9(suppl 2):S39-S50.
55. Donohue CL, Ryan AM, Reynolds JV. Cancer cachexia: Mechanisms and clinical implications. *Gastroenterol Res Pract* 2011; doi:10.155/2011/601434.
56. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossom A, Sleek S, et al. Diagnostic criteria for malnutrition- An ESPEN consensus statement. *Clin Nutr* 2015;34:335-40
57. Cancer Cachexia Hub. About cancer cachexia [Internet]. 2014 [accessed 2014 Feb 14]. Available from: <http://www.cancercachexia.com/about-cancer-cachexia>
58. Arends J. ESPEN Guidelines: nutrition support in Cancer. 36th ESPEN Congress 2014
59. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991;325(8):525-32.
60. Wang C, Li ZH, Wu G, et al. Perioperative artificial nutrition in World J Gastroenterol. 2006;12(15):2441-4.
61. Ruiz GV, Lopez-Briz E, Corbonell Sanchis R, Gonzavez Paraes JL, Bort-Marti S. Megesterol acetate for treatment of cancer-cachexia syndrome (review). *The Cochrane Library* 2013, issue 3
62. Arends J. Nutritional Support in Cancer: Pharmacologic Therapy. ESPEN Long Life Learning Programme. Available from: http://nutrition.com/mod_III/TOPI26/m_264.pdf
63. Tazi E, Errihani H. Treatment of cachexia in oncology. *Indian J Palliat Care* 2010;16:129-37
64. Argiles JM, Olivan M, Busquets S, Lopez-Soriano FJ. Optimal management of cancer anorexia-cachexia syndrome. *Cancer Manag Res* 2010;2:27-38
65. Radbruch L, Elsner F, Trottenberg P, Strasser F, Baracos V, Fearon K. Clinical practice guideline on cancer cachexia in advanced cancer patients with a focus on refractory cachexia. Aachen: Departement of Palliative Medicinen/European Palliative Care Research Collaborative: 2010.
66. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition : Non Surgical Oncology. *Clin Nutr* 2006;25:245-59.
67. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit of colorectal cancer patients: long-term follow-up of randomized controlled trial of nutritional therapy. *Am J Clin Nutr* 2012;96: 1346-53.
68. Choudry HA, Pan M, Karinch AM, Souba WW. Branched-chain amino acid-enriched nutritional support in surgical and cancer patients. *J Nutr* 2006;136: 314S-318S.
69. Cangiano C, Laviano A, Meguid MM, Mulieri M, Conversano L, Preziosa I, et al. Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *J Natl Cancer Inst* 1996;88:550-2.
70. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immuno-metabolic host response and outcome after colorectal resection for cancer. *Surgery*. 2002;132(5):805-814.
71. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. *Surgery*. 1992;112(1):56-67.
72. de Luis DA, Izaola O, Cuellar L, Terroba MC, Aller R. Randomized clinical trial with an enteral arginine-enhanced formula in early postsurgical head and neck cancer patients. *Eur J Clin Nutr*. 2004;58(11):1505-1508.
73. van Bokhorst-de van der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. *Am J Clin Nutr*. 2001;73(2):323-332.
74. Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. *J Nutr*. 2000;130:396S-402S.
75. NCCN Clinical Practice Guideline in Oncology. Breast Cancer. Version 1.2016
76. Ligibe JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA., Chlebowski RT, et al. American Society of Clinical Oncology Position Statement on Obesity and Cancer. *J Clin Oncol* 2014;32:3568-3574
77. August DA, Huhmann MB, American Society of Parenteral and Enteral Nutrition (ASPEN) Board of Directors. ASPEN clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *J Parent Ent Nutr* 2009; 33(5): 472-500. Arends J. ESPEN Guidelines: nutrition support in Cancer. 36th ESPEN Congress 2014
78. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossom A, Sleek S, et al. Diagnostic criteria for malnutrition-An ESPEN consensus statement. *Clin Nutr* 2015;34:335-40
79. Evan WJ, Morley JE, Argiles J, Bales C, Baracos V, et al. Cachexia: A new definition. *Clin Nutr* 2008;27:793-799.
80. Fearon K, Strasser F, Anker S, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489-95

81. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition : Non Surgical Oncology. *Clin Nutr* 2006;25:245–59.
82. Cohen DA, Sucher KP. Neoplastic disease. In: Nelms M, Sucher KP, Lacey K, Roth SL, eds. Nutrition therapy and pathophysiology. 12 ed. Belmont: Wadsworth; 2011:702-74.
83. Grant BL, Hamilton KK. Medical nutrition therapy for cancer prevention, treatment, and recovery. In: Mahan LK, Escott-Stump S, Raymond JL, eds. Krause's food & nutrition therapy. 13 ed. Missouri: Saunders Elsevier; 2013:832-56
84. Cangiano C, Laviano A, Meguid MM, Mulieri M, Conversano L, Preziosa I, et al. Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *J Natl Cancer Inst*.1996;88:550-2.
85. T. Le Bricon. Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *Clin Nutr Edinb Scott* 1996;15:337.
86. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit of colorectal cancer patients: long-term follow-up of randomized controlled trial of nutritional therapy. *Am J Clin Nutr* 2012;96: 1346–53.
87. Ruiz GV, Lopez-Briz E, Corbonell Sanchis R, Gonzavez Paraes JL, Bort-Marti S. Megesterol acetate for treatment of cancer-cachexia syndrome (review). *The Cochrane Library* 2013, issue 3
88. Arends J. Nutritional Support in Cancer: Pharmacologic Therapy. ESPEN Long Life Learning Programme. Available from: Illnutrition.com/mod_III/TOPI26/m_264.pdf
89. Tazi E, Errihani H. Treatment of cachexia in oncology. *Indian J Palliant Care* 2010;16:129-37
90. Argiles JM, Olivan M, Busquets S, Lopez-Soriano FJ. Optimal management of cancer anorexia-cachexia syndrome. *Cancer Manag Res* 2010;2:27-38
91. Radbruch L, Elsner F, Trottenberg P, Strasser F, Baracos V, Fearon K. Clinical practice guideline on cancer cachexia in advanced cancer patients with a focus on refractory cachexia. Aachen: Departement of Palliative Medicinen/European Paliative Care Research Collaborative: 2010.
92. Wiser W, Berger A. Practical management of chemotherapy-induced nausea and vomiting. *Oncology* 2005;19:1-14; Ettinger DS, Kloth DD, Noonan K, et al. NCCN Clinical Practice Guideline in Oncology: Antiemetisis. Version 2:2006
93. Tulaar ABM, Wahyuni L.K, Nuhonni S.A., et al. Pedoman Pelayanan Kedokteran Fisik dan Rehabilitasi pada Disabilitas. Jakarta: Perdosri; 2015. p.13-7; 339-79.
94. Wahyuni LK, Tulaar ABM. Pedoman Standar Pengelolaan Disabilitas Berdasarkan Kewenangan Pemberi Pelayanan Kesehatan. Jakarta: Perdosri; 2014. p. 95-6.
95. Nuhonni, S.A, Indriani, et.al. Panduan Pelayanan Klinis Kedokteran Fisik dan Rehabilitasi: Disabilitas Pada Kanker. Jakarta: Perdosri; 2014. P. 9-33
96. Campbell KL, Pusic AL, Zucker DS, McNeely ML, Binkley JM, Cheville AL, et al. A prospective Model of Care for Breast Cancer Rehabilitation. *Function. Cancer*. 2012;118:2300-11.
97. Vargo MM, Smith RG, Stubblefield MD. Rehabilitation of the cancer patient. In: DeVita, Hellman, and Rosenberg's Cancer : principles & practice of oncology. 8th Ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 2879-81.
98. Black JF. Cancer and Rehabilitation. 2013 March 19. [cited 2014 Sept 10] Available from: <http://emedicine.medscape.com/article/320261-overview>
99. Vargo MM, Riuta JC, Franklin DJ. Rehabilitation for patients with cancer diagnosis. In: Frontera W, DeLisa JA, Gans BM, Walsh NE, Robinson LR, et al, editors. Delisa's Physical Medicine and Rehabilitation, Principal & Practice, 5th Edition. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 1167
100. Keyorkian CG. History of cancer rehabilitation. In: Stubblefield DM, O'dell MW. Cancer Rehabilitation, Principles and Practice. New York: Demos Medical Publishing; 2009. p. 8.
101. Stubblefield DM, O'dell M, Tuohy MS. Savodnik A. Postsurgical rehabilitation in cancer. In: Stubblefield DM, O'dell MW. Cancer Rehabilitation, Principles and Practice. New York: Demos Medical Publishing; 2009. p. 813-23.
102. The British Pain Society. Cancer pain management. London: The British Pain Society; 2010. p. 7-8.
103. Scottish Intercollegiate Guideline Network. Control of pain in adult with cancer. A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guideline Network; 2008. p. 14.
104. Silver JK. Nonpharmacologic pain management in the patient with cancer. In: Stubblefield DM, O'dell MW. Cancer Rehabilitation, Principles and Practice. New York: Demos Medical Publishing; 2009. p. 479-83.
105. McNeely ML, Campbell K, Ospina M, Rowe BH, Dabbs K, Klassen TP, et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment (review). *The Cochrane Collaboration*. JohnWiley & Sons, Ltd; 2010. p. 6-16.
106. Lacombe MT, Sanchez MJ, Goni AZ, Merino DP, Tellez EC, Mogollon EM. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomized, single blinded, clinical trial. *BMJ*. 2010;340:b5396.
107. Box RC, Reul-Hirce HM, Bullock-Saxton JE, Furnival CM. Shoulder movement after breast cancer surgery : result of a randomised controlled study of postoperative physiotherapy. *Breast Cancer Res Treat*. 2002;75:35-50.
108. Scaffidi M, Vulpiani MC, Vetrano M, Conforti F, Marchetti MR, Bonifacino A, et al. Early rehabilitation reduces the onset of complications in the upper limb following breast cancer surgery. *Eur J Phys Rehabil Med*. 2012;48:601-11.49

109. Shamley DR, Barker K, Simonite V, Beardshaw A. Delayed versus immediate exercise following surgery for breast cancer : a systematic review. *Breast Cancer Res Treat.* 2005;90:263-71.
110. Harris SR, Schmitz KH, Campbell KL, McNeely ML. Clinical practice guidelines for breast cancer rehabilitation. *Cancer.* 2012;118:2312-24.
111. National Cancer Institute. Lymphedema. 2014 March 18. [cited 2014 July 11]. Available from: <http://www.cancer.gov/cancertopics/pdq/supportivecare/lymphedema/healthprofessional/page2>.
112. Lymphoedema Framework. Best practice for the management of lymphoedema. International consensus. London: Medical Education Partnership; 2006. p. 23.
113. Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role for adjunctive intermittent pneumatic compression. *Cancer.* 2002;95(11):2260-7.
114. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med.* 2009;361(7):664-73.
115. Schmitz KH, Troxel AB, Grant LL, Cheville A, Bryan CJ, Gross CR, et al. Physical activity and lymphedema (The PAL Trial): Assessing the safety of progressive strength training in breast cancer survivors. *Contemp Clinical Trials.* 2009;30(3):233-45.
116. Wahyuni LK, Tulaar ABM. Cedera medula spinalis (Spinal cord injury - SCI). Dalam: *Panduan Pelayanan Klinis Kedokteran Fisik Dan Rehabilitasi.* Jakarta: Perdosri; 2012. p. 10-4.
117. Wahyuni LK, Tulaar ABM. Sindroma Dekondisi. Dalam: *Panduan Pelayanan Klinis Kedokteran Fisik Dan Rehabilitasi.* Jakarta: Perdosri; 2012. p. 226-39.
118. Black JF. Cancer and Rehabilitation. 2013 March 19. [cited 2013 Sept 10] Available from: <http://emedicine.medscape.com/article/320261-overview>.
119. Kevorkian CG. History of Cancer Rehabilitation. In: Stubblefield DM, O'dell M. *Cancer Rehabilitation, Principles and Practice.* New York: demosMedical; 2009. p. 8.
120. Stubblefield DM, O'dell M, Tuohy MS, Savodnik A. Postsurgical Rehabilitation in Cancer. In: Stubblefield DM, O'dell M. *Cancer Rehabilitation, Principles and Practice.* New York: demosMedical; 2009. p. 813-23.
121. McNeely ML, Campbell K, Ospina M, Rowe BH, Dabbs K, Klassen TP, et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. *Cochrane Database Syst Rev.* 2010; p. 6-16.
122. Lacomba TM, Goni ZA, Merino PD. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomized, single blinded, clinical trial. *BMJ* 2010;340:b5396
123. National Cancer Institute. Lymphedema. 2014 March 18. [cited 2014 July 11] <http://www.cancer.gov/cancertopics/pdq/supportivecare/lymphedema/healthprofessional/page2>.
124. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med* 2009;361(7):664-73.
125. Schmitz KH, Troxel A, Cheville A, et al. Physical Activity and Lymphedema (The PAL Trial): Assessing the safety of progressive strength training in breast cancer survivors. *Contemp Clinical Trials.* NIH-PA 2009;30(3):233–245.
126. Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role for adjunctive intermittent pneumatic compression. *Cancer* 2002;95(11):2260-7.
127. national cancer institute http://m.cancer.gov/topics/factsheets/followup_followup_care_after_cancer_treatmen (cited 17/05/2010), diambil 30 agustus 2014.
128. universitas twente, NL , http://www.utwente.nl/mb/htsr/QR%20Code%20%28downloads%29/2011/SDM%20Chicago%202011/optimization%20breast%20cancer%20follow-up,optimization_of_breast_cancer_follow_up, diambil 30 agustus 2014
129. Pandey M, Thomas BC, SreeRekha P, et al, Quality of life determinants in women with breast cancer undergoing treatment with curative intent. *World J Surg Oncol.* 2005 Sep 27;3:63.

TUGAS



Membuat paper berisi:

- ▶ Kasus
- ▶ Analisis kasus menggunakan metode SOAP
- ▶ Pembahasan : pemilihan terapi, KIE, monitoring
- ▶ Literatur yang mendukung/daftar pustaka (EBM dan referensi ilmiah lain)
- ▶ Sertakan minimal satu EBM (mahasiswa direkomendasikan untuk tidak asal memilih EBM namun harus menyertakan alasan yang kuat mengapa EBM tersebut layak untuk digunakan sebagai acuan dalam pemilihan tata laksana terapi)

Learning Outcome dari tugas tsb adalah :

1. Mahasiswa dapat menjelaskan kondisi yang memerlukan antikanker
2. Mahasiswa dapat menjelaskan macam dan penggolongan antikanker
3. Mahasiswa dapat menjelaskan farmakoterapi antikanker
4. Mahasiswa dapat menjelaskan kombinasi antikanker
5. Mahasiswa dapat menjelaskan prinsip pemilihan antikanker berdasarkan kondisi (stase kanker)
6. Mahasiswa dapat menjelaskan faktor risiko kanker
7. Mahasiswa dapat menjelaskan monitoring efek samping obat dan pencegahan penyebaran penyakit kanker

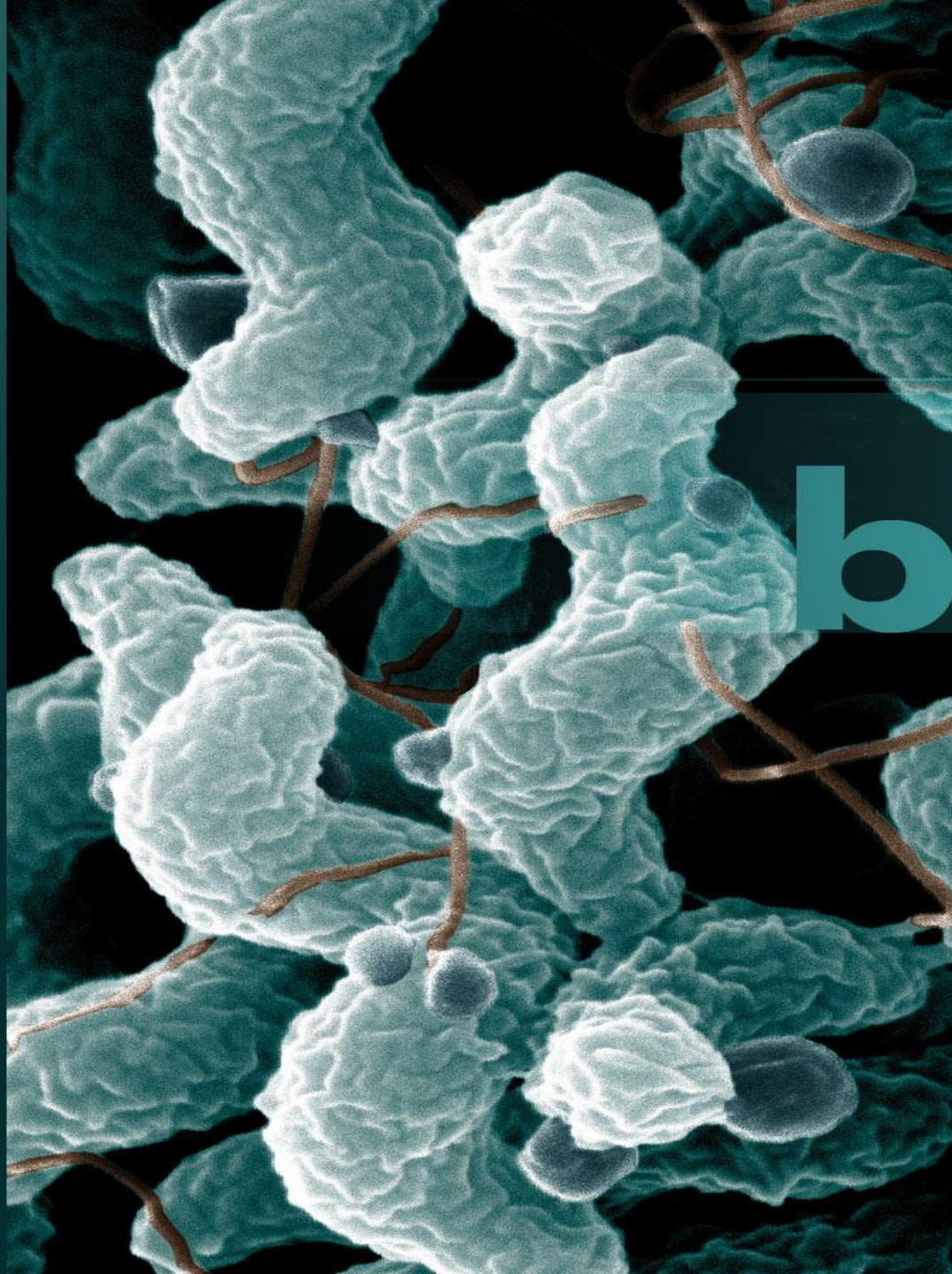
SOAL STUDI KASUS

Aspek Penilaian

Aspek Penilaian	Persentase
Penyusunan Subjektif & Objektif	5 %
Assessment	50 %
Care Plan	25 %
Presentasi/Diskusi Kasus	20 %

Penilaian Skor Akhir Tugas

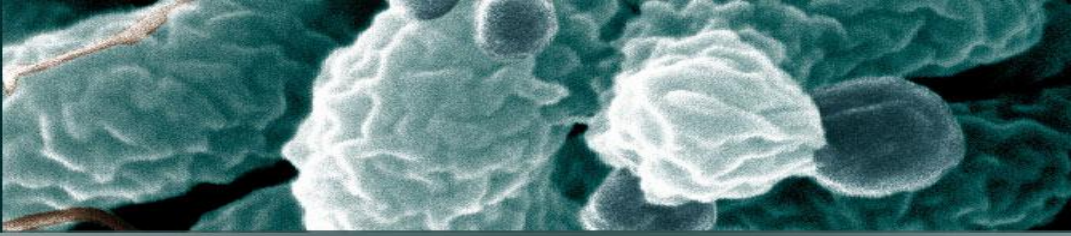
Rentang Skor Total (Skala 100)	Rentang Nilai (skala 4)	
	Angka	Huruf
≥ 85	4.00	A
80 – 84	3.70	A-
75 – 79	3.30	B+
70 – 74	3.00	B
65 – 69	2.70	C+
60 – 64	2.00	C
55 – 59	1.00	D
< 55	0.00	E



bacteria

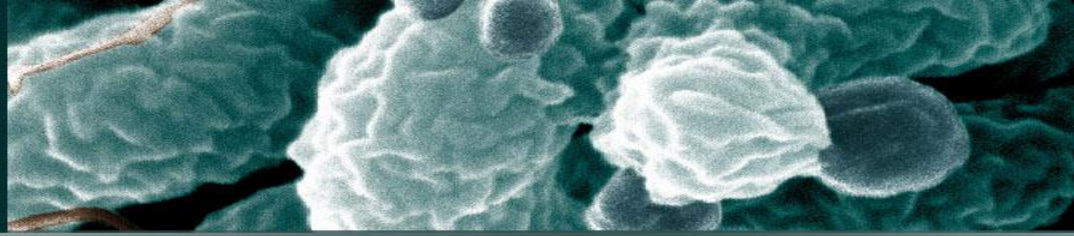
INFEKSI

(Penyakit Infeksi)



INFEKSI

Infeksi adalah peristiwa masuk dan penggandaan micro organisme (agen) didalam tubuh penjamu (host)

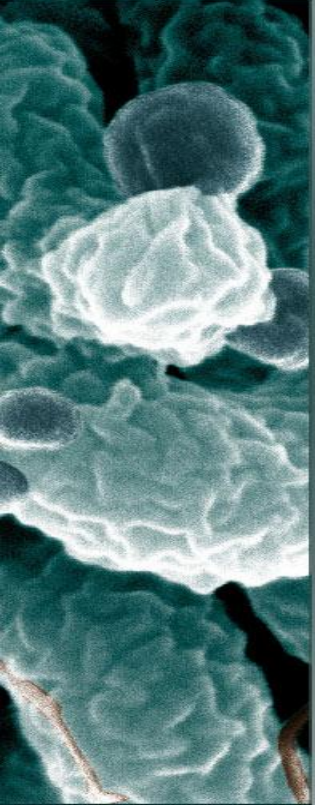


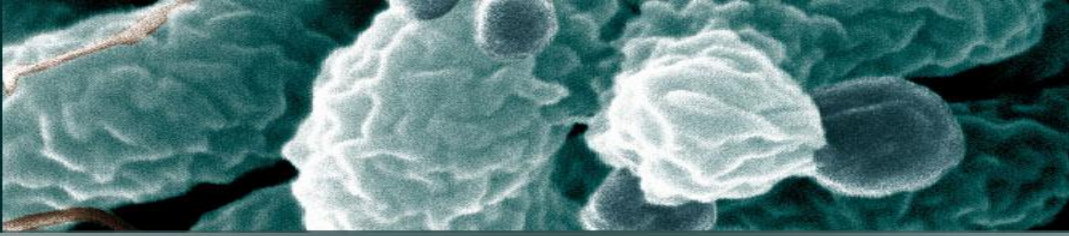
PENYAKIT INFEKSI

**Adalah manifestasi klinik bila terjadi
Kerusakan jaringan / fungsi, bila terjadi
reaksi radang (imun) pejamu.**

Penyakit infeksi dapat disebabkan oleh

- bakteri,
- virus,
- riketsia
- jamur,
- cacing
dsb



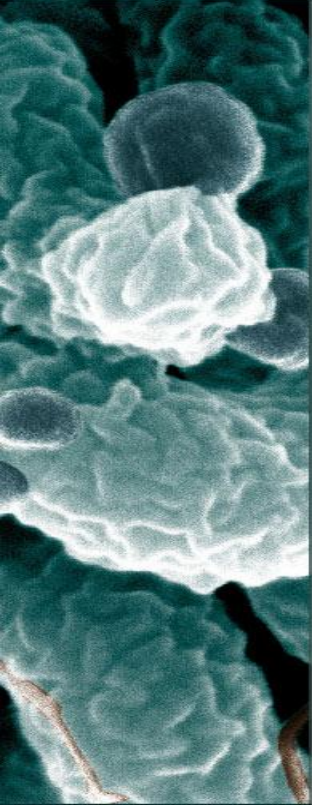


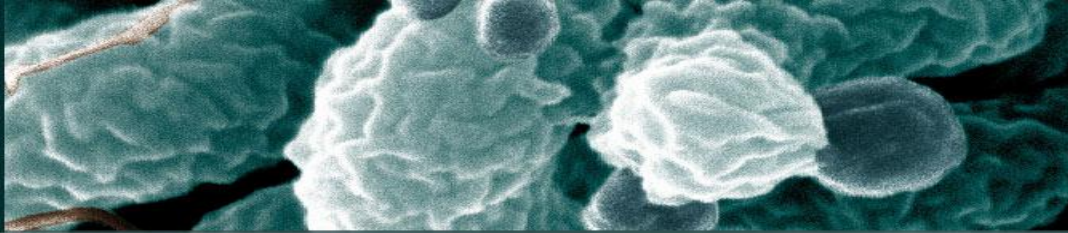
Masuknya agen infeksi melalui :

- kontak langsung, misal peny. Kelamin
- Kontaminasi dan luka, misal infeksi luka dan rabies
- Inokulasi, misal gigitan serangga (malaria), suntikan (serum hepatitis)
- Menelan makan dan minuman yg terkontaminasi (Hepatitis A, poliomielitis, kolera)
- Menghirup debu dan droplet, misal influenza, tbc

Pejamu mempunyai benteng terhadap infeksi yaitu :

- ✓ KULIT
- ✓ MULUT
- ✓ SALURAN PENCERNAAN
- ✓ SALURAN PERNAFASAN
- ✓ SALURAN KEMIH
- ✓ CONYUNTIVA MATA
- ✓ VAGINA





FAKTOR - HOSPES

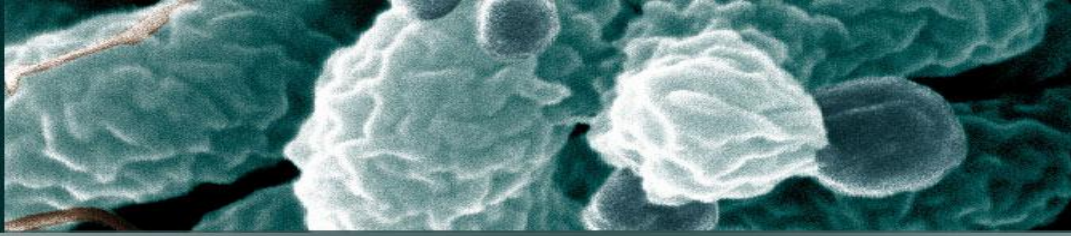
Faktor Hospes pada Infeksi :

- Mekanisme pertahanan tubuh terhadap agen menular :
- Barrier mekanis tubuh (pertahanan mekanik):

a. Kulit dan mukosa orofaring

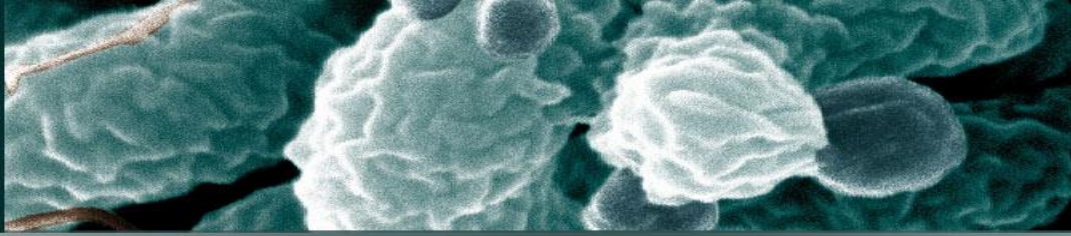
Kulit dan mukosa orofaring yg utuh merupakan barrier mekanis sederhana yg baik terhadap infeksi

- **Dekontaminasi fisik**, kulit dapat melepaskan mikroorganisme yg menempel ketika lapisan kulit mengelupas. Aliran saliva yg menghanyutkan partikel secara mekanis pada mukosa orofaring
- **Dekontaminasi kimiawi**, sekresi kelenjar sebasea. Zat-zat yg terdapat pada saliva akan membersihkan kulit dan mukosa orofaring dari mikroorganisme penyebab infeksi
- **Dekontaminasi biologis**, kulit dan mukosa orofaring memiliki flora normal yg dapat menghambat pertumbuhan mikroorganisme.



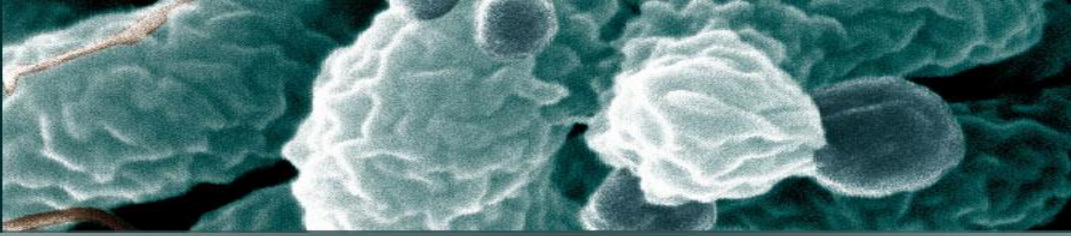
b. Saluran Pencernaan

- Tingkat Keasaman yg tinggi pada lambung merupakan kondisi yg tidak menguntungkan bagi kuman.
- Gerakan peristaltic usus dapat mempertahankan jumlah populasi bakteri tetap sedikit.
- Adanya mucus yg disekresi lapisan usus dapat sebagai pelindung yg viskus pd permukaan usus kemudian didorong olh peristaltic usus
- Secret usus mengandung antibody yg menghambat bakteri.
- Lapisan dalam usus besar banyak flora normal sebagai pesaing makteri dalam mendapat makanan serta mengeluarkan substansi antibakteri



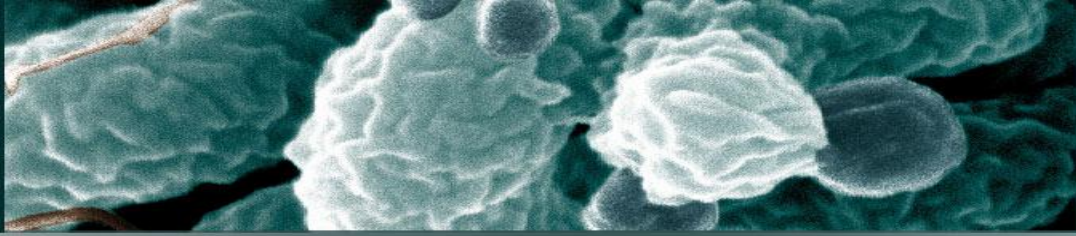
c. Saluran pernafasan

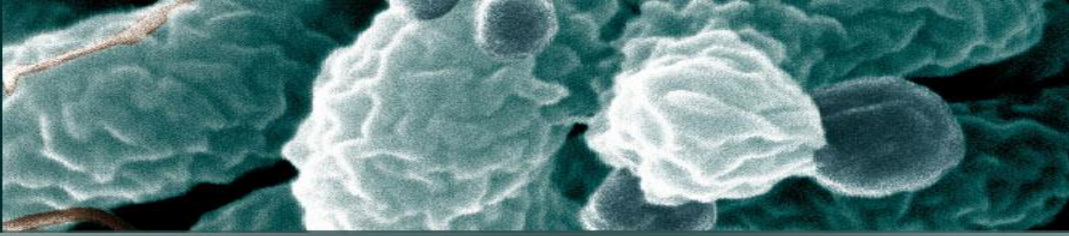
- Beberapa epitel saluran pernafasan menghasilkan mucus dan sebagian besar memiliki silia pada permukaan lumen yang mampu menangkap dan mengeluarkan bakteri. bakteri yang terhirup dikeluarkan dengan cara digerakan keluar, dibatukan atau ditelan.
- Adanya antibody di dalam secret
- Adanya makrofag dalam alveolus.



RADANG SEBAGAI PERTAHANAN

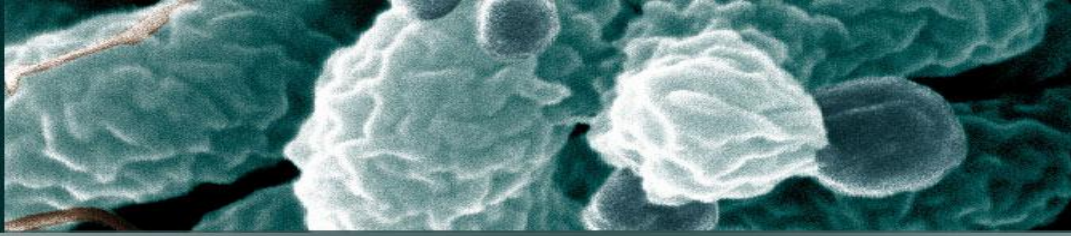
- Jika agen menular berhasil menembus barrier tubuh dan memasuki jaringan maka pertahanan berikutnya adalah reaksi peradangan akut.





Jika reaksi peradangan akut tidak sanggup mengatasi penyerang , infeksi tersebut dapat menyebar lebih luas keseluruh tubuh.

- Biasanya organisme dibawa oleh cairan tubuh, penyebaran cenderung terjadi pada ruang yang berdekatan misal terjadi perforasi usus dan terjadi penyebaran ke peritoneum. Pada jaringan penyambung (misal sepanjang otot), selaput otak.



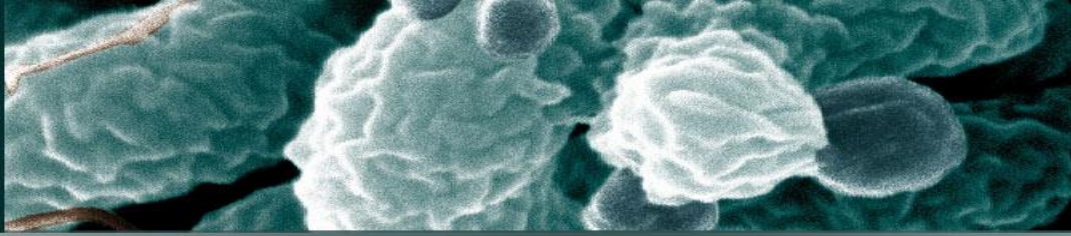
PEMBULUH LIMPHE

- Agen penyakit kadang kadang ikut menyebar sepanjang pembuluh lymphhe , terjadi limphangitis

PERTAHANAN TERAKHIR

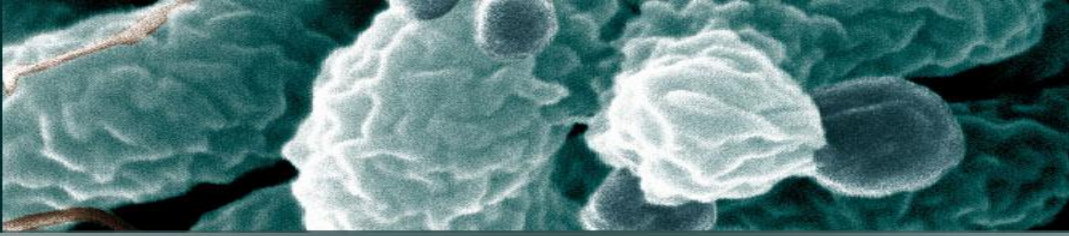
- Jika penyebaran agen tidak berhenti pada kelenjar lymphhe atau jika agen langsung memasuki vena maka dapat terjadi infeksi pada aliran darah.

Kumpulan bakteri dalam aliran darah disebut **bakteriemia**



Jika organisme tsb jumlahnya cukup besar, dan resisten maka sistim makrofag dapat ditaklukkan, maka organisme tsb dapat menetap dalam darah dan menimbulkan gejala :
malaise, demam, menggigil,
keadaan ini disebut **septicemia atau sepsis**.

Akhirnya kalau organismenya sedemikian besar, mereka bersirkulasi dalam gumpalan-gumpalan,
menimbulkan banyak mikro abses disebut **PIEMIA**



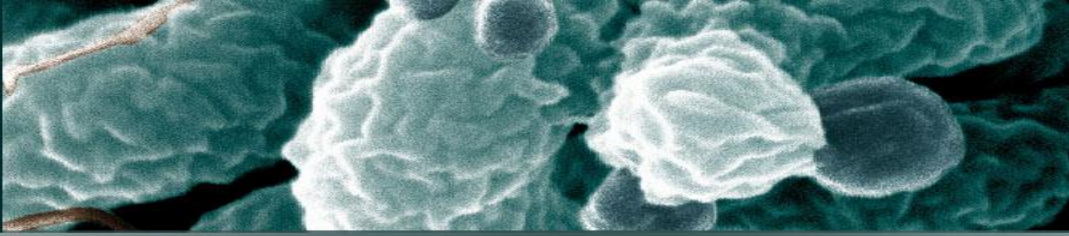
- **REAKSI HOSPES DENGAN JASAD RENIK**

Cara interaksi hospes dengan mikroorganisme :

Komensalisme, antara hospes dan agen menular tidak saling menyerang atau menguntungkan bagi yg satu tanpa menimbulkan cedera pada yang lain.

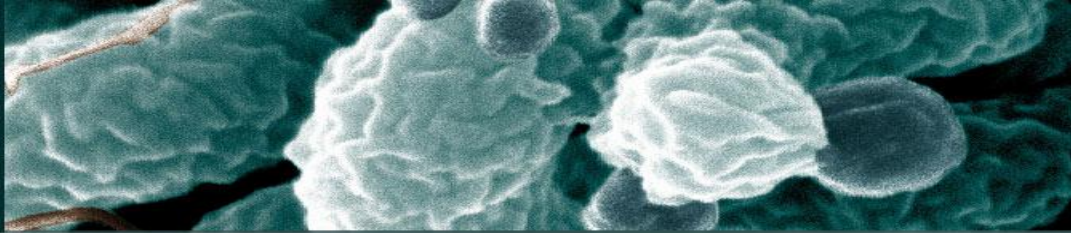
Mutualisme, interaksi hospes dan mikroorganisme saling menguntungkan.

Parasitisme, Menguntungkan bagi yg satu tetapi merugikan bagi yang lain.



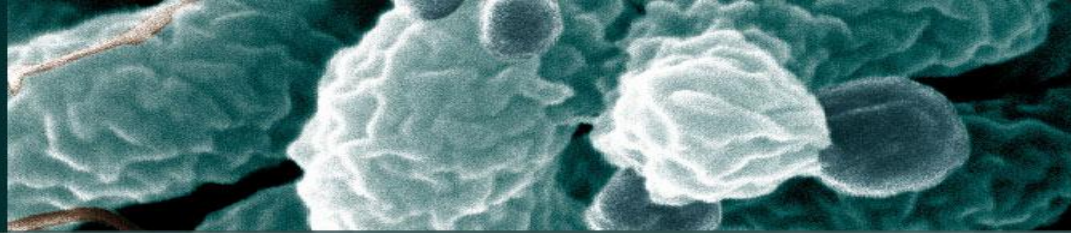
FAKTOR JASAD RENIK

- **Daya Transmisi**
 - **Daya Invasi**



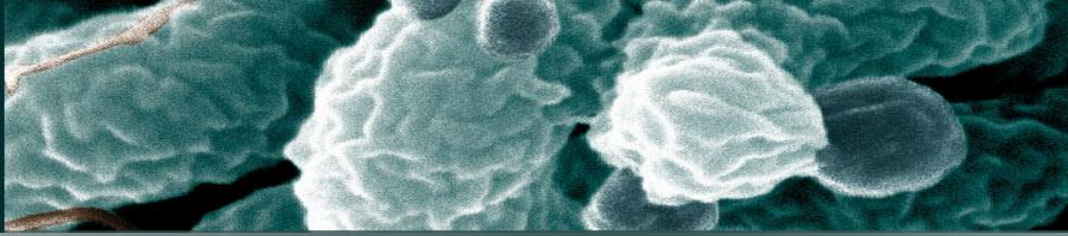
DAYA TRANSMISI

- **Cara pemindahan infeksi**
- **Secara langsung yaitu melalui batuk, bersin, berciuman**
- **Secara tidak langsung : Individu yang terinfeksi mengeluarkan organisme kelingkungannya, dapat juga organisme tadi sampai ketanah, air, makanan, atau kalau di R.S. melalui eksudat dan excreta, tranfusi darah, dapat juga melalui vektor serangga**



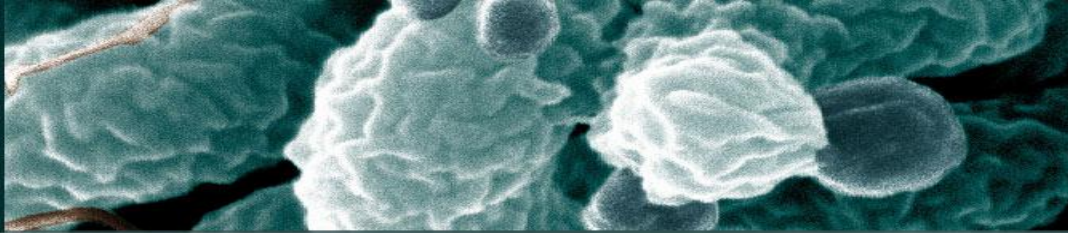
DAYA INVASI

- **Jasad renik harus mampu bertahan dalam hospes tsb untuk dapat menimbulkan infeksi.**
- Misal kolera : tidak pernah memasuki jaringan, tetapi hanya menduduki epitel usus, melekat kuat sehingga tidak terhanyut gerakan usus
- Disentri basile hanya memasuki lapisan superfisial usus
- Typoid tidak hanya memasuki lapisan superficial usus tapi dapat menyebar keseluruh tubuh melalui aliran darah
- Sypilis : kuman spiroketa dapat menembus membran mukosa atau kulit melalui pintu masuk dan menyebar melalui aliran darah
- Tetanus tidak menyebar keseluruh tubuh, tapi mensekrsikan racun, dan racun ini dibawa aliran darah dan menyebar



Cara cara microorganisme menerobos barrier hospes atau menghindari dari mekanisme pertahanan hospes

- **Membentuk kapsul berlendir, sehingga sel fagosit tidak menelannya**
- **Penyebaran enzimatik, melalui proses pencernaan kimia**
- **Mensekresi racun**
- **Membentuk daya tahan intraseluler, dan organisme ini cenderung menetap sebagai parasit intra seluler**



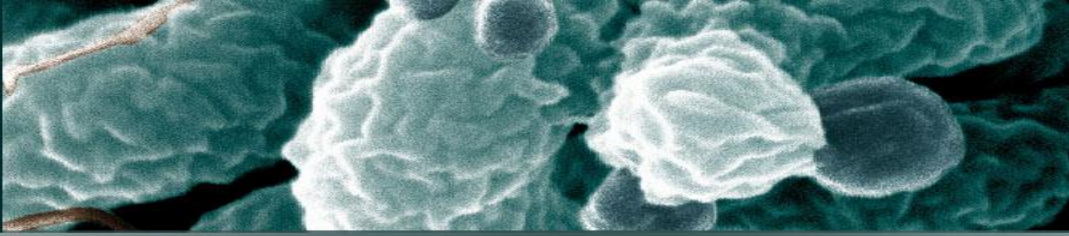
Klasifikasi Agen infeksi

1. Berdasarkan bangunan/Struktur

- bangunan yang sederhana : virus
- bangunan yang majemuk : protozoa juga dapat dikelompokkan pada komponen yg lebih rinci misal : Virus DNA, virus RNA, bakteri kokus atau batang dll

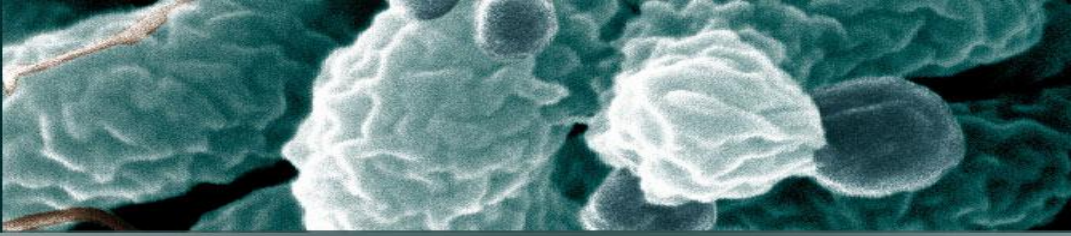
2. Berdasarkan Patogenitas,

- Kemampuan menimbulkan penyakit , dikelompokkan: Patogen rendah dan tinggi (virulensi)



Letak penggandaan, baik di dalam maupun diluar sel dibagi menjadi

- **Organisme intrasel obligat**, hanya dapat tumbuh dan berkembang di dalam sel penjamu, kultur organisme ini perlu sel hidup
- **Organisme intrasel fakultatif**, mampu tumbuh baik di dalam maupun di luar sel. Pertumbuhan dalam sel biasanya pada sel makrofag, kebanyakan organisme ini dikultur pada media buatan
- **Organisme Ekstrasel**, tumbuh dan berkembang di luar sel, dapat dikultur pada media buatan



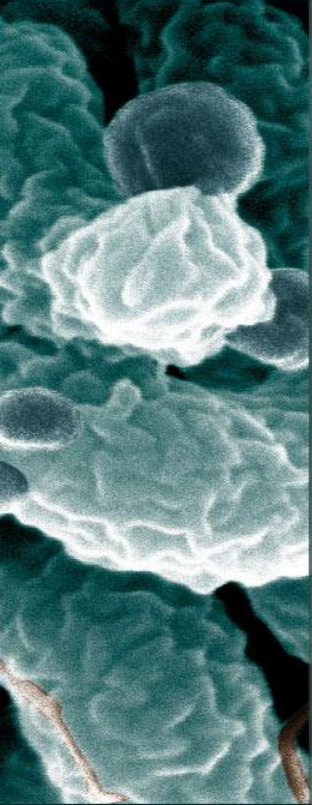
Perubahan Jaringan pada Infeksi

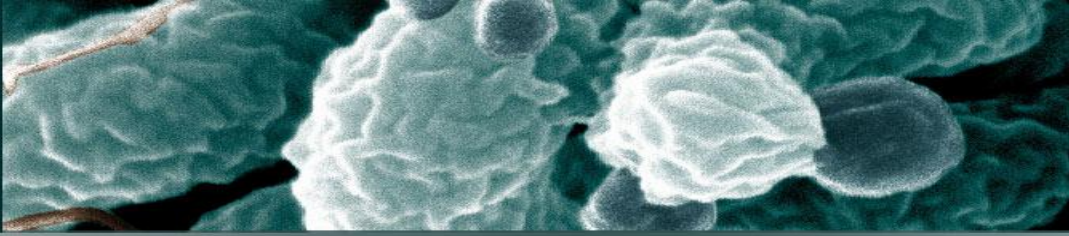
Pada infeksi , perubahan jaringan yg bersifat patologik dapat disebabkan oleh 3 hal yaitu :

- Kerusakan yg diinduksi agen
- Reaksi radang pejamu
- reaksi imun pejamu

Perubahan patologik kerusakan jaringan akibat infeksi tergantung pada sifat agen:

- Organisme intrasel obligat
- Organisme intrasel fakultatif
- Organisme ekstra sel





Organisme Intrasel obligat, dapat mengakibatkan:

1. Nekrosis sel

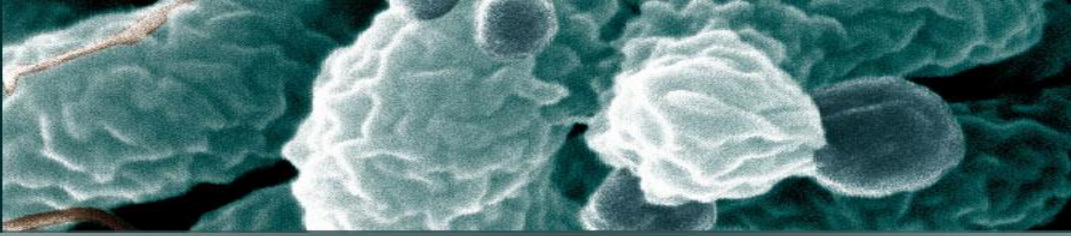
Nekrosis akut terjadi jika penggandaan agen di dalam sel disertai perubahan yg menghentikan fungsi sel

2. Pembengkakan sel

- Pembentukan inclusion body
- Pembentukan sel datia

Organisme Ekstra sel

- Pelepasan enzim
- Menyebabkan vasculitis lokal
- Menghasilkan toksin

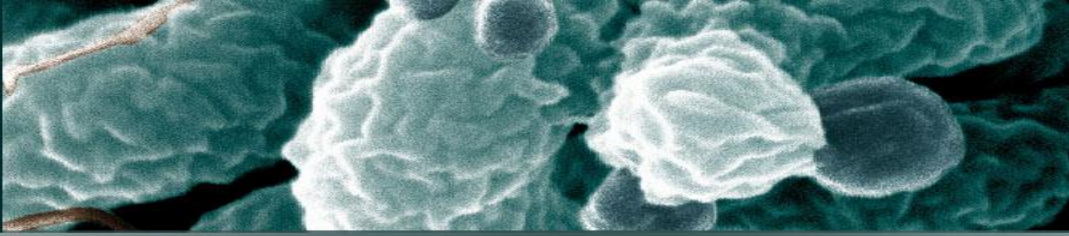


Perubahan jaringan akibat respon pejamu terhadap infeksi

Penggandaan agen infeksi menyebabkan □ reaksi imun dan peradangan

Reaksi peradangan yg berfungsi membuat agen infeksi tidak aktif:

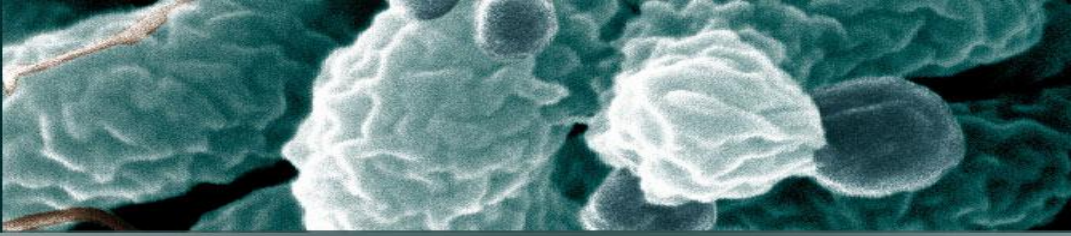
- radang akut,
- radang supuratif dan radang kronik,
- radang gabungan supuratif dan granulomatosa.



JENIS-JENIS PENYAKIT INFEKSI

1. Bakteri :

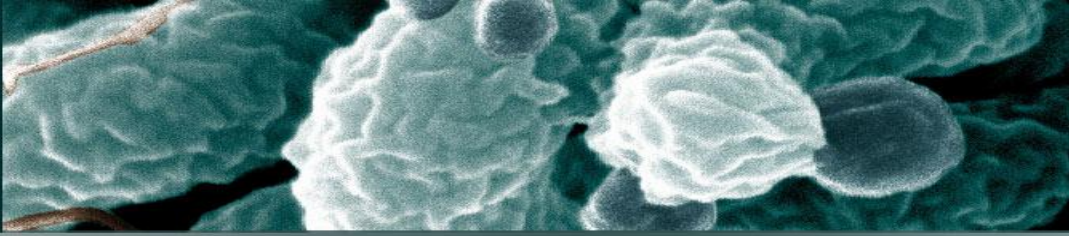
- bakteri merupakan sel hidup terkecil
- berukuran 0,1 – 10 micron.
- dibagi menjadi type gram positif dan gram negatif
- bakteri bentuk bulat dan oval disebut coccus, bentuk panjang disebut bacillus, bentuk melengkung disebut vibrio



Bakteri gram positif piogenik

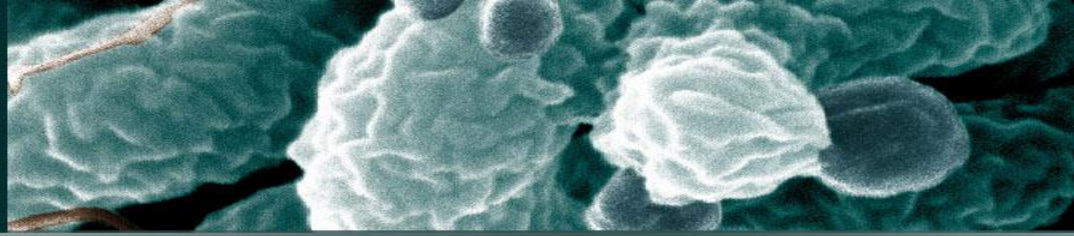
Staphylococcus aureus

- bentuk coccus
- gram positif tumbuh berkelompok
- bakteri ini normal berada dikulit dan siap untuk tumbuh di jaringan yg lebih dalam
- menimbulkan infeksi supuratif



Penyakit yg disebabkan oleh *Staphylococcus Aureus*

- Furunkel ; infeksi disekitar folikel rambut
- Carbuncle
- Osteomyelitis
- Infeksi saluran nafas
- Arthritis bakteri
- Endokarditis bakteri

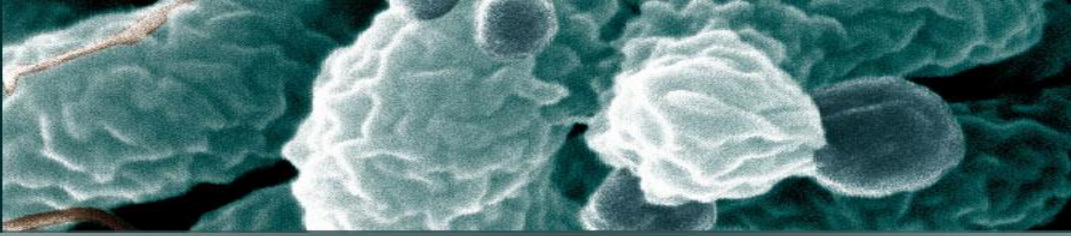


Streptococcus Pyogenes

- Bakteri coccus, gram positif
- Merupakan flora dikulit dan oraofaring
- Dikenal dengan streptococcus grup A

Penyakit yg disebabkan Streptococcus

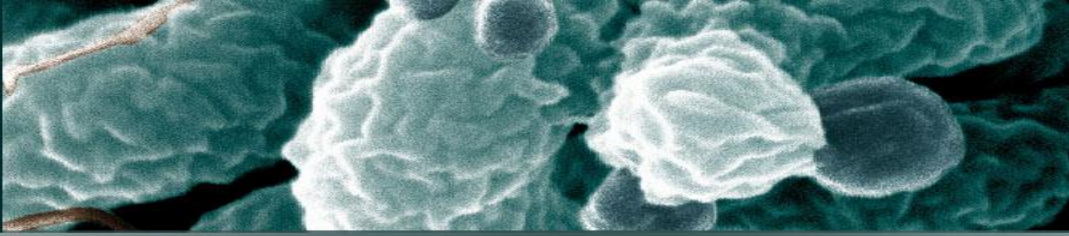
- Faringitis akut
- Erisipelas
- Impetigo(pyoderma)
- Cellulitis



Streptococcus Pneumonia

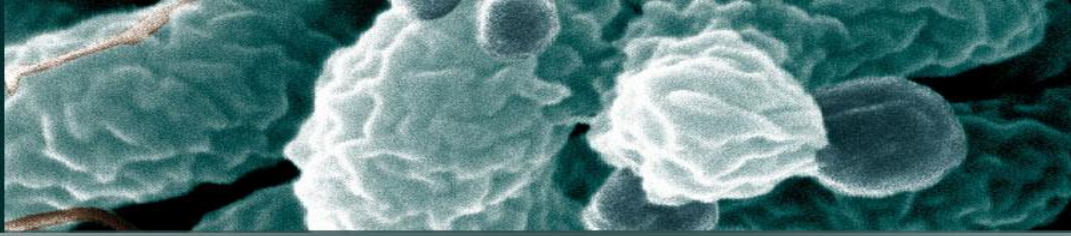
Menimbulkan penyakit :

- pneumonia,
- otitis media,
- sinusitis,
- meningitis



Infeksi bakteri pada anak

- Neiseria meningitis
- Hemophilus influenza
- Bordella petusis
- Corynebakterium diphtheriae
- Clostridia
- Yersinia pestis



Neisseria meningitidis

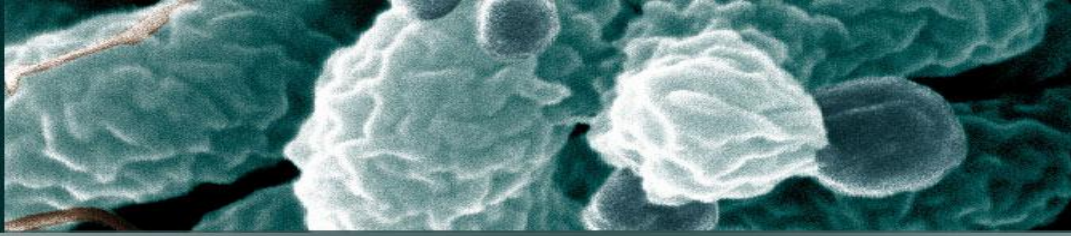
- Sering disebut meningokok, gram negatif, penyebab merningitis
- Penyebaran kuman didalam darah sering disertai shok dan kelainan koagulasi darah

Hemophilus influenza

- Bacil gram negatif, cocus
- Penyebab infeksi piogenik terutama mengenai telinga tengah, sinus, kulit muka, meningen, paru, epiglotis, sendi

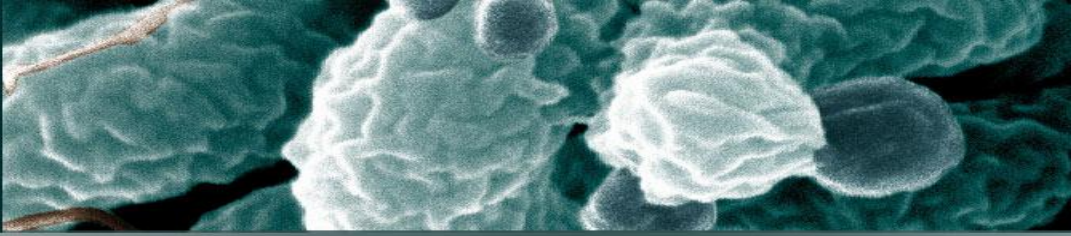
Bordetella pertusis

- Gram negatif, kokus
- Penyebab batuk rejan atau pertussis yaitu infeksi jalan nafas yg berkepanjangan disertai batuk berulang



Corynebakterium difteri

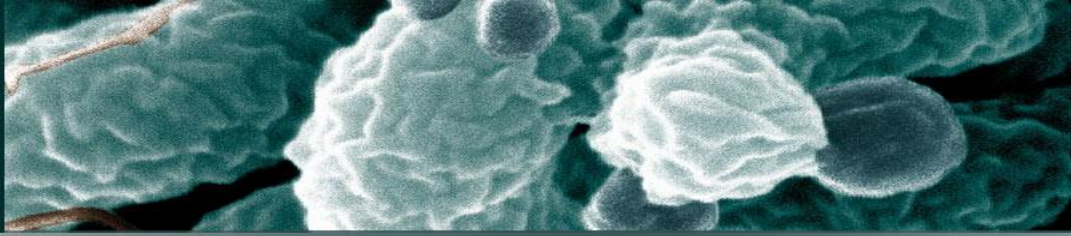
- Bakteri gram positif, penyebab penyakit difteri
- Difteri dimulai dengan masuknya C.difteri melalui faring dan berproliferasi di tonsil
- Karakteristik terbentuk membran tebal, abu-abu, membrane terdiri atas sel epitel lepas, materi necrotik, netrofil, fibrin, bakteri
- Disaluran nafas yg terkena terjadi edema, dan akan mengganggu pernafasan, toksin difteri merusak otot jantung.



Clostridia

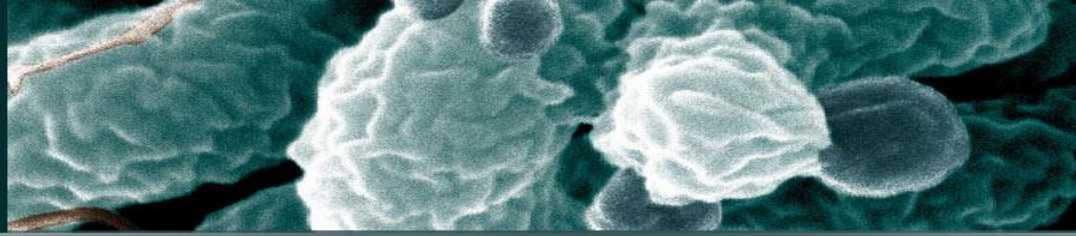
Bacil gram positif mampu membentuk spora, tumbuh mutlak anaerob, Dibagi menjadi :

- Clostridiun tetani
- Clostridium perfringen
- Clostridium botulinum



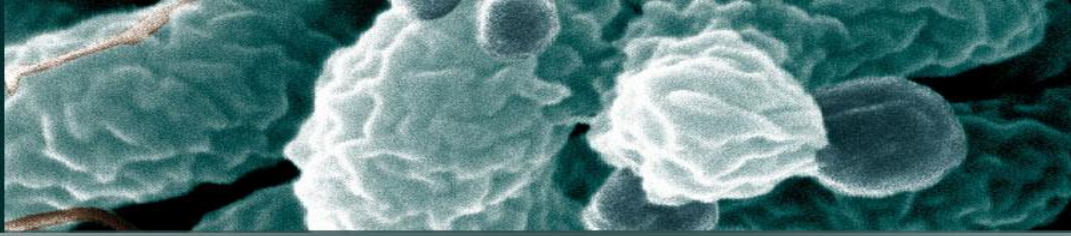
Yersinia pestis

- Penyebab penyakit Pes, infeksi bakteri yg disertai pembesaran dan nyeri pada kelenjar getah bening, infeksi dimulai pada rodent yg kemudian menyebar ke manusia
- Patologi : terlihat perdarahan dan necrosis kelenjar limfoid yg terkena



Bakteri entero patogen

- Salmonella
- Shigella
- Vibrio cholerae

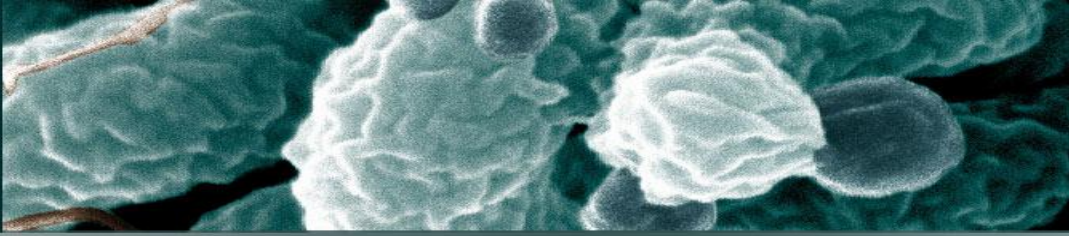


Mycobacterium

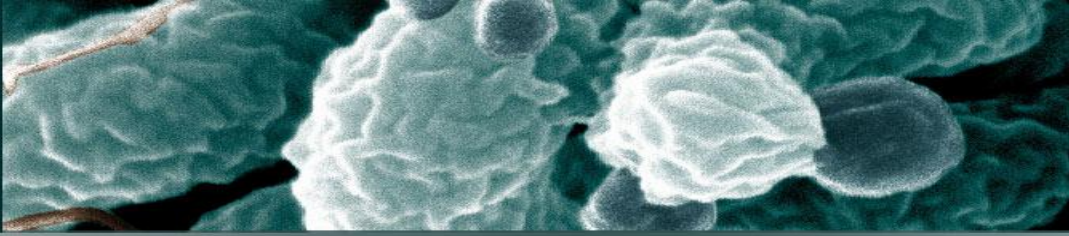
- Merupakan bakteri gram positif
- Merupakan kuman tahan asam (tetap menahan karbolfuchsin setelah dibilas dengan alkohol asam) disebut BTA (Bakteri Tahan Asam)
- Tumbuh lebih lambat daripada bakteri lain
- Penyakit yg ditimbulkan kronik residif

Jenis mycobacterium

- Mycobacterium tuberculosis: menyerang paru paru
- Mycobacterium leprae ; menyerang kulit dan serabut saraf tepi
- Mycobacterium atipik menyerang kelenjar limfoid

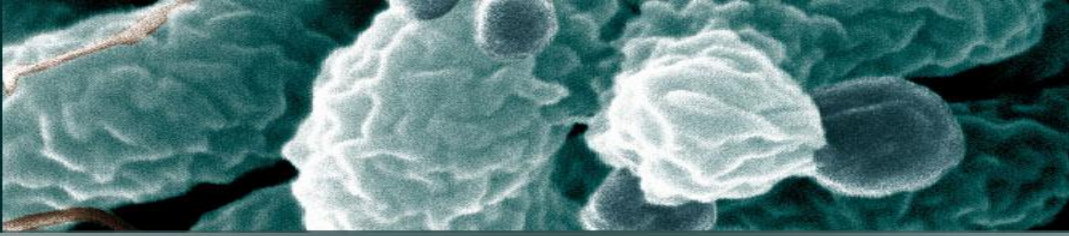


- Sebagian membentuk kapsul sehingga mampu bertahan pada sistem imun penjamu.
- Dapat bersifat aerob dan anaerob.
- Sebagian mengeluarkan toksin
- Bakteri Gram positif mengeluarkan eksotoksin, pada pewarnaan akan berwarna ungu.
- Gram negative pada pewarnaan berwarna merah.



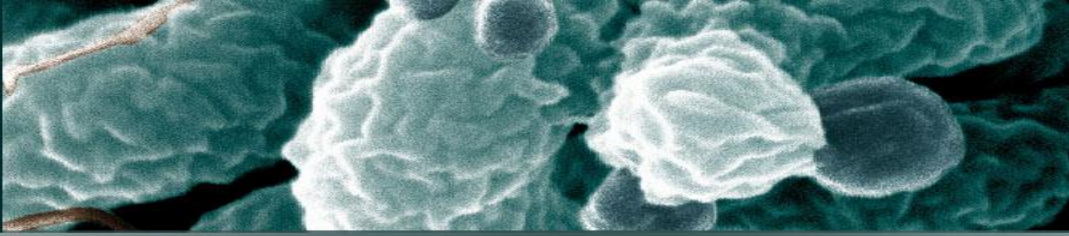
Infeksi Virus

- Adalah organisme patogen terkecil
- Mengandung R.N.A atau D.N.A dan memiliki selubung protein
- Organisme ini tidak mampu bermetabolisme mandiri, memerlukan organel sel terinfeksi untuk berkembang biak



CONTOH PENYAKIT VIRUS

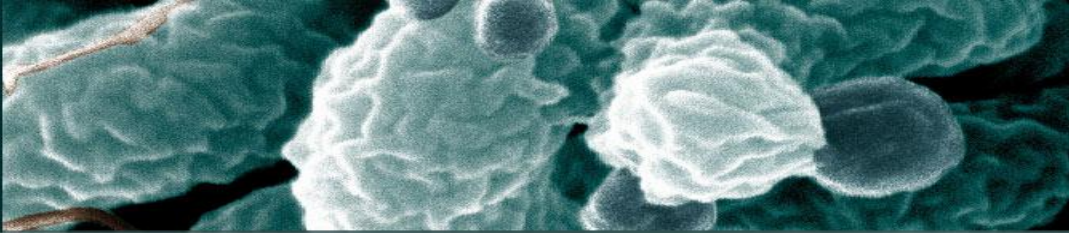
- ✓ Influenza
- ✓ Morbilli (Rubeola)= campak
- ✓ Rubella
- ✓ Mumps (parotitis epidemika)
- ✓ Rota virus
- ✓ Herpes Citomegalo virus
- ✓ Human papiloma virus
- ✓ HIV-AIDS
- ✓ Hepatits
- ✓ Covid



Mikoplasma

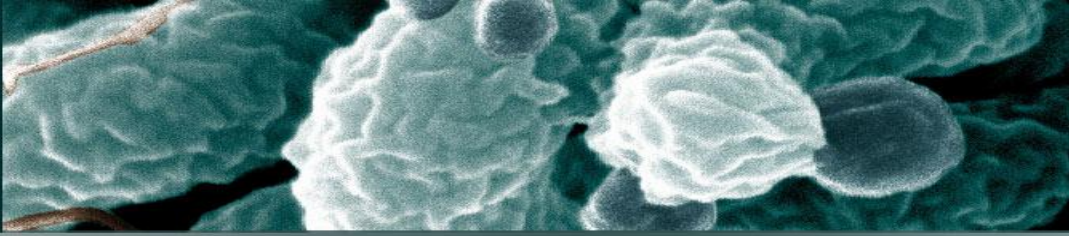
Mikroorganisme unisel mirip bakteri tetapi lebih kecil dan tidak mengandung peptidoglikan

Contoh penyakit : pneumonia mikoplasma.



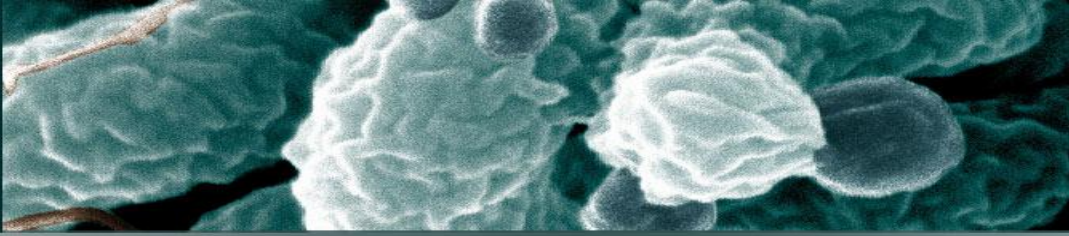
Riketsia

- Memerlukan penjamu untuk bereproduksi secara seksual
- Mengandung DNA dan RNA
- Memiliki dinding petidoglikan
- Ditularkan memlaui gigitan kutu
- Contoh penyakit : Tifus dan Rocky Mountain fever
- Infeksi Riketsia menimbulkan :
 - Ruam kulit
 - Demam menggigil
 - Mialgia
 - Pembentukan thrombus di organ-organ



Klamidia

- Organisme unisel
- Bereproduksi secara aseksual dlm penjamu dan mengalami siklus replikasi Contoh : infeksi urogenital
- Infeksi oleh klamidia Uretritis menimbulkan Servisititis, disertai pengeluaran mukopurulen, gatal dan rasa terbakar saat berkemih.



JAMUR

- ✓ Mencakup ragi (yeast) dan kapang (mold)
- ✓ Memiliki inti sel dan dinding sel
- ✓ Cth : kandidiasi mulut, vagina, kurap
- ✓ Infeksi Jamur:
 - Gatal dikulit atau kepala (superficial)
 - Ruam atau perubahan warna kuku
 - Plak putih pada rongga mulut
 - Tanda-tanda pneumonia

PARASIT

- ✓ Parasit : protozoa, cacing, dan arthropoda
- ✓ Infeksi Parasit;
 - Diare oleh parasit sal cerna
 - Demam disertai malaria
 - Gatal dan ruam pada infeksi kulit

ANTIBIOTIKA

DEFINISI

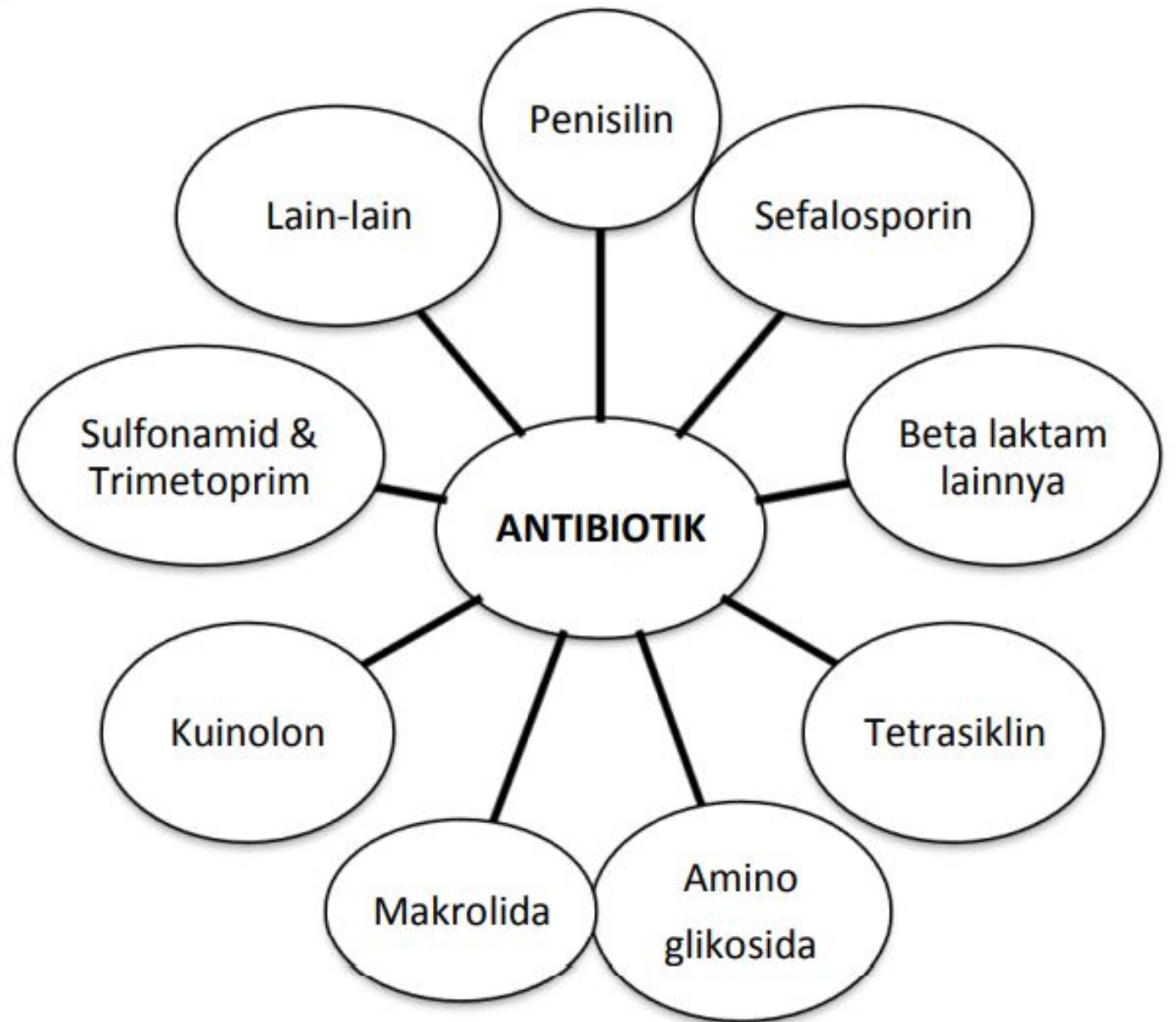
Antimicrobial Agent (Agen antimikroba)

- Semua senyawa alami, semi sintetik ataupun murni sintetik yang mampu membunuh atau menghambat pertumbuhan mikroorganisme.
- Contohnya : enrofloxacin, penicillin, monensin.

Antibiotik

- Suatu senyawa yang diproduksi oleh suatu mikroorganisme yang mampu membunuh atau menghambat pertumbuhan mikroorganisme lain.
- Semua antibiotik adalah agen antimikroba, khususnya disini adalah yang terbuat dari bahan alami karena antibiotik berasal dari

GOLONGAN ANTIBIOTIK



1. GOLONGAN PENISILIN

- a) Penisilin Spektrum Gram Positif, yang rusak oleh Enzim Penisilinase. Contoh : Penisilin G , Penisilin V
- b) Penisilin Spektrum Luas, yang rusak oleh Enzim Penisilinase. Contoh : Ampisilin, Amoksisilin, Bakampisilin
- c) Penisilin yang tahan oleh Enzim Penisilinase. Contoh : Kloksasilin, Flukoksasilin ,Co Amoksiklav
 - Penisilin yang tahan dari Enzim Penisilinase ini memang dimodifikasi oleh ahli farmasi untuk itu. caranya ???
Dengan diberi Beta Laktamase Inhibitor (BLI) pada strukturnya.
Ada 3 macam BLI :
 1. Asam Klavulanat □ Co Amoksiklav (Amoksisilin + Asam klavulanat)
 2. Sulbactam □ Onasin (Ampisilin + sulbactam)
 3. Tazobactam

d) Penisilin Antipseudomonas.

Contoh : Tikarsilin, Piperasilin, Sulbenisilin

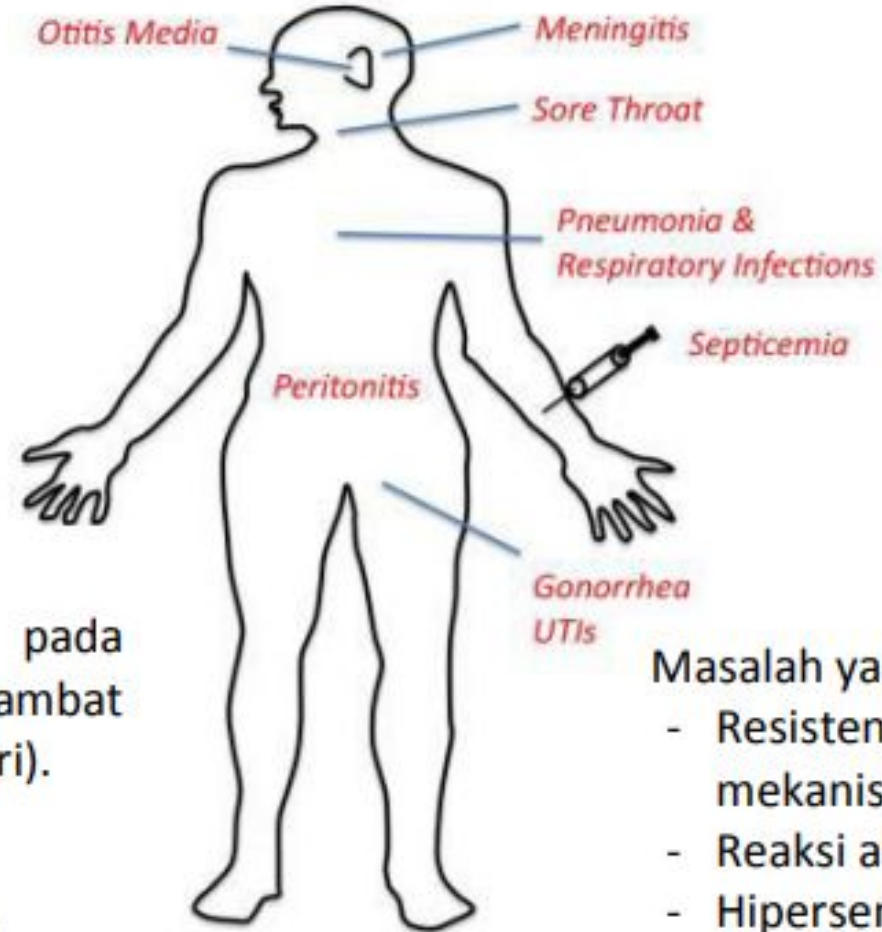
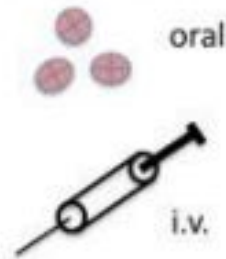
Kenapa Pseudomonas jadi perhatian ???

Pseudomonas arabinosa adalah bakteri yang sangat berbahaya merupakan penyebab kematian terbesar di dunia

Oleh karena itu beberapa kasus infeksi yang berat terutama infeksi Nosokomial (infeksi yang didapat dari rumah sakit, biasanya timbul demam pada 2-3 hari kemudian) perlu diobati oleh antibiotik khusus karena gol. antibiotika lain tidak ada yang bisa melawan

Penicillin Uses

Routes:



Mekanisme :

Menghambat *transpeptidase* pada dinding sel bakteri (menghambat pembentukan dinding sel bakteri).

Sifatnya :

Bakterisidal (membunuh bakteri).

Masalah yang diketahui :

- Resisten (β -laktamase & mekanisme lainnya)
- Reaksi alergi
- Hipersensitif silang (1-3% dengan Sefalosporin)

Note :

Perlu diketahui kalau enzim penisilase itu nama lainnya dari β -laktamase yaitu suatu enzim yang dimiliki bakteri untuk merusak cincin laktam dari obat yang menyebabkan obatnya rusak dan tidak berefek lagi.”

2. GOLONGAN SEFALOSPORIN

a) Generasi pertama

Efektifitas : bakteri gram (+)

Contoh : Sefadroksil, Sefalekssin, Sefradin, Sefazolin, Sefalotin.

b) Generasi kedua

Efektifitas : bakteri gram (-)

Contoh : Sefaklor, Sefuroksim, Sefamandol, Sefoksitin.

c) Generasi ketiga

Efektifitas : >> gram (-) , enterobacteriaceae dan kadang pseudomonas

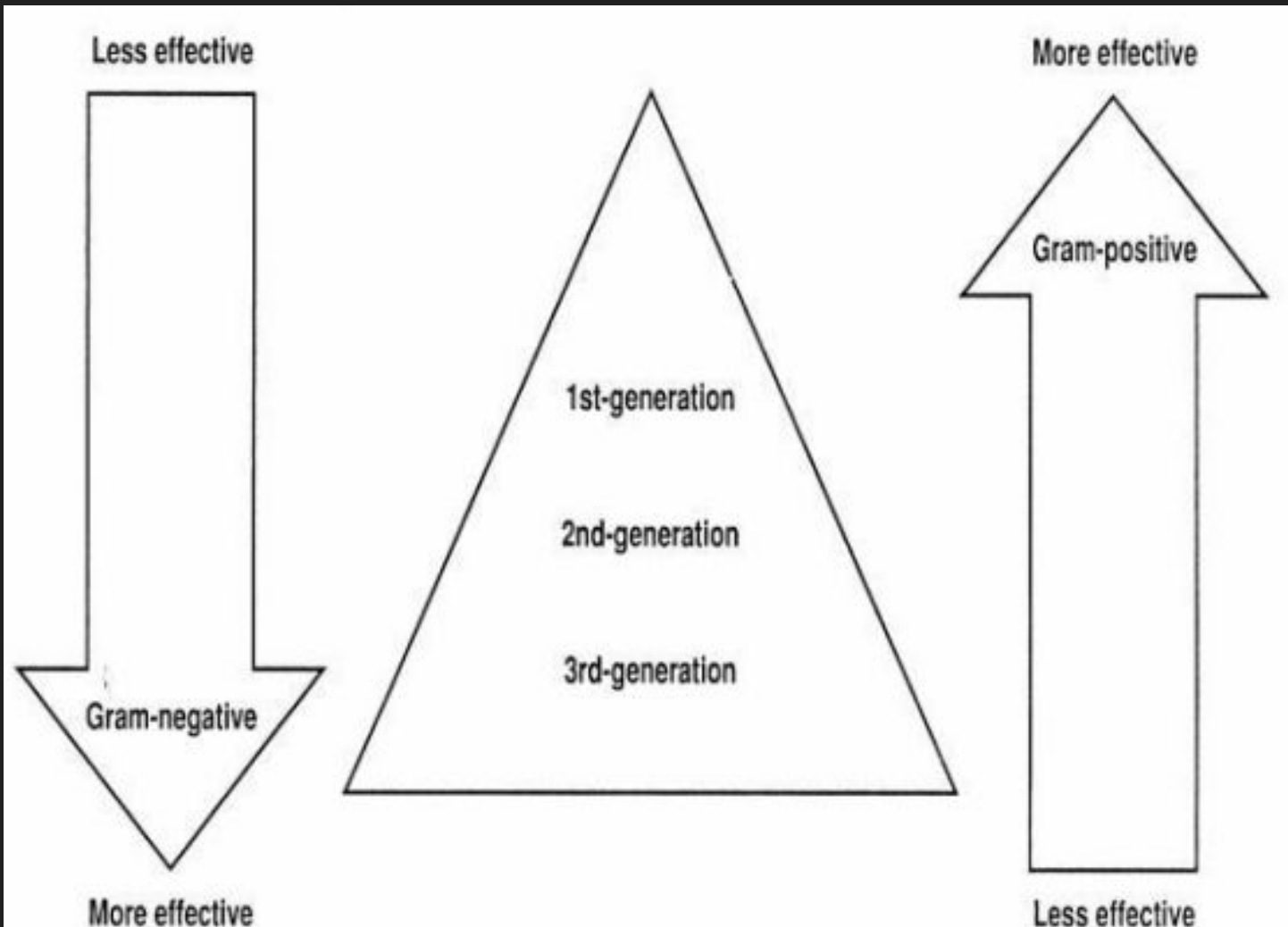
Contoh : Sefoperazon, Sefotaksim, Seftriakson, Seftazidim.

d) Generasi keempat

Efektifitas : bakteri gram +/-

Contoh : Sefepim

Jarang digunakan, harganya mahal



Umumnya pada golongan antibiotik lain makin tinggi generasinya maka spektrumnya akan semakin luas. Namun beda pada gol. sepalosporin.

Dari gambar disamping dapat dijelaskan bahwa :

- ✓ Pada golongan sepalosporin semakin tinggi generasinya maka efektivitas pada gram (+) semakin berkurang namun efektivitas pada gram (-) akan meningkat.
- ✓ Kecuali pada golongan ke-4
Golongan ini memiliki aktivitas gram (+) seperti generasi pertama dan aktivitas gram (-) nya lebih baik dari generasi lainnya.

3. GOLONGAN BETALAKTAM LAIN

a) Monobaktam

Efektifitas : bakteri Gram (-) dan Pseudomonas

Contoh : Aztreonam

b) Carbapenem

Efektifitas : Spektrum luas (gram (+/-) & aerob/anaerob)

Contoh : Imipenem (+silastatin) dan meropenem

- Kenapa Imipenem dikombinasi dengan silastatin ??
- Sebenarnya imipenem resisten/tahan terhadap betalaktamase tapi sifat ini dinaktifkan
- oleh dihidropeptidase dalam tubulus ginjal, oleh karena itulah dalam penggunaanya di klinik dikombinasi dihidropeptidase silastatin

4. GOLONGAN TETRASIKLIN

- Efektifitas : gram (+/-)
- Sifatnya : Bakteriostatik
- Kerjanya menghambat pertumbuhan bakterinya, yang membunuhnya yaitu sistem imun tubuh. Namun kelemahannya karena sifatnya hanya menghambat jadi banyak ditemukan kasus resisten terhadap golongan ini.
- Resistensi yang sudah banyak terjadi pada klamidia, riketsia & mikoplasma
- Contoh : Tetrasiklin, Demeklosiklin hidroklorida, Doksisiklin, Minosiklin, Oksitetrasiklin

5. GOLONGAN AMINOGLIKOSIDA

- Efektifitas : bakterisid, gram (-) & <<< gram (+), antipseudomonas
- Toksisitas : nefrotoksik & ototoksik
- Contoh : Gentamisin, Amikasin, Kanamisin, Neomisin sulfat, Netilmisin, Tobramisin, Streptomisin (akhirannya –isin)
- Tidak tersedia dalam bentuk sediaan oral

Aminoglycoside Uses

Routes:



im or iv,
topical

Oral neomycin before
elective bowel surgery
(not absorbed)

Almost always used along with a
cell-wall synthesis inhibitor

Pneumonia, MRSA,
wide variety of G-
& some G+ bacteria
Upper Resp. Tract Procedures

Rx Endocarditis

Bacteremia, Sepsis
(aerobes only)

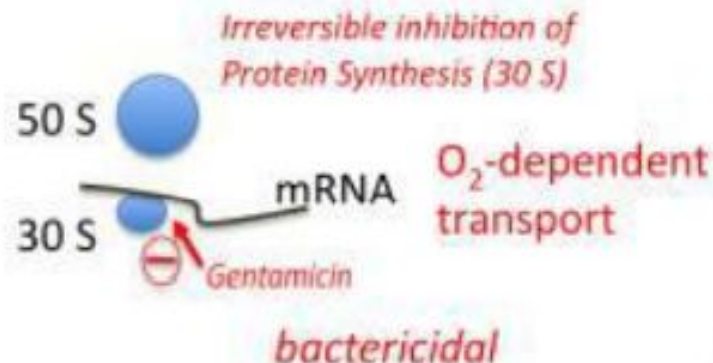
Skin infections
(topical)

UTIs
GI/GU procedures

Pharmacokinetics:

- Vd = ECS (25% body weight)
- adjust maintenance dosing
based upon [creatinine]
- plasma monitoring necessary

Mechanism:



Adverse Effects:

- Ototoxicity (rev vestibular
& irrev auditory)
- Nephrotoxicity (rev)
- NMJ blockade (high dose)
- Pregnancy Cat C (8th nerve)

6. GOLONGAN MAKROLIDA

- Efektifitas : gram (+/-), Atypical organism (klamidia, riketsia & mikoplasma), alternative alergi penisilin, Pneumonia
- Note :
 - Atypical organism adalah organisme yang tidak dapat dikalahkan oleh antibiotik biasa.
 - Hanya 2 golongan yang mampu membasminya yaitu Makrolida dan Tetrasiklin.
- Contoh : Eritromisin, Azitromisin, Klaritromisin, Roksitromisin, Spiramisin. (akhiran -misin)

Rute :

Oral, intravena

Mekanisme :

Berikatan dengan 50s dan memblok tahap translokasi pada proses sintesis protein

Sifat : Bakteriostatik

Efek samping :

- Mual, muntah, diare, nyeri abdomen
- Hepatotoksik
- Eritromisin adalah inhibitor P450 (perhatikan interaksi obatnya)

Routes:

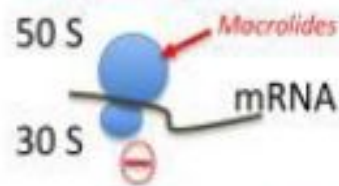


Pharmacokinetics:

- Azithromycin $t_{1/2}$ = 3 days
- a 1 g dose provides 7 day coverage
- common therapy consists of 500 mg loading dose & 250 mg/day for 4 more days.

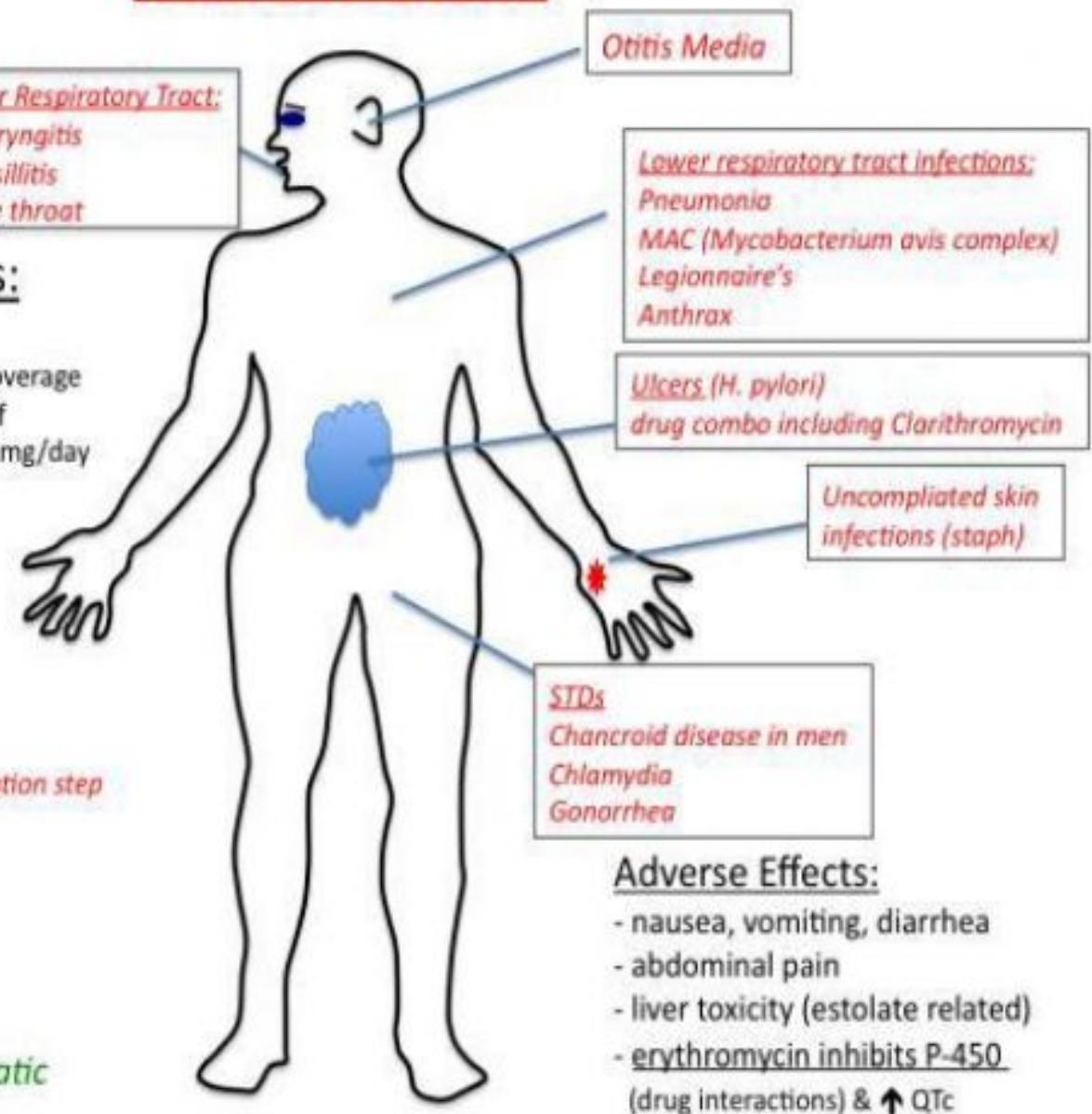
Mechanism:

Bind to 50S & block translocation step in protein synthesis



bacteriostatic

Macrolide Uses



7. GOLONGAN KUINOLON

- Efektifitas : Gram (+/-) , Enterobacteriaceae, Pseudomonas
- Contoh : Asam nalidiksat, Asam pipemidat, Siprofloksasin, Ofloksasin, Norfloksasin , Pefloksasin, Fleroksasin, Sparfloksasin, Levofloksasin

8. GOLONGAN SULFONAMID & TRIMETOPRIM

- Efektifitas : Gram (+/-), resistensi ??
- Contoh : Trimetoprim, Kotrimoksazol, Sulfadiazin, Sulfadimidin, Sulfasalazin

9. GOLONGAN ANTIBIOTIK LAIN

a) AMFENIKOL

Efektifitas : Gram (+/-), Mikoplasma, dll

ESO : Anemia aplastika (Salmonella typhi & H influenzae)

Contoh : Kloramfenikol, Tiamfenikol

b) LINKOSAMID

Efektifitas : Gram (+) & Bakteroides

Antistap : Pada infeksi tulang & sendi, PMC ??

Contoh : Klindamisin, Linkomisin

c) VANKOMISIN

Efektifitas : Gram (+)

d) POLIMIKSIN

Efektifitas : Gram (-),

Pseudomonas

Contoh : Kolistin

ANTIBIOTIK	BAKTERI AEROB														
	GRAM (+)						GRAM (-)								
	SA	MR SA	SE	MR SE	St	Ec	E Coli	KP	EB	PM	SM	PA	HI	HI*	
Penisilin	+	-	+	-	++++	++	-	-	-	-	-	-	-	-	
Ampisilin	+	-	+	-	++++	++	++	-	-	+++	-	-	++++	-	
Tikarsilin	+	-	+	-	++++	-	++	+	++	+++	+++	++	+++	-	
Co-amoxiclav	++++	+	++++	-	++++	++	+++	++	-	++++	-	-	++++	++++	
Cefazolin	++++	-	++++	-	++++	-	+++	+++	-	++++	-	-	+	-	
Cefuroxime	++++	-	++++	-	++++	-	+++	+++	+	++++	+	-	++++	++++	
TGC	+++	-	++	-	++++	-	++++	++++	+	++++	++++	+	++++	++++	
Cefepime	+++	-	++++	-	++++	-	++++	++++	++++	++++	++++	++++	++++	++++	
Cotrimoxazol	++++	+++	++++	+	++++	+	+++	+++	++++	++++	+++	-	++++	++++	
Eritromisin	++	-	+	-	++++	-									
Gentamisin							++++	++++	++++	++++	++++	+++	++	++	
Ciprofloksazin	+++	++	+++	++	+	+	++++	++++	++++	++++	++++	+++	++++	++++	
Fluoroquinolon	++++	++	+++	++	++++	++	++++	++++	++++	++++	++++	++++	++++	++++	
Imipenem	++++	+	++++	-	++++	++	++++	++++	++++	+++	++++	++++	++++	++++	
Aztreonam	-	-	-	-	-	-	++++	++++	+	++++	++++	+++	++++	++++	
Vancomisin	++++	++++	++++	++++	+++	+++									

ANTIBIOTIK	BAKTERI AN-AEROB				KETERANGAN
	BF	P	PS	C	
Penisilin	+	-	+	-	SA = Staphylococcus aureus
Ampisilin	+	-	+	-	SE = Staphylococcus epidermidis
Tikarsilin	+	-	+	-	St = Streptococci
Co-amoxiclav	++++	+	++++	-	Ec = Enterococci
Cefazolin	++++	-	++++	-	KP = Klebsiella pneumoniae
Cefuroxime	++++	-	++++	-	EB = Enterobacteriaceae
TGC	+++	-	++	-	PM = Proteus Mirabilis
Cefepime	+++	-	++++	-	SM = Serratia marcescens
Cotrimoxazol	++++	+++	++++	+	PA = Pseudomonas aeruginosa
Eritromisin	++	-	+	-	HI = Haemophilus Influenzae
Gentamisin					BF = Bacteroides fragilis
Ciprofloksazin	+++	++	+++	++	P = Peptococcus
Fluoroquinolon	++++	++	+++	++	PS = Peptostreptococcus
Imipenem	++++	+	++++	-	C = Clostridia
Aztreonam	-	-	-	-	
Vancomisin	++++	++++	++++	++++	

Ket : - = tidak memiliki aktivitas

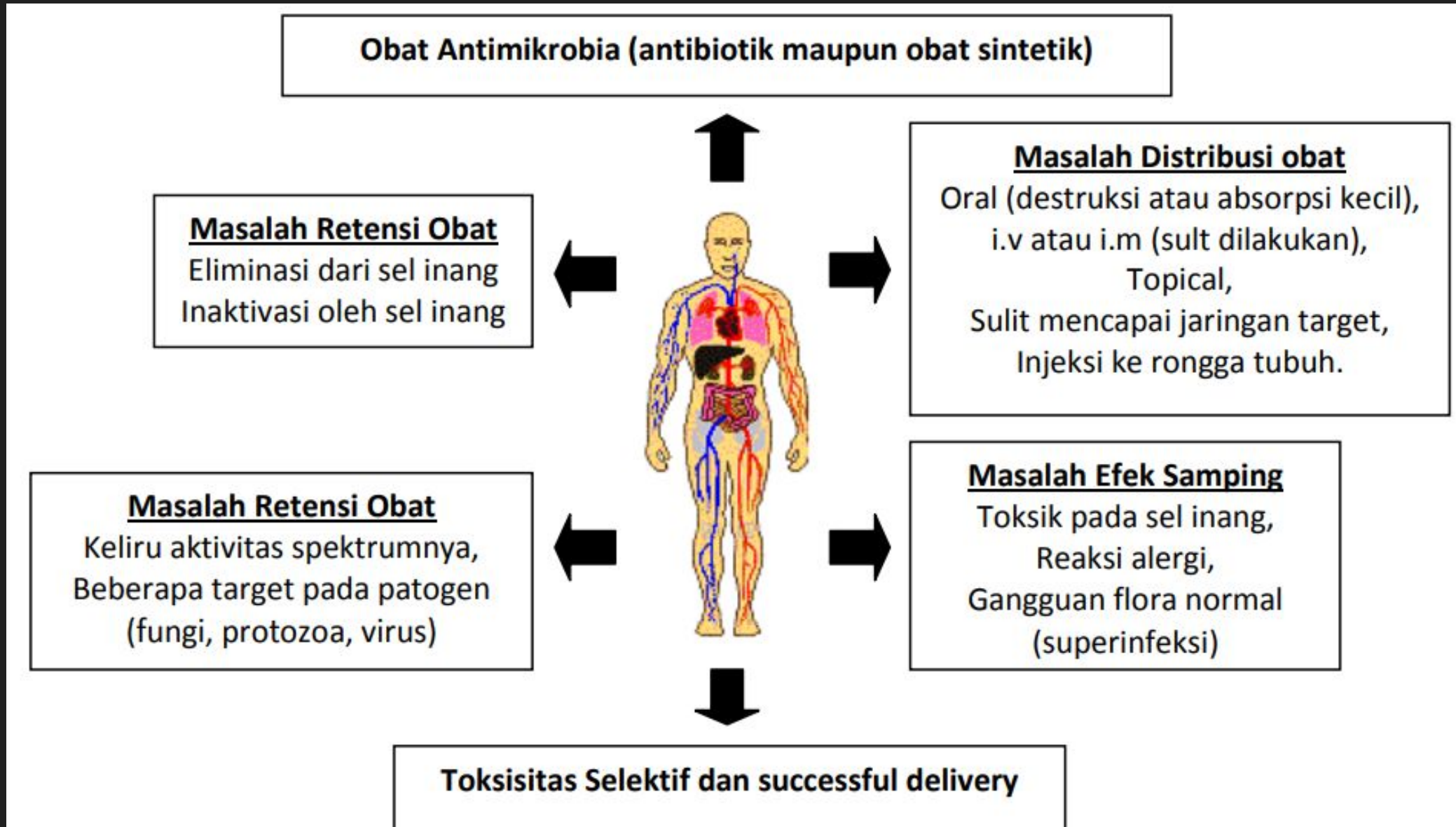
+ = aktivitasnya kecil

++ = aktivitasnya cukup baik

+++ = aktivitasnya baik

++++ = aktivitasnya sangat baik

Kompleksitas terapi antimikroba



Interaksi Antibiotik dengan Obat lain

ANTIBIOTIK	OBAT LAIN	MEKANISME AKSI/EFEK	PENGATASAN
Aminoglikosida	Nefrotoksik atau ototoksik (misal: Amphotericin B, Cisplatin, Cyclosporine, Furosemid, NSAIDs, Vancomycin)	Adverse effect ditingkatkan (<i>additive</i>)	Monitor konsentrasi Aminoglikosida dan fungsi renal
Kloramfenikol	Fenitoin, tolbutamid, etanol	Menurunkan metabolisme obat lain	Monitor fenitoin, gula darah
Isoniazid	Carbamazepin, fenitoin	Menurunkan metabolisme obat lain (mual, muntah, nystagmus, ataksia)	Monitor obat
Makrolida	Digoksin	Menurunkan bioavailabilitas dan metabolisme digoksin	Monitor digoksin hindari jika memungkinkan
	Teofilin	Menurunkan metabolisme teofilin	Monitor teofilin
Penisilin dan sefalosporin	Probenesid, aspirin	Penghambatan ekskresi β -laktam	Gunakan jika konsentrasi β -laktam jangka panjang sangat digunakan
Ciprofloxacin/norfloxacin	Teofilin	Menurunkan metabolisme teofilin	Monitor teofilin
Quinolon	Antiarritmia kelas I-a dan III	Menaikkan interval Q-T	Hindari
	Kation multivalen (antasida, iron sucralfate, zinc, vitamin)	Menurunkan absorpsi quinolon	Pemberian terpisah dengan selang waktu 2 jam
Sulfonamide	Sulfonilurea, fenitoin, warfarin	Menurunkan metabolisme obat lain	Monitor gula darah, PT
Tetrasiklin	Antasida, iron kalsium, sucralfate	Menurunkan absorpsi tetrasiklin	Pemberian terpisah dengan selang waktu 2 jam
	Digoksin	Menurunkan bioavailabilitas dan metabolisme digoksin	Monitor digoksin, hindari jika dimungkinkan

Keamanan Antibiotik Pada Wanita Hamil

KATEGORI	CONTOH ANTIBIOTIK
A	
B	Amoksisilin, Ampisilin, Sefalekssin, Makrolida
C	Cotrimoksazol, Ciprofloksazin
D	Aminoglikosida, Tetrasiklin
X	

nOte :

Antibiotik hanya dikategorikan 3 golongan pada ibu hamil, yaitu :

1) Kategori B

Pada kategori ini termasuk golongan Penisilin, golongan Sefalosporin dan golongan Makrolida.

2) Kategori C

Pada kategori ini terdapat antibiotik Cotrimoksazol dan Ciprofloksazin. (*untuk bantu mengingat, kata kuncinya disini adalah huruf "C")

3) Kategori D

Termasuk di dalamnya golongan aminoglikosida dan tetrasiklin. Dimana seperti kita ketahui tetrasiklin mampu menembus sawar plasenta dan akan mengganggu pertumbuhan tulang dan gigi janin.

Efek Samping Utama Antibiotik

No	ANTIBIOTIK	EFEK SAMPING
1	Golongan aminoglikosida	Kerusakan pada organ pendengar dan kerusakan pada ginjal pada pemakaian jangka panjang
2	Golongan sefalosporin	Efek pada gastrointestinal (mual, muntah, diare)
3	Golongan miscellaneous β laktam	Gangguan lambung, reaksi kulit
4	Kloramfenikol	<i>Gray baby syndrom</i> pada neonatus
5	Golongan makrolida	Gangguan gastrointestinal
6	Golongan penisillin	Reaksi alergi akibat hipersensitif
7	Golongan quinolon	Gangguan gastrointestinal, ruam kulit, efek neurologi
8	Golongan sulfonamid	Sakit kepala, reaksi alergi, agranulositosis dan anemia hemolitik pada penggunaan jangka panjang
9	Tetrasiklin	Gangguan lambung-usus, membentuk kompleks dengan kalsium-fosfor sehingga mengganggu struktur kristal dari gigi pada janin dan anak-anak yang sedang tumbuh, fotosensitivitas

IMUNISASI / VAKSINASI



DEFINISI



- Vaksin (dari kata vaccinia, penyebab infeksi cacar sapi yang ketika diberikan kepada manusia, akan menimbulkan pengaruh kekebalan terhadap cacar),
- Bahan antigenik yang digunakan untuk menghasilkan kekebalan aktif terhadap suatu penyakit sehingga dapat mencegah atau mengurangi pengaruh infeksi organisme alami atau "liar."



- Salah satu caranya mencegah penyakit.
- Vaksin mengandung **antigen** yang sama atau **bagian dari antigen** yang menyebabkan penyakit, tetapi antigen dalam vaksin adalah dalam keadaan **sudah dibunuh atau sangat lemah**.



- Vaksinasi sangat membantu untuk mencegah **penyakit-penyakit infeksi yang menular** baik karena virus atau bakteri, misalnya **polio, campak, difteri, pertusis (batuk rejan), rubella (campak Jerman), meningitis, tetanus, Haemophilus influenzae tipe b (Hib), hepatitis, dll.**



- setiap anak lahir dengan sistem kekebalan penuh terdiri dari sel, kelenjar, organ, dan cairan yang berada di seluruh tubuh nya untuk melawan bakteri dan virus menyerang.
- Sistem kekebalan mengenali kuman yang memasuki tubuh sebagai penjajah “asing”, atau antigen, dan menghasilkan zat protein yang disebut **antibodi** untuk melawan mereka.



- Jutaan antibodi □ menyerang antigen □ ketika antigen / “serangan” sudah terlalu banyak □ tubuh tidak dapat bertahan □ sakit
- Sel memori □ sel yang terlibat dalam produksi antibodi, □ mengingat antigen asli □ mempertahankan diri ketika antigen yang sama mencoba menginfeksi kembali □ **IMUNITAS**

MENGAPA VAKSIN PENTING ?



- bayi baru lahir kebal terhadap banyak penyakit karena mereka memiliki antibodi yang mereka dapatkan dari ibu □ namun, durasi imunitas ini berlangsung hanya sekitar sebulan sampai setahun

KAPAN VAKSIN DIBERIKAN ?



- Vaksin bekerja dengan baik ketika mereka diberikan pada usia tertentu.
- Vaksin campak diusahakan diberikan pada anak paling tidak 1 tahun
- Vaksin DPT diberikan secara berkala dalam suatu periode waktu

MACAM KEKEBALAN



- AKTIF :
TUBUH TERPAJAN → MEMBUAT
- PASIF :
TUBUH LANGSUNG MEMAKAI

SISTEM KEKEBALAN

KEKEBALAN PASIF

- DAPAT TERJADI DENGAN PEMBERIAN ANTIBODY YANG BERASAL DARI HEWAN ATAU MANUSIA KE MANUSIA LAIN.
- KEKEBALAN PASIF MEMBERI PERLINDUNGAN TERHADAP BEBERAPA INFEKSI TETAPI SIFATNYA SEMENTARA , KADAR ANTIBODY AKAN BERKURANG SETELAH BEBERAPA MINGGU ATAU BULAN DAN PENERIMA TIDAK LAGI KEBAL TERHADAP PENYAKIT TERSEBUT
- KEKEBALAN PASIF YANG PALING UMUM ADALAH BAYI YANG MENDAPAT KEKEBALAN DARI IBUNYA, ANTIBODY INI AKAN MELINDUNGI BAYI DARI PENYAKIT TERTENTU SAMPAI BAYI USIA 1 BULAN SAMPAI 1 TAHUN.

KEKEBALAN AKTIF

- TERJADI SEBAGAI AKIBAT STIMULASI IMUNOLOGI YANG MENGHASILKAN ANTIBODY DAN KEKEBALAN SELULAR.
- BIASANYA KEKEBALAN BERTAHAN UNTUK BEBERAPA TAHUN DAN SERING SAMPAI SEUMUR HIDUP.
- SALAH SATU CARA UNTUK MENDAPATKAN KEKEBALAN AKTIF ADALAH BILA SESEORANG MENDERITA SUATU PENYAKIT , SETELAH SEMBUH MENJADI KEBAL TERHADAP PENYAKIT TERSEBUT SAMPAI SEUMUR HIDUP.
- CARA LAIN UNTUK MENDAPATKAN KEKEBALAN AKTIF YAITU DENGAN IMUNISASI.

MACAM VAKSINASI



- Untuk anak
- Untuk dewasa
- Untuk lansia

JENIS



- Hepatitis B
- *Hemophilis influenza* tipe B (Hib)
- Polio
- Diphteri, pertussis (batuk rejan) dan tetanus
- Pneumokokus □ mencegah infeksi saluran nafas
- Rotavirus □ mencegah infeksi saluran cerna
- Hepatitis A



- Influenza
- MMR (*measles, mumps* and rubella) □ mencegah sakit campak, gondongan, campak jerman
- Varicella □ mencegah cacar air
- Meningokokokus □ mencegah infeksi meningitis
- Virus Human Papiloma □ mencegah kanker serviks

IMUNISASI DASAR PADA ANAK



- BCG
- HEPATITIS B
- DPT
- POLIO
- CAMPAK

EFEK SAMPING VAKSINASI



- Vaksin terhadap **difteri, tetanus, batuk rejan, polio dan Hib** □ menyebabkan area merah dan bengkak di tempat vaksinasi atau demam
- **vaksin pneumokokus** □ reaksi di tempat suntikan (seperti rasa sakit, nyeri, kemerahan atau bengkak), demam dan lekas marah mungkin juga mengantuk.
- Vaksin MMR --> dingin, reaksi kulit, demam atau kelenjar ludah membengkak.



- Vaksin Meningiitis : beberapa pembengkakan dan kemerahan di tempat suntikan diberikan dan demam
- **Efek samping** umum lainnya antara lain : sakit kepala, sakit otot atau sendi, kemerahan dan bengkak di tempat suntikan, demam, pusing iritasi kulit, seperti gatal dan ruam, gangguan usus, seperti mual dan muntah, diare, sakit perut.

IMUNISASI DASAR ANAK



- Imunisasi BCG (Bacillus Calmette-Guerin) sekali untuk mencegah penyakit Tuberkulosis. Diberikan segera setelah bayi lahir di tempat pelayanan kesehatan atau mulai 1 (satu) bulan di Posyandu.
- Imunisasi Hepatitis B sekali untuk mencegah penyakit Hepatitis B yang ditularkan dari ibu ke bayi saat persalinan.
- Imunisasi DPT-HB (tiga) kali untuk mencegah penyakit Difteri, Pertusis (batuk rejan), Tetanus dan Hepatitis B. Imunisasi ini pertama kali diberikan saat bayi berusia 2 (dua) bulan. Imunisasi berikutnya berjarak waktu 4 minggu. Pada saat ini pemberian imunisasi DPT dan Hepatitis B dilakukan bersamaan dengan vaksin DPT-HB.



- Imunisasi Polio diberikan 4 (empat) kali dengan jeda waktu (jarak) 4 minggu. Imunisasi polio untuk memberikan kekebalan terhadap penyakit polio
- Imunisasi campak untuk mencegah penyakit campak. Imunisasi campak diberikan saat bayi berumur 9 bulan.



JADWAL IMUNISASI 2011-2012 REKOMENDASI IKATAN DOKTER ANAK INDONESIA

JENIS VAKSIN	UMUR PEMBERIAN																	
	BULAN												TAHUN					
	L H R	1	2	3	4	5	6	7	8	9	12	15	18	24	3	5	6	7
	R																	8
BCG			1															9
HEPATITIS B	1	2				3												10
POLIO	0		1		2		3								4		6	12
DTP			1		2		3							4		5		6(Td)
CAMPAK										1							2	7(Td)
Hib			1		2		3						4					
PCV			1		2		3				4							
ROTAVIRUS			1		2		3											
INFLUENZA																		
VARISELA																		
MMR																		
TIFOID																		
HEPATITIS A																		
HPV																		

DIBERIKAN SETIAP TAHUN

1x

1

2

ULANGAN TIAP 3 TAHUN

2x, INTERVAL 6-12 BULAN

3x

SAMPAI BERAPA LAMA PERLINDUNGAN VAKSINASI BERTAHAN



- *Difteri dan tetanus*: setidaknya selama 10 tahun, atau mungkin lebih lama.
- *Batuk rejan*: setidaknya selama tiga tahun. Namun, ini masih sedang dipelajari.
- *Meningitis*: perlindungan jangka panjang.
- *Polio*: perlindungan seumur hidup.
- *Campak, mumps dan rubella* (campak Jerman): menawarkan perlindungan yang tahan lama yang sangat mungkin seumur hidup.



- *Meningitis C*: menawarkan perlindungan yang tahan lama yang sangat mungkin seumur hidup.
- *Kanker serviks*: studi menunjukkan bahwa perlindungan berlangsung setidaknya selama lima tahun. Penelitian lebih lanjut sedang berlangsung untuk membuktikan apakah *booster* akan dibutuhkan.

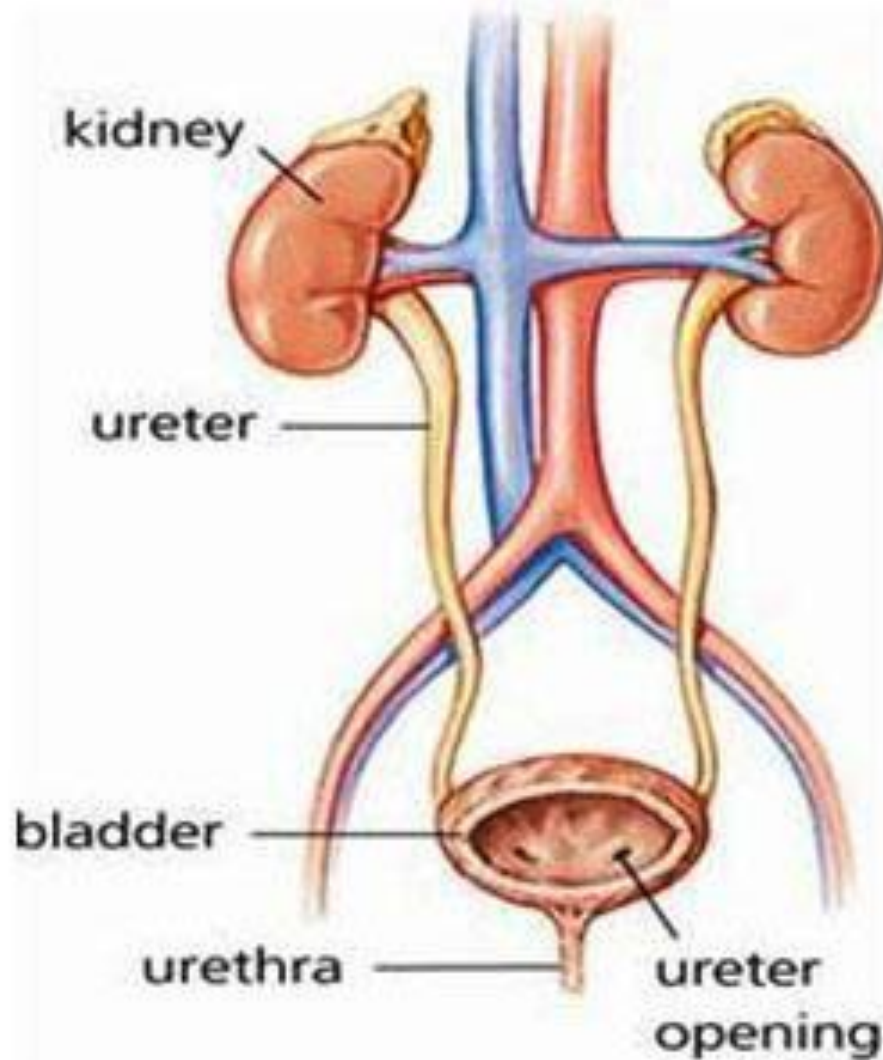


TERIMA KASIH

Infeksi Saluran Kemih

Urinary Tract Infections

FARMAKOTERAPI



ANATOMI KANDUNG KEMIH

Adalah suatu keadaan adanya infasi mikroorganisme pada saluran kemih

Infeksi saluran kemih (ISK) didefinisikan sebagai adanya mikroorganisme dalam urin yang tidak dapat dijelaskan melalui kontaminasi.

Organisme memiliki potensi untuk menyerang jaringan saluran kemih dan struktur yang berdekatan.

DEFINISI

- **Infeksi saluran bawah** meliputi
 1. sistitis (kandung kemih),
 2. uretritis (uretra),
 3. prostatitis (kelenjar prostat), dan
 4. epididimitis.
- **Infeksi saluran atas** melibatkan ginjal dan disebut sebagai pielonefritis.

Jenis ISK berdasarkan lokasi infeksi

- **ISK tanpa komplikasi** tidak berhubungan dengan kelainan struktural atau neurologis yang dapat mengganggu aliran normal urin atau mekanisme berkemih.
- **ISK terkomplikasi** adalah hasil dari lesi predisposisi saluran kemih, seperti kelainan kongenital atau distorsi saluran kemih, batu, kateter, hipertrofi prostat, obstruksi, atau defisit neurologis yang mengganggu aliran urin normal dan pertahanan saluran kemih.

Jenis ISK

- Dua atau lebih ISK yang terjadi dalam 6 bulan atau tiga atau lebih dalam 1 tahun, ditandai dengan episode simtomatik multipel dengan periode asimtomatik yang terjadi di antara episode-episode ini.
- Infeksi ini disebabkan oleh infeksi ulang atau kambuh. Infeksi ulang disebabkan oleh organisme yang berbeda dan merupakan penyebab utama ISK berulang.
- Kambuh merupakan perkembangan infeksi berulang yang disebabkan oleh organisme awal yang sama.

ISK rekuren

ISK dapat didapat melalui tiga kemungkinan jalur: jalur asendens, hematogen, atau limfatik.

- **Ascending**

- ✓ Masuknya mikroorganisme dalm kandung kemih
- ✓ Naiknya bakteri dari kandung kemih ke ginjal

- **Hematogen (aliran darah)**

pasien yang system imunnya rendah sehingga mempermudah penyebaran infeksi secara hematogen

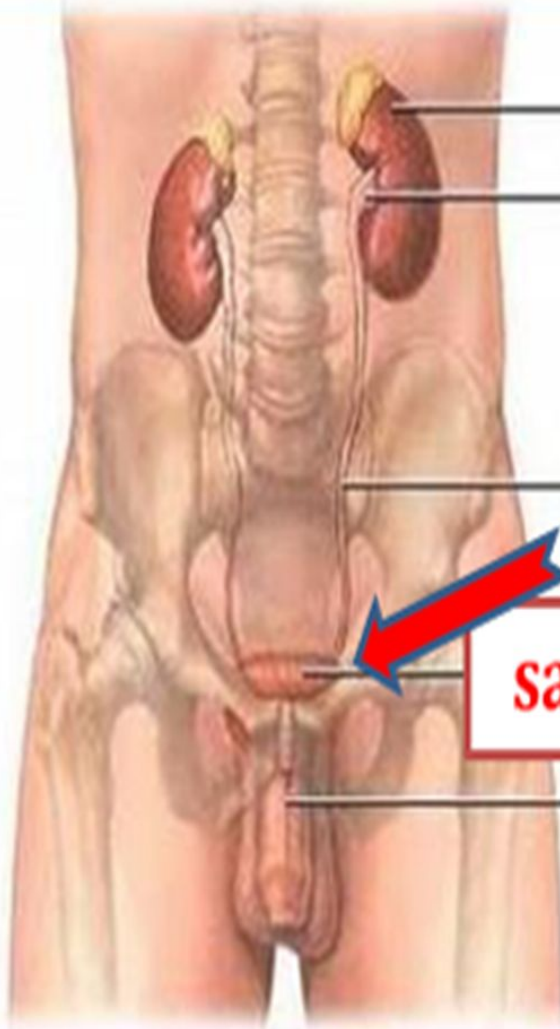
Jalur ISK

- Pria
 - Tidak disunat
 - Usia □ terjadi hiperplasia prostat
- Wanita
 - Hubungan seksual
 - Penggunaan kontrasepsi (diafragma dan spermisida)
 - DM

FAKTOR RESIKO

Laki - laki

Wanita



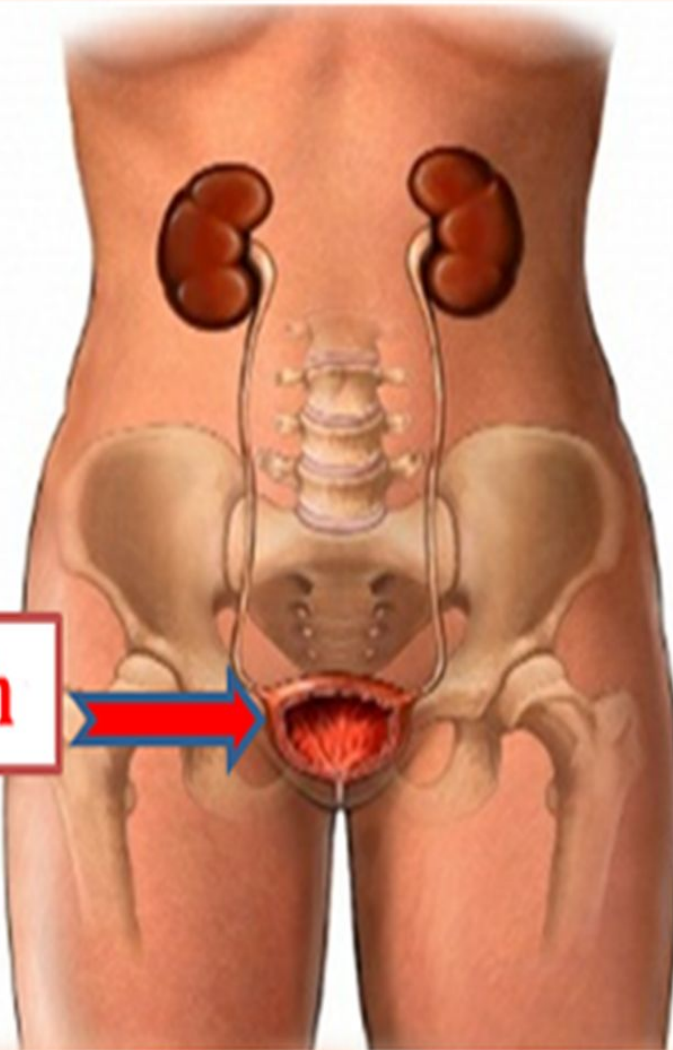
Ginjal

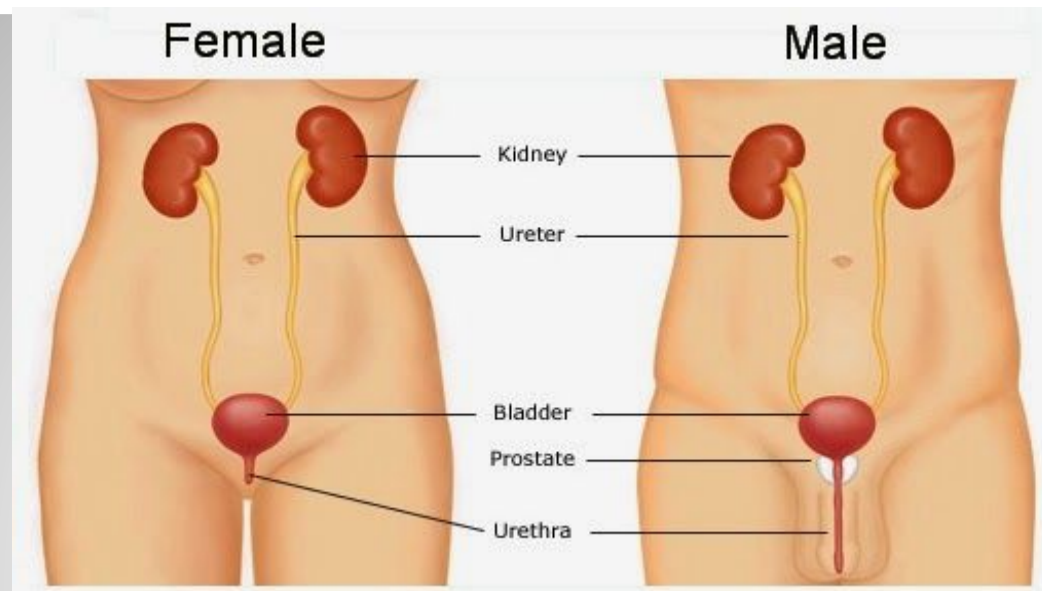
Pelvis renalis

Infeksi

saluran kemih

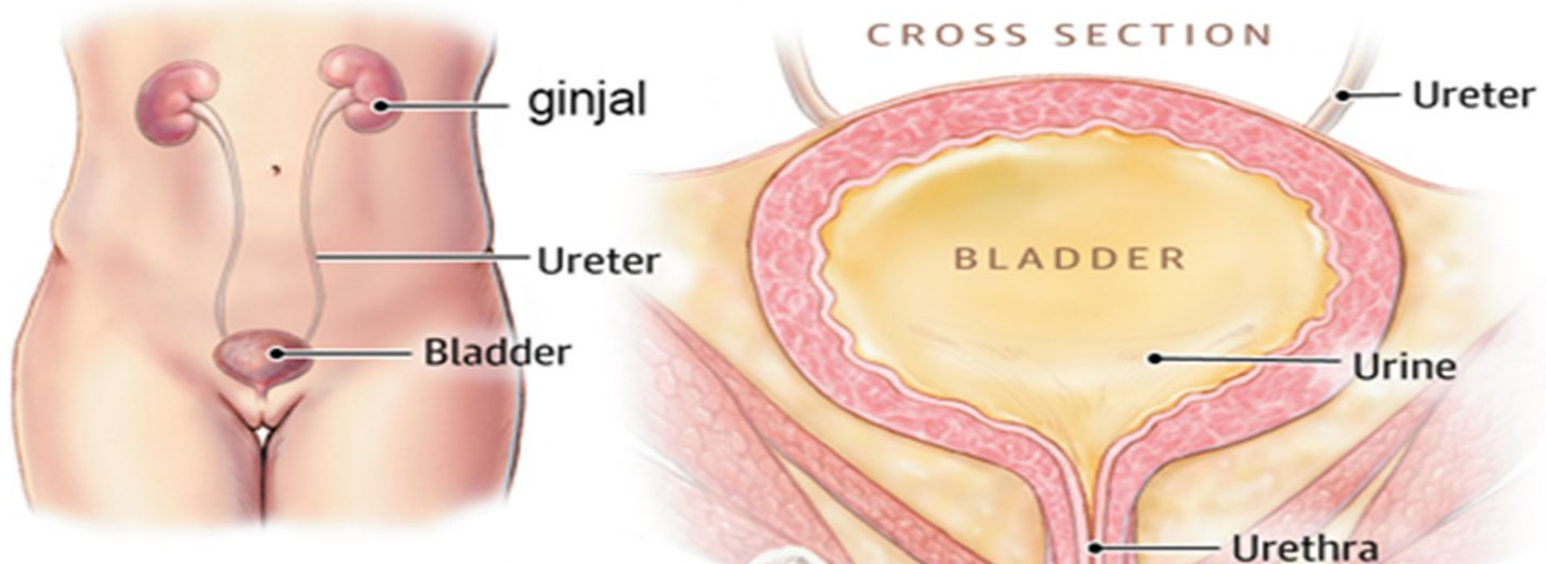
Uretra



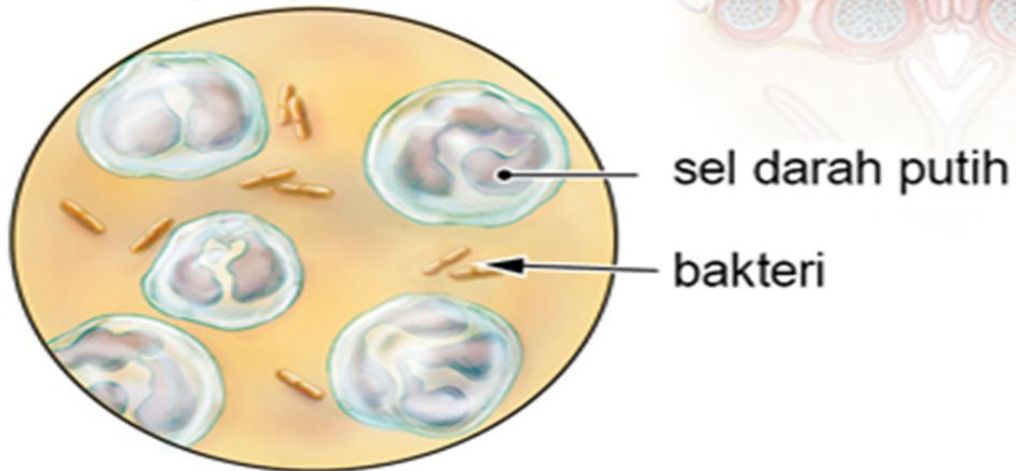


Saluran kemih

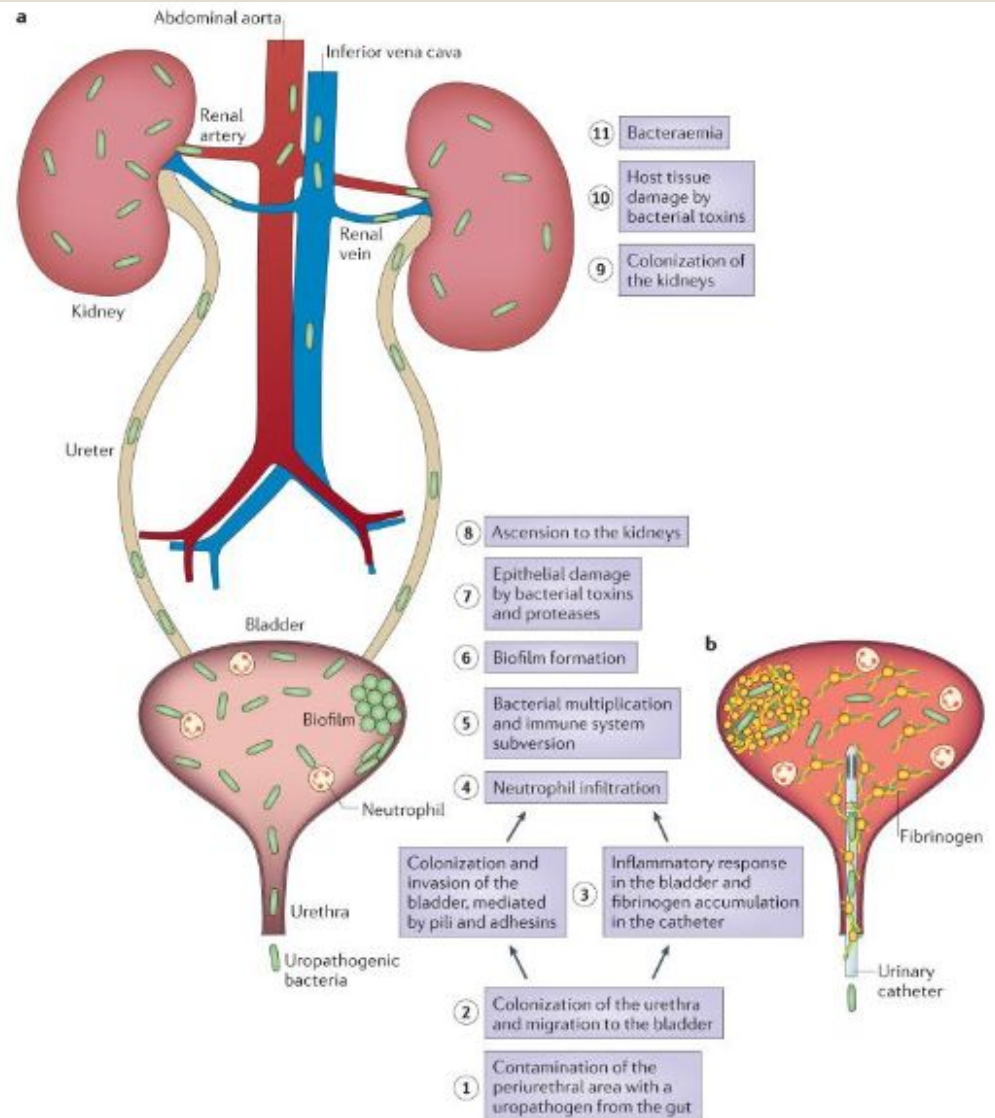
Anatomi Saluran Kemih



Urine yang terinfeksi



- Bakteri penyebab ISK biasanya berasal dari flora usus pejamu.



Gambar 1. Patogenesis dan patofisiologi dari ISK.⁴

PATOFISIOLOGI

- Bakteri uropatogenik yang melekat pada sel uroepitelial □ merobek lapisan *glucoprotein mucin layer* (yang berfungsi anti bakteri) □ membentuk koloni dan menembus epitel □ peradangan □ dapat naik ke ureter dan sampai ginjal melalui lapisan tipis cairan (*films of fluids*).
- Bila hanya vesica urinaria yang terinfeksi □ iritasi dan spasme otot polos □ *urgency, frequency, dysuri*

PATOFISIOLOGI

- Pada wanita, panjang uretra yang pendek dan kedekatannya dengan daerah perirektal memungkinkan terjadinya kolonisasi pada uretra.
- Bakteri kemudian diyakini memasuki kandung kemih dari uretra.
- Setelah di kandung kemih, organisme berkembang biak dengan cepat dan dapat naik ureter ke ginjal.

ISK pada wanita

Tiga faktor menentukan perkembangan ISK:

- ukuran inokulum,
- virulensi mikroorganisme, dan
- kompetensi mekanisme pertahanan inang alami.

- *Escherichia Coli*: 90 % penyebab ISK *uncomplicated (simple)*
- *Pseudomonas, Proteus, Klebsiella* : penyebab ISK *complicated*
- *Enterobacter, staphylococcus epidemidis, enterococci*, dan-lain-lain.

MO PENYEBAB ISK

- Nyeri panggul
- Nyeri abdomen
- Simptom sistemik
demam, mual muntah, rasa tidak enak badan, sakit kepala

**GEJALA DAN TANDA PADA ISK
BAGIAN ATAS**

- *Dysuria* (nyeri dan sukar saat berkemih)
- Frekuensi (sering kencing tanpa peningkatan volume harian)
- *Nocturia* (berkemih pada malam hari)
- *Urgency* (selalu ingin kencing)

GEJALA DAN TANDA ISK BAGIAN BAWAH

- Urin bau dan keruh
- Haematuria
- Demam

GEJALA LAIN

Pyelonephritis akut. □ **ISK atas**

- Pada tipe ini, infeksi pada ginjal mungkin terjadi setelah meluasnya infeksi yang terjadi pada kandung kemih. Infeksi pada ginjal dapat menyebabkan rasa sakit pada punggung atas dan panggul, demam tinggi, gemetar akibat kedinginan, serta mual atau muntah.

Cystitis. □ **ISK atas**

- Inflamasi atau infeksi pada kandung kemih dapat menyebabkan rasa tertekan pada pelvis, ketidaknyamanan pada perut bagian bawah, rasa sakit pada saat urinasi, dan bau yang menyengat dari urin.

Uretritis □ **ISK bawah**

- Inflamasi atau infeksi pada uretra menimbulkan rasa terbakar pada saat urinasi. Pada pria, uretritis dapat menyebabkan gangguan pada penis.

GEJALA SPESIFIK

- Sisa urin dalam kandung kemih yang meningkat akibat pengosongan kandung kemih yang tidak lengkap atau kurang efektif.
- Mobilitas menurun
- Nutrisi yang sering kurang baik
- System imunnitas yng menurun
- Adanya hambatan pada saluran urin
- Hilangnya efek bakterisid dari sekresi prostat.

Pasien lanjut usia sering tidak mengalami gejala kencing yang spesifik, tetapi mereka akan datang dengan perubahan status mental, perubahan kebiasaan makan, atau gejala GI.

ISK PADA LANSIA

- Diarrhea
- Menangis tanpa henti yang tidak dapat dihentikan dengan usaha tertentu (misalnya: pemberian makan, dan menggendong)
- Kehilangan nafsu makan
- Demam
- Mual dan muntah
- Pada anak – anak, mengompol juga menandakan gejala adanya infeksi saluran kemih.
- Lemah
- Adanya rasa sakit pada saat berkemih.

ISK PADA ANAK

- Gejala saja tidak dapat diandalkan untuk diagnosis ISK bakteri.
- Kunci untuk diagnosis ISK adalah kemampuan untuk menunjukkan sejumlah besar mikroorganisme yang ada dalam spesimen urin yang sesuai untuk membedakan kontaminasi dari infeksi.

Diagnosis ISK

menunjukkan jumlah bakteri yang signifikan pada spesimen urin

- **Urinalisis**

- Leukosuria atau piuria: merupakan salah satu petunjuk penting adanya ISK. Leukosuria positif bila terdapat lebih dari 5 leukosit/lapang pandang besar (LPB) sediment air kemih
- Hematuria: hematuria positif bila terdapat 5-10 eritrosit/LPB sediment air kemih. Hematuria disebabkan oleh berbagai keadaan patologis baik berupa kerusakan glomerulus ataupun urolitiasis.

- **Bakteriologis**

- Mikroskopis
- Biakan bakteri

- **Kultur urine** untuk mengidentifikasi adanya organisme spesifik

- **Hitung koloni**: hitung koloni sekitar 100.000 koloni per milliliter urin dari urin tampung aliran tengah atau dari specimen dalam kateter dianggap sebagai criteria utama adanya infeksi.

DIAGNOSIS

TABLE 114–1. Diagnostic Criteria for Significant Bacteriuria

$\geq 10^2$ CFU coliforms/mL or $\geq 10^5$ CFU noncoliforms/mL in a symptomatic female
$\geq 10^3$ CFU bacteria/mL in a symptomatic male
$\geq 10^5$ CFU bacteria/mL in asymptomatic individuals on two consecutive specimens
Any growth of bacteria on suprapubic catheterization in a symptomatic patient
$\geq 10^2$ CFU bacteria/mL in a catheterized patient

Etiologi

- Terjadi pada saluran genito urinary (GU) yang abnormal
- Pasien dengan penyakit GU lainnya
- Pasien dengan pemasangan kateter

ISK COMPLICATED

- Proteus sp
- Klebsiella sp
- Enterobacter sp
- Pseudomonas
- Staphylococcus

Mikroorganisme Penyebab

- Terjadi pada Genituo urinary yang normal
- MO Penyebab paling sering □
 - E. Coli
 - Staphylococcus

ISK UNCOMPLICATED

- RELAPS -> timbulnya enfeksi lagi dengan penyebab organisme yang sama dengan infeksi awal
- REINFEKSI □ disebabkan organisme baru yang berbeda dengan organisme awal

RELAPS DAN REINFEKSI

Tujuan pengobatan ISK adalah

- ❑ untuk mencegah atau mengobati konsekuensi sistemik dari infeksi,
- ❑ membasmi organisme yang menyerang,
- ❑ mencegah terulangnya infeksi.

Tujuan terapi

- Penatalaksanaan pasien ISK meliputi
 - evaluasi awal,
 - pemilihan agen antibakteri dan
 - durasi terapi,
 - serta evaluasi tindak lanjut.
- Pemilihan awal agen antimikroba (antibiotic) untuk pengobatan ISK terutama didasarkan pada
 - tingkat keparahan
 - tanda dan gejala yang muncul,
 - tempat infeksi, dan
 - apakah infeksi ditentukan sebagai komplikasi atau tidak.

Penatalaksanaan

- Kemampuan untuk membasmi bakteri dari saluran kemih berhubungan langsung dengan sensitivitas organisme dan konsentrasi agen antimikroba yang dapat dicapai dalam urin.
- Penatalaksanaan terapeutik ISK paling baik dilakukan dengan terlebih dahulu mengkategorikan jenis infeksi:
 - ✓ sistitis akut tanpa komplikasi,
 - ✓ abakteriuria simtomatik,
 - ✓ bakteriuria asimtomatik,
 - ✓ ISK terkomplikasi,
 - ✓ infeksi berulang, atau
 - ✓ prostatitis.

PENGOBATAN FARMAKOLOGI

ANTIBIOTIK YANG DAPAT DIGUNAKAN PADA ISK

Agent	Comments
Oral Therapy	
Sulfonamides	These agents generally have been replaced by more agents due to resistance.
Trimethoprim-sulfamethoxazole (TMP-SMX)	This combination is highly effective against most aerobic enteric bacteria except <i>Pseudomonas aeruginosa</i> . High urinary tract tissue levels and urine levels are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections.
Penicillins	
Ampicillin	Ampicillin is the standard penicillin that has broad-spectrum activity. Increasing <i>Escherichia coli</i> resistance has limited amoxicillin use in acute cystitis. Drug of choice for enterococci sensitive to penicillin.
Amoxicillin-clavulanic acid	Amoxicillin-clavulanate is preferred for resistance problems. Carbenicillin indanyl is only indicated for the treatment of urinary tract infections.
Carbenicillin indanyl	
Cephalosporins	
Cephalexin	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. They may be useful in cases of resistance to amoxicillin and trimethoprim-sulfamethoxazole. These agents are not active against enterococci.
Cephadrine	
Cefaclor	
Cefadroxil	
Cefuroxime	
Cefixime	
Cefzil	
Cefpodoxime	
Tetracyclines	
Tetracycline	These agents have been effective for initial episodes of urinary tract infections; however, resistance develops rapidly, and their use is limited. These agents also lead to candidal overgrowth. They are useful primarily for chlamydial infections.
Doxycycline	
Minocycline	
Fluoroquinolones	
Ciprofloxacin	The newer quinolones have a greater spectrum of activity, including <i>P. aeruginosa</i> . These agents are effective for pyelonephritis and prostatitis. Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations.
Norfloxacin	
Levofloxacin	
Nitrofurantoin	This agent is effective as both a therapeutic and prophylactic agent in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy. Adverse effects may limit use (GI intolerance, neuropathies, pulmonary reactions).
Azithromycin	Single-dose therapy for chlamydial infections.
Methanamine hippurate-mandalate	These agents are reserved for prophylactic therapy or suppressive use between episodes of infection.
Fosfomycin	Single-dose therapy for uncomplicated infections.

Parenteral Therapy

Aminoglycosides

Gentamicin
Tobramycin
Amikacin
Netilmicin

Gentamicin and tobramycin are equally effective; gentamicin is less expensive. Tobramycin has better pseudomonal activity, which may be important in serious systemic infections. Amikacin generally is reserved for multiresistant bacteria.

Penicillins

Ampicillin
Ampicillin-sulbactam
Ticarcillin-clavulanate
Piperacillin
Piperacillin-tazobactam

These agents generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and enterococci and often are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided.

Cephalosporins, first-, second-, and third-generation

Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria but are not active against enterococci and have limited activity against *P. aeruginosa*. Ceftazidime and cefepime are active against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens.

Carbapenems

Imipenem-cilastatin
Meropenem
Ertapenem
Aztreonam

These agents have broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria.

Imipenem and meropenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. All may be associated with candidal superinfections.

A monobactam that is only active against gram-negative bacteria, including some strains of *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients.

Quinolones

Ciprofloxacin
Levofloxacin
Gatifloxacin

These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function.

TERAPI ISK BAGIAN BAWAH UNTUK OUTPATIENT

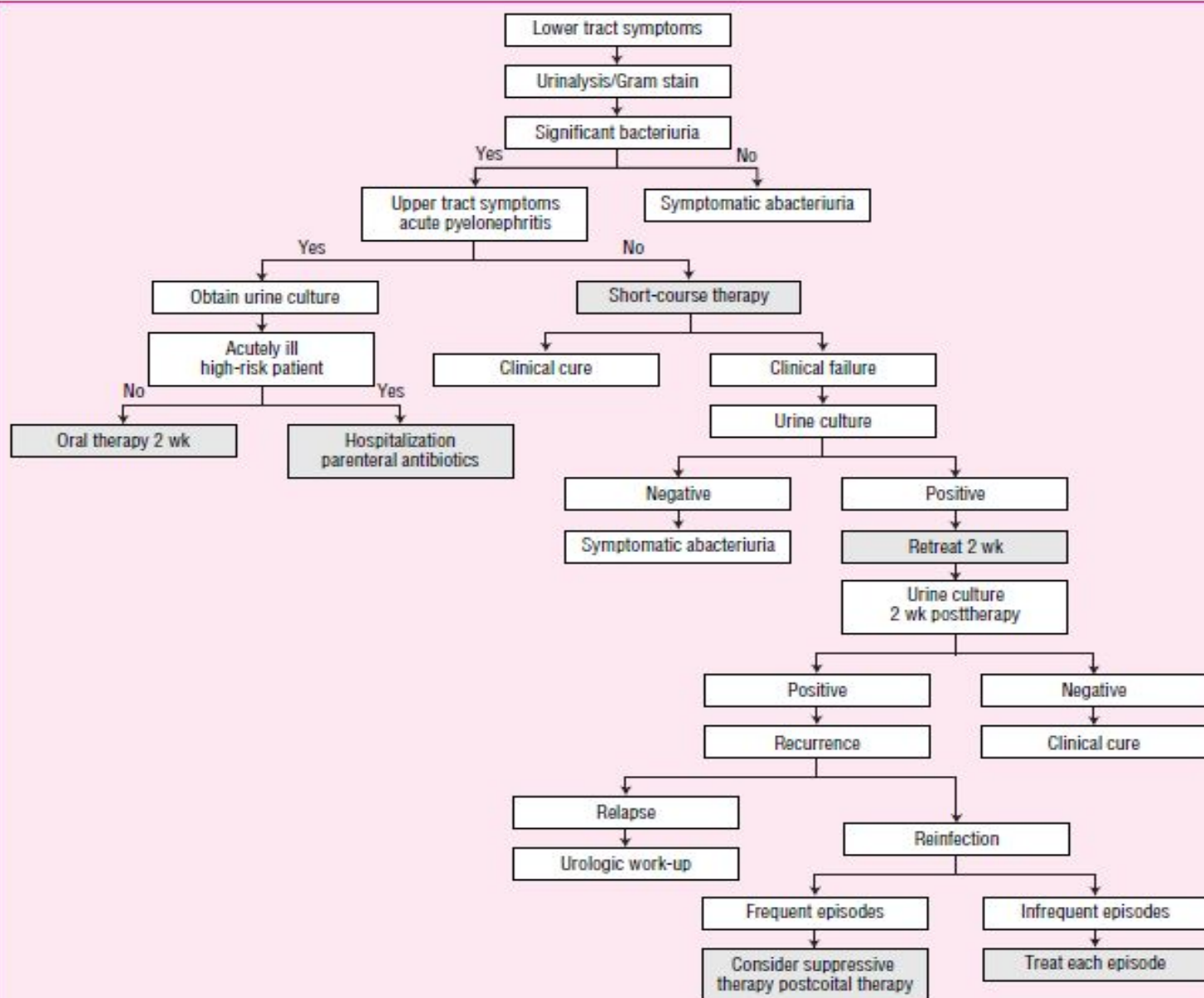
Indications	Antibiotic	Dose ^a	Interval	Duration	
Lower tract Infections	Uncomplicated	2 DS tablets	Single dose	1 day	
		1 DS tablet	Twice a day	3 days	
		Ciprofloxacin	250 mg	Twice a day	3 days
		Norfloxacin	400 mg	Twice a day	3 days
		Gatifloxacin	200–400 mg	Once a day	3 days
		Levofloxacin	250 mg	Once a day	3 days
		Lomefloxacin	400 mg	Once a day	3 days
		Enoxacin	200 mg	Once a day	3 days
		Amoxicillin	6 × 500 mg	Single dose	1 day
	Complicated	500 mg	Twice a day	3 days	
		Amoxicillin-clavulanate	500 mg	Every 8 hours	3 days
		Trimethoprim	100 mg	Twice a day	3 days
		Nitrofurantoin	100 mg	Every 6 hours	3 days
		Fosfomycin	3 g	Single dose	1 day
		Trimethoprim-sulfamethoxazole	1 DS tablet	Twice a day	7–10 days
		Trimethoprim	100 mg	Twice a day	7–10 days
		Norfloxacin	400 mg	Twice a day	7–10 days
		Ciprofloxacin	250–500 mg	Twice a day	7–10 days
Recurrent Infections	Gatifloxacin	400 mg	Once a day	7–10 days	
	Moxifloxacin (PO only)	400 mg	Once a day	7–10 days	
	Lomefloxacin	400 mg	Once a day	7–10 days	
	Levofloxacin	250 mg	Once a day	7–10 days	
	Amoxicillin-clavulanate	500 mg	Every 8 hours	7–10 days	
	Nitrofurantion	50 mg	Once a day	6 months	
	Trimethoprim	100 mg	Once a day	6 months	
	Trimethoprim-sulfamethoxazole	1/2 ss tablet	Once a day	6 months	
	Acute urethral syndrome	Trimethoprim-sulfamethoxazole	1 DS	Twice a day	3 days
		Azithromycin	1 g	Single dose	
	Failure of TMP-SMX	Doxycycline	100 mg	Twice a day	7 days
		Acute pyelonephritis	Trimethoprim-sulfamethoxazole	1 DS tablet	Twice a day
Ciprofloxacin	500 mg		Twice a day	14 days	
Gatifloxacin	400 mg		Once a day	14 days	
Norfloxacin	400 mg		Twice a day	14 days	
Levofloxacin	250 mg		Once a day	14 days	
Lomefloxacin	400 mg		Once a day	14 days	
Enoxacin	400 mg		Twice a day	14 days	
Amoxicillin-clavulanate	500 mg		Every 8 hours	14 days	

^aDosing intervals for normal renal function.

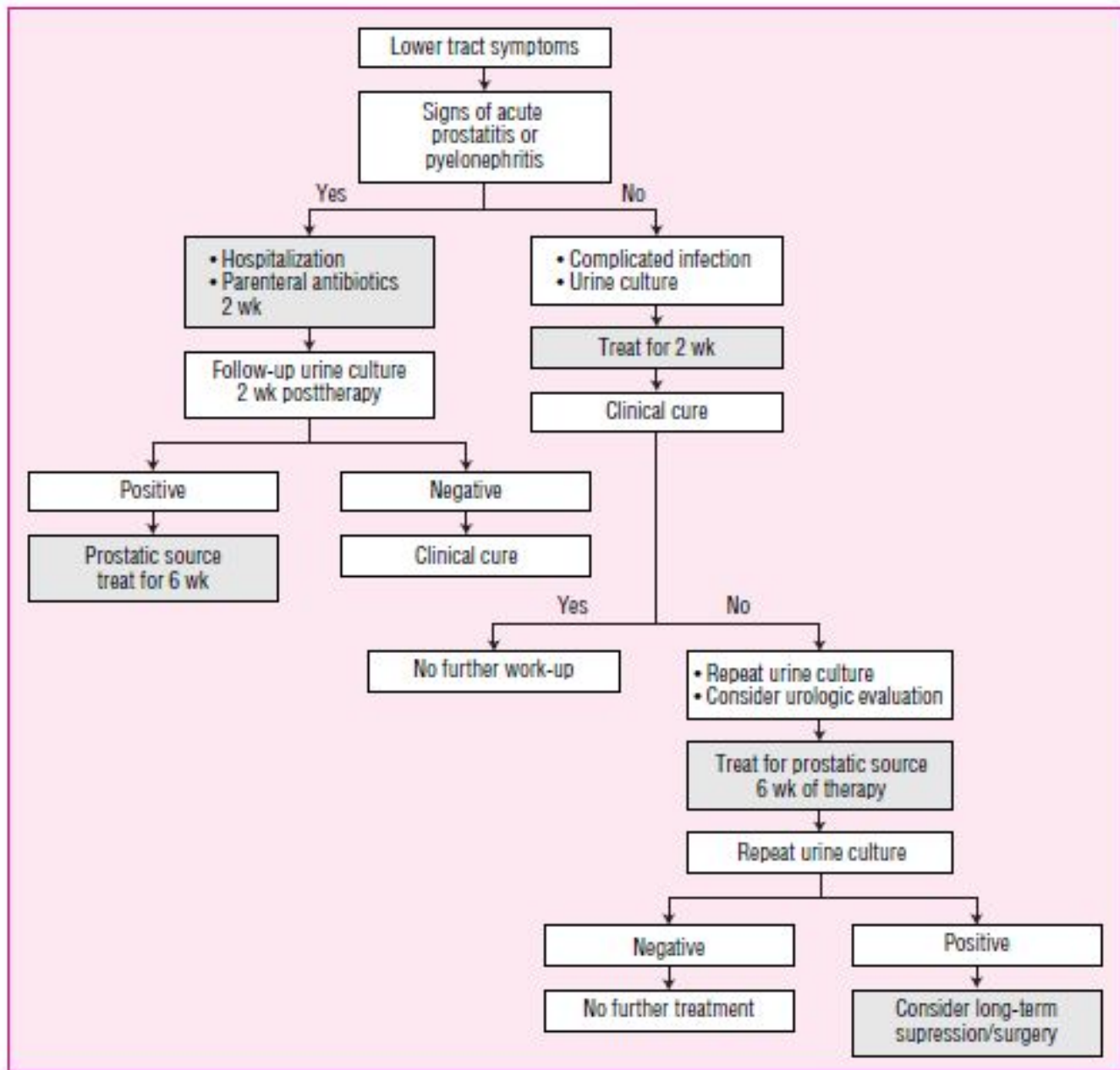
TERAPI EMPIRIS

Diagnosis	Pathogens	Treatment	Comments
Acute uncomplicated cystitis	<i>E. coli</i> <i>S. saprophyticus</i>	1. Trimethoprim-sulfamethoxazole × 3 days 2. Quinolone × 3 days	Short-course therapy more effective than single dose
Pregnancy	As above	1. Amoxicillin-clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim-sulfamethoxazole × 7 days	Avoid trimethoprim-sulfamethoxazole during third trimester
Acute pyelonephritis			
Uncomplicated	<i>E. coli</i>	1. Trimethoprim-sulfamethoxazole × 14 days 2. Quinolone × 14 days	Can be managed as outpatient
Complicated	<i>E. coli</i> <i>Proteus mirabilis</i> <i>K. pneumoniae</i> <i>Pseudomonas aeruginosa</i> <i>E. fecalis</i>	1. Quinolone × 14 days 2. Extended-spectrum penicillin Plus aminoglycoside	Severity of illness will determine duration of IV therapy. Culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	<i>E. coli</i> <i>K. pneumoniae</i> <i>Proteus spp</i> <i>P. aeruginosa</i>	1. Trimethoprim-sulfamethoxazole × 4–6 weeks 2. Quinolone × 4–6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

MANAGEMENT TERAPI ISK PADA WANITA



MANAGEMENT TERAPI ISK PADA PRIA



- Dilatasi pada pelvis renal dan ureter dapat menurunkan peristaltik ureteral
- Asymptomatic bacteriuria (4%-7% pasien) □ 20-40% dapat berkembang menjadi pyelonephritis akut □
- Jika tdk diterapi dapat menyebabkan prematuritas, BBLR
- Bakteri yang sering muncul E.coli
- Alternatif Terapi : sulfonamid, amoxicillin, amox-clavulanat, cephalexin □ 70-80% pasien efektif □ diberikan selama 7 hari
- Tetracilin KI karena teratogen
- Sulfonamida KI pada trimester ketiga □ dapat berakibat hiperbilirubinemia
- Fluoroquinolon KI □ menghambat kartilage dan perkembangan tulang pada bayi baru lahir

TERAPI PADA WANITA HAMIL

- Bakteri dapat masuk dari kandung kemih ke uretra
- Jika pasien menggunakan kateter < 30 hari (asymptomatic bacteria) penggunaan antibiotik dapat ditunda dan kateter segera dilepas
- Symptomatic □ kateter dilepas dan terapi dengan antibiotik dapat dimulai

PASIEN DENGAN KATETERISASI

- Menjaga kebersihan
- Menjaga agar tetap kering
- Selalu mengganti segala hal yang digunakan di daerah intim (kateter, pembalut, dll)
- Hindari berganti-ganti pasangan

TERIMA KASIH

MENINGITI S

FARMAKOTERAPI

PENDAHULUAN

- Meningitis □ infeksi meninges.
- Meninges : membran yang mengelilingi otak dan sumsum tulang belakang.
- Meningitis adalah infeksi yang menular.
- Dapat disebabkan oleh
 - mikroorganisme (seperti virus, bakteri, jamur, atau parasit yang menyebar dalam darah ke cairan otak), luka fisik,
 - kanker, atau obat-obatan tertentu.
- Dapat menyebabkan kerusakan kendali gerak, pikiran, bahkan kematian.

EPIDEMIOLOGI

- Di Amerika Serikat, meningitis bakteri mempengaruhi sekitar 3 dalam 100.000 orang setiap tahun, dan meningitis virus mempengaruhi sekitar 10 di 100.000.
- Pada tahun 1996 di Afrika terjadi wabah meningitis dimana 250.000 orang menderita penyakit ini dengan 25.000 korban jiwa.
- Di Eropa, penyebab terbesar meningitis adalah bakteri *N. Meningitidis* group B dan C, sedangkan group A meningococci lebih sering terjadi di Cina dan para peziarah Haji.
- Di Indonesia, pada tahun 1987, tercatat 99 jamaah haji Indonesia yang meninggal akibat meningitis.
- Sementara sejak periode 1998-2005 tidak ada lagi dilaporkan jamaah haji yang meninggal, setelah penggunaan vaksin.
- Sebagian besar (sekitar 70%) kasus meningitis terjadi pada anak-anak di bawah usia 5 atau pada orang yang berusia di atas 60.

ETIOLOGI

- Bakteri penyebab meningitis terbanyak disebabkan oleh:
 - Hemophilus influenzae,
 - Streptococcus pneumoniae dan
 - Neisseria meningitidis.
- Penyebab meningitis terbagi atas beberapa golongan umur:
 1. Neonatus : Eserichia coli, Streptococcus beta hemolitikus, Listeria monositogenes
 2. Anak di bawah 4 tahun : Hemofilus influenza, meningococcus, Pneumococcus.
 3. Anak di atas 4 tahun dan orang dewasa : Meningococcus, Pneumococcus,

Lanjutan...

- Faktor predisposisi untuk terjadinya meningitis:
 - Infeksi jalan napas bagian atas,
 - Otitis media,
 - mastoiditis,
 - Anemia sel sabit dan hemoglobinopatis lain,
 - Prosedur bedah saraf baru,
 - trauma kepala, dan
 - pengaruh immunologis.

PATOGENESIS

- Jenis Meningitis :
 - Viral meningitis
 - Bakteri meningitis
 - Meningitis jamur

Lanjutan....

Agen penyebab



Invasi ke SSP melalui aliran darah



Bermigrasi ke lapisan subarahnoid



Respon inflamasi di piamatter, arahnoid,CSF dan ventrikuler



Exudat menyebar di seluruh saraf cranial dan saraf spinal



Kerusakan neurologist

GEJALA & TANDA KLINIK

- Gejala awal meningitis bakteri mirip dengan kondisi penyakit lain, dan meliputi:
 - sakit kepala berat
 - demam
 - mual (rasa sakit)
 - muntah (yang sakit)
 - umumnya merasa tidak sehat

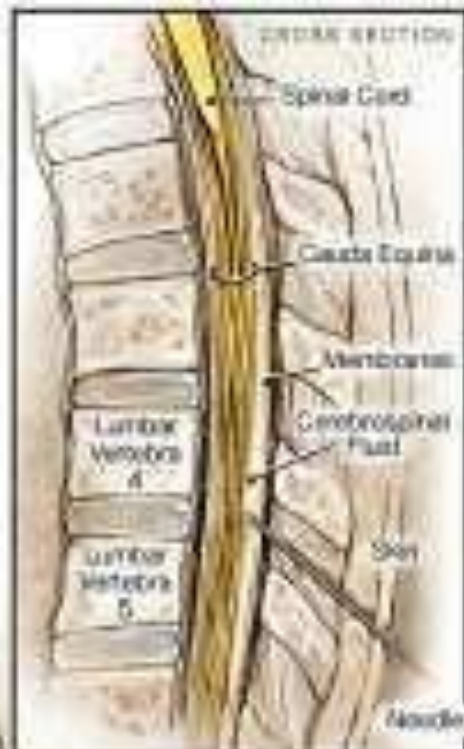
Tanda Klinik

Jenis meningitis	Glukosa	protein	Sel
Bakteri akut	Rendah	tinggi	<u>PMNs</u> , sering $> 300/\text{mm}^3$
Virus akut	Normal	normal atau tinggi	<u>mononuklear</u> $< 300/\text{mm}^3$
Berkekaan dgn penyakit TBC	Rendah	tinggi	mononuklear dan PMNs, $< 300/\text{mm}^3$
Jamur	Rendah	tinggi	$< 300/\text{mm}^3$
<u>Ganas</u>	Rendah	tinggi	biasanya mononuklear

DIAGNOSIS

- Pemeriksaan fisik
 - leher kaku, sakit kepala parah, dan demam.
 - pembengkakan di mata, yang menunjukkan tekanan intrakranial meningkat, dan ruam kulit.
- Tes darah
- Computed tomography (CT scan) atau magnetic resonance imaging (MRI scan) dari otak
- Spinal tap

Lumbar Puncture
Top view



Tujuan terapi

- Menghilangkan infeksi dengan menurunkan tanda-tanda dan gejala
- Mencegah kerusakan neurologic seperti kejang, tuli, koma, dan kematian

Algoritma Terapi Pada Orang Dewasa

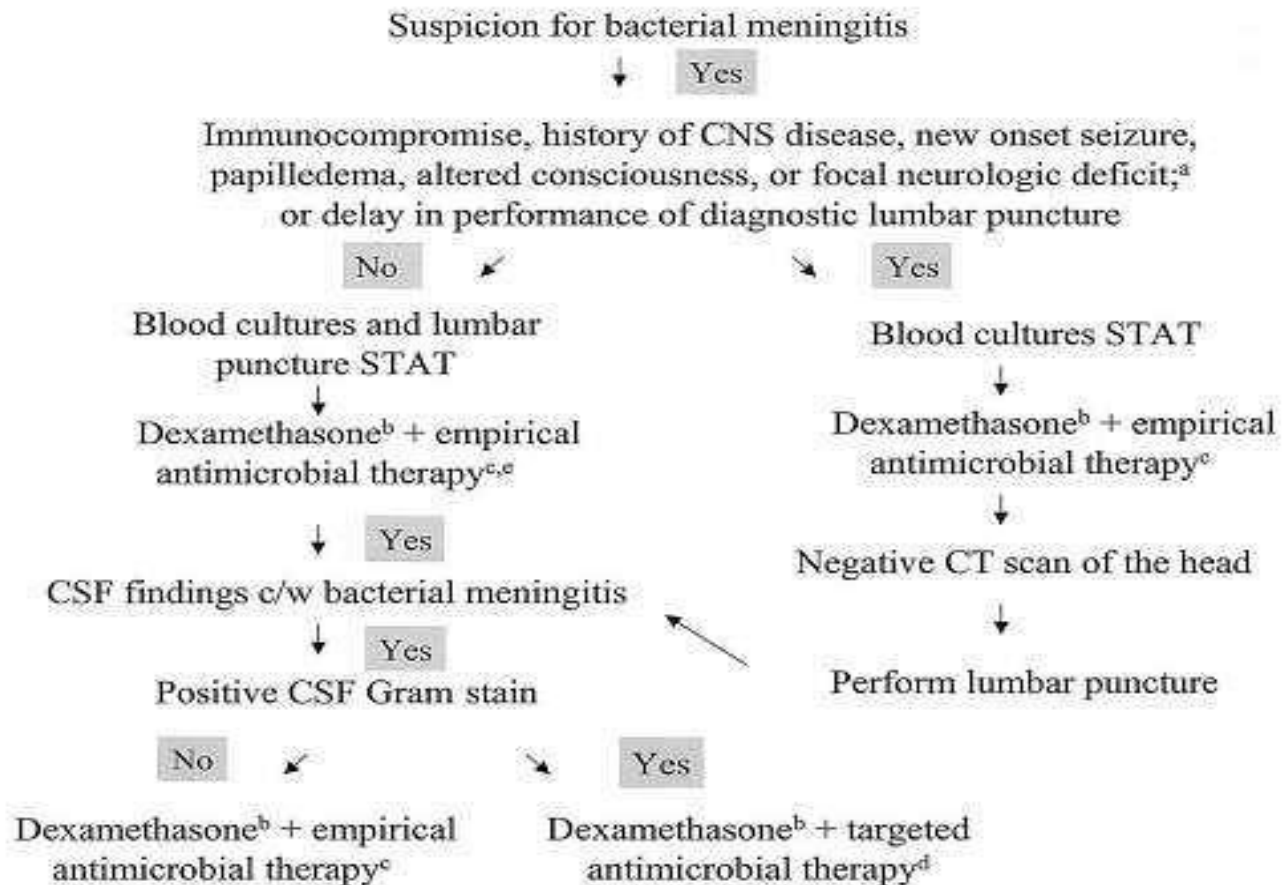


Figure 2. Management algorithm for adults with suspected bacterial meningitis. "Stat" indicates that the intervention should be done emergently. ^aSee table 2. ^bSee text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. ^cSee table 4. ^dSee table 3. ^eDexamethasone and antimicrobial therapy should be administered immediately after CSF is obtained.

Bayi dan Anak-anak

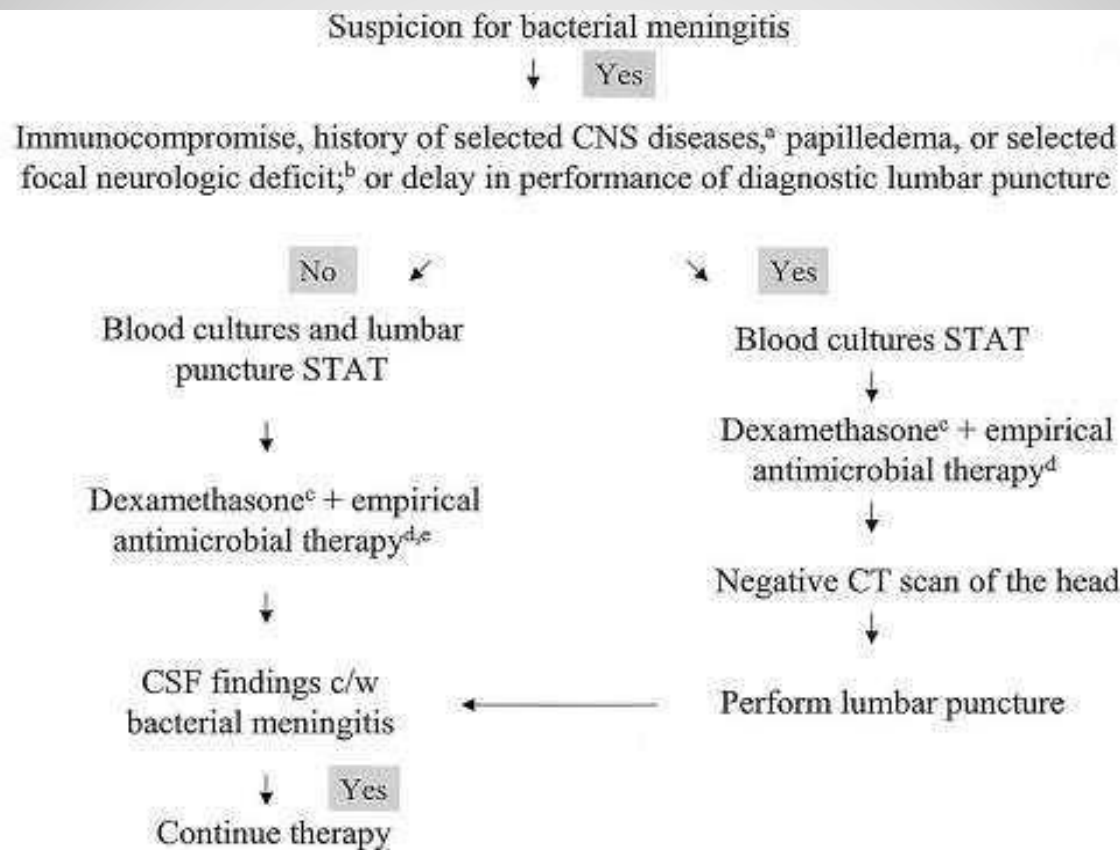


Figure 1. Management algorithm for infants and children with suspected bacterial meningitis. "Stat" indicates that the intervention should be done emergently. C/W, consistent with. ^aIncludes those associated with CSF shunts, hydrocephalus, or trauma, those occurring after neurosurgery, or various space-occupying lesions. ^bPalsy of cranial nerve VI or VII is not an indication to delay lumbar puncture. ^cSee text for recommendations for use of adjunctive dexamethasone in infants and children with bacterial meningitis. ^dSee table 4. ^eDexamethasone and antimicrobial therapy should be administered immediately after CSF is obtained.

Terapi Meningitis

Terapi meningitis bacterial

- ❑ terapi antibiotik yang digunakan harus dapat menembus sawar darah otak, contohnya rifampicin, chloramphenicol, dan quinolones (konsentrasi serum sekitar 30%-50%)
- ❑ Terapi antibiotik diberikan secepatnya setelah didapatkan hasil kultur.
- ❑ Pada orang dewasa, Benzyl penicillin G dengan dosis 1-2 juta unit diberikan secara intravena setiap 2 jam.
- ❑ Pada anak dengan berat badan 10-20 kg. Diberikan 8 juta unit/hari, anak dengan berat badan kurang dari 10 kg diberikan 4 juta unit/hari.
- ❑ Ampicillin dapat ditambahkan dengan dosis 300-400 mg/KgBB/hari untuk dewasa dan 100-200 mg/KgBB/ untuk anak-anak.
- ❑ Untuk pasien yang alergi terhadap penicillin, dapat diberikan sampai 5 hari bebas panas.

Terapi meningitis TB

- diberikan prednison 1-2 mg/kgBB/hari selama 4 minggu kemudian penurunan dosis (tapering-off) selama 8 minggu sehingga pemberian prednison keseluruhan tidak lebih dari 2 bulan.

Terapi meningitis viral

- diberi anti emetik seperti ondansetron dosis dewasa 4-8 mg IV tiap 8jam, dosis pediatrik 0,1 mg/kg IV lambat max 4 mg/dosis dan dapat diulang tiap 12 jam
- diberi antiviral seperti acyclovir, diberikan secepatnya ketika didiagnosis herpetic meningoencephalitis, dosis dewasa 30 mg/kg IV tiap 8 jam

Terapi meningitis jamur

- Meningitis kriptokokus diobati dengan obat antijamur. Dapat digunakan :
- Flukonazol, obat ini tersedia dengan bentuk pil atau infus
- Jika pasien intoleran dengan flukonazol dapat digunakan dengan amfoterisin B dan kapsul flusitosin. Mempunyai efek samping besar pada amfoterisin B, dapat diatasi dengan pemberian ibuprofen setengah jam sebelum amfoterisin B dipakai.

Terapi suportive

- memelihara status hidrasi dengan larutan infuse elektrolit dan oksigenasi
- Direkomendasikan pemberian heparin 5000-10.000 unit diberikan dengan pemberian cepat secara intravena dan dipertahankan pada dosis yang cukup untuk memperpanjang clotting time dan partial thromboplastin time menjadi 2 atau 3 kali harga normal.
- Untuk mengontrol kejang diberikan antikonvulsan, contohnya Fenitoin 5 mg/kg/24 jam, 3 kali sehari.
- Jika demam diberikan Antipiretika : parasetamol atau salisilat 10 mg/kg/dosis
- Pada udem cerebri dapat diberikan osmotik diuretik atau corticosteroid, tetapi hanya bila didapatkan tanda awal dari impending herniasi.

Table 4. Recommendations for empirical antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition (A-III).

Predisposing factor	Common bacterial pathogens	Antimicrobial therapy
Age		
<1 month	<i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Klebsiella</i> species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1–23 months	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>S. agalactiae</i> , <i>Haemophilus influenzae</i> , <i>E. coli</i>	Vancomycin plus a third-generation cephalosporin ^{a,b}
2–50 years	<i>N. meningitidis</i> , <i>S. pneumoniae</i>	Vancomycin plus a third-generation cephalosporin ^{a,b}
>50 years	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>L. monocytogenes</i> , aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin ^{a,b}
Head trauma		
Basilar skull fracture	<i>S. pneumoniae</i> , <i>H. influenzae</i> , group A β -hemolytic streptococci	Vancomycin plus a third-generation cephalosporin ^a
Penetrating trauma	<i>Staphylococcus aureus</i> , coagulase-negative staphylococci (especially <i>Staphylococcus epidermidis</i>), aerobic gram-negative bacilli (including <i>Pseudomonas aeruginosa</i>)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Postneurosurgery	Aerobic gram-negative bacilli (including <i>P. aeruginosa</i>), <i>S. aureus</i> , coagulase-negative staphylococci (especially <i>S. epidermidis</i>)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
CSF shunt	Coagulase-negative staphylococci (especially <i>S. epidermidis</i>), <i>S. aureus</i> , aerobic gram-negative bacilli (including <i>P. aeruginosa</i>), <i>Propionibacterium acnes</i>	Vancomycin plus cefepime, ^c vancomycin plus ceftazidime, ^c or vancomycin plus meropenem ^c

^a Ceftriaxone or cefotaxime.

^b Some experts would add rifampin if dexamethasone is also given.

^c In infants and children, vancomycin alone is reasonable unless Gram stains reveal the presence of gram-negative bacilli.

dosis yang direkomendasikan untuk terapi antimikroba dengan bakteri meningitis

Table 6. Recommended dosages of antimicrobial therapy in patients with bacterial meningitis (A-III).

Antimicrobial agent	Total daily dose (dosing interval in hours)			
	Neonates, age in days		Infants and children	Adults
	0-7 ^a	8-28 ^a		
Ampicillin ^b	15-20 mg/kg (12)	30 mg/kg (8)	20-30 mg/kg (8)	15 mg/kg (8)
Ampicillin	150 mg/kg (8)	200 mg/kg (8-8)	300 mg/kg (8)	12 g (4)
Aztreonam	—	—	—	6-8 g (8-8)
Cefepime	—	—	150 mg/kg (8)	8 g (8)
Cefotaxime	100-150 mg/kg (8-12)	150-200 mg/kg (8-8)	225-300 mg/kg (8-8)	8-12 g (4-8)
Ceftazidime	100-150 mg/kg (8-12)	150 mg/kg (8)	150 mg/kg (8)	8 g (8)
Ceftriaxone	—	—	80-100 mg/kg (12-24)	4 g (12-24)
Chloramphenicol	25 mg/kg (24)	50 mg/kg (12-24)	75-100 mg/kg (8)	4-8 g (8) ^c
Ciprofloxacin	—	—	—	800-1200 mg (8-12)
Gatifloxacin	—	—	—	400 mg (24) ^d
Gentamicin ^e	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5 mg/kg (8)
Meropenem	—	—	120 mg/kg (8)	8 g (8)
Maxifloxacin	—	—	—	400 mg (24) ^d
Nafcillin	75 mg/kg (8-12)	100-150 mg/kg (8-8)	200 mg/kg (8)	9-12 g (4)
Oxacillin	75 mg/kg (8-12)	150-200 mg/kg (8-8)	200 mg/kg (8)	9-12 g (4)
Penicillin G	0.15 mL/kg (8-12)	0.2 mL/kg (8-8)	0.3 mL/kg (4-8)	2.4 mL (4)
Rifampin	—	10-20 mg/kg (12)	10-20 mg/kg (12-24) ^f	600 mg (24)
Tobramycin ^g	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5 mg/kg (8)
TMP-SMZ ^h	—	—	10-20 mg/kg (8-12)	10-20 mg/kg (8-12)
Vancomycin ⁱ	20-30 mg/kg (8-12)	30-45 mg/kg (8-8)	60 mg/kg (8)	30-45 mg/kg (8-12)

NOTE: TMP-SMZ, trimethoprim-sulfamethoxazole.

^a Smaller doses and longer intervals of administration may be advisable for very low-birth weight neonates (<2000 g).

^b Need to monitor peak and trough serum concentrations.

^c Higher dose recommended for patients with pneumococcal meningitis.

^d No data on optimal dosage needed in patients with bacterial meningitis.

^e Maximum daily dose of 600 mg.

^f Dosage based on trimethoprim component.

^g Maintain serum trough concentrations of 15-20 µg/mL.

Monitoring

- Tekanan darah
- Glukosa
- Respirasi
- RR dan HR
- Volume output urin

Outcome Terapi

- Mencapai masa penyembuhan tepat waktu, tanpa bukti penyebaran infeksi endogen atau keterlibatan orang lain.
- Mempertahankan tingkat kesadaran biasanya/membaik dan fungsi motorik/sensorik, mendemonstrasikan tanda-tanda vital stabil.
- Tidak mengalami kejang/penyerta atau cedera lain.
- Melaporkan nyeri hilang/terkontrol dan menunjukkan postur rileks dan mampu tidur/istirahat dengan tepat.
- Tampak rileks, ansietas berkurang