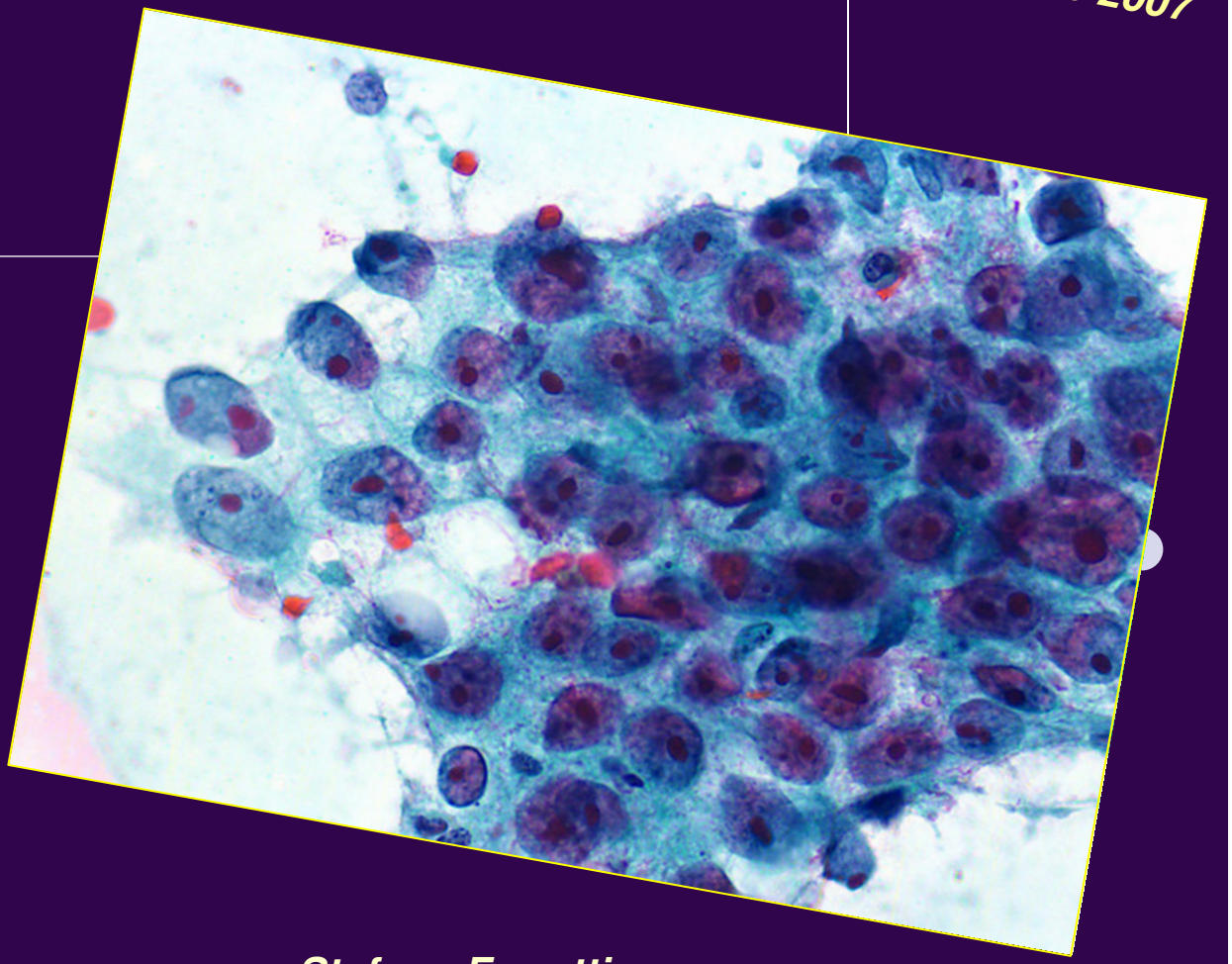
Associazione Italiana Registri Tumori
Registro Tumori di Reggio-Emilia

corso di base sulla registrazione dei tumori
princìpi e metodi

Reggio Emilia, 3 dicembre 2007

Biologia dei tumori

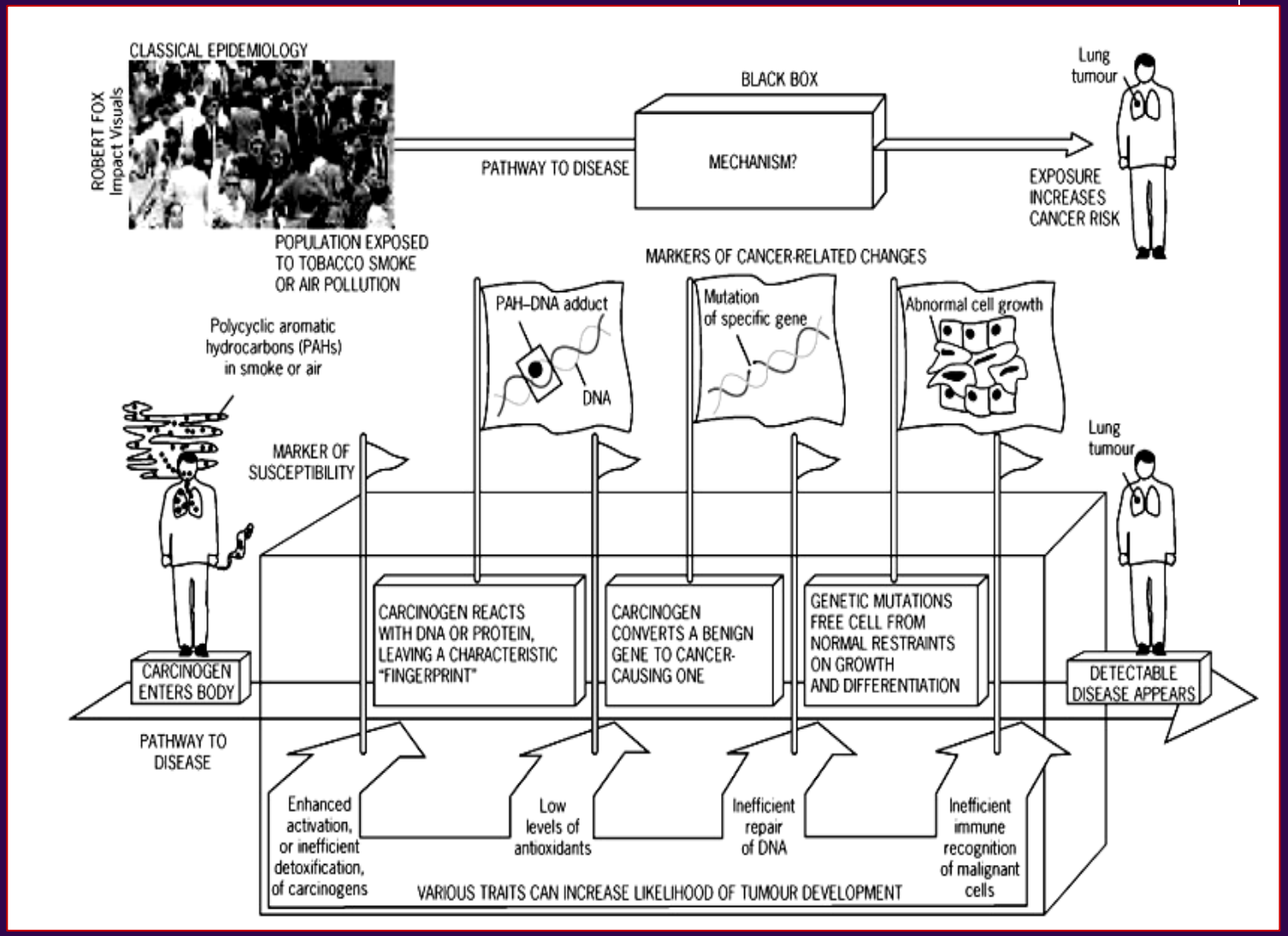


Stefano Ferretti
Registro Tumori della Provincia di Ferrara

La storia naturale del cancro

cancerogenesi

Genetica e ambiente



Agenti cancerogeni

infezioni

Infectious agents associated with human cancers

Infectious agents	Types of cancer	No. of cancer cases attributable to infections (1990, world total)
Epstein–Barr virus (1964)	Burkitt's lymphoma	6100
	Nasopharyngeal carcinoma	56 200
	Hodgkin's disease	26 200
	Post-transplant lymphomas	
Hepatitis B (1965)	Hepatocell	228 900
HLTV-1 (1980)	Adult T-cell leukaemia	2600
Human papilloma viruses (1983)	Cancer of the cervix	327 000
	Ano-genital cancer	26 400
	Skin	
	Head and neck	
Human immunodeficiency virus (1983) associated with:		
Human herpes virus-8 (1994)	Kaposi's sarcoma	43 600
Epstein–Barr virus	B-cell lymphoma	8800
Human papilloma viruses (2000)	*In situ* cancer of the cervix, vulva/vagina and penis	
Hepatitis C (1988)	Hepatocell lar carcinoma	109 700
Helicobacter pylori (1983)	Gastric cancer	337 800
	Gastric lymphoma	8300
Schistosomes	Bladder cancer	9500
Liver flukes	Cholangiocarcinoma	800
	Total	1 191 900

Agenti cancerogeni

radiazioni

Radiazioni ultraviolette
- UVA (320-400 nm)
- UVB (280-320 nm) – tumori cutanei
- UVC (200-280 nm) – potente azione mutagena

Effetti:
- Inibizione della divisione cellulare
- Inattivazione di enzimi
- Induzione di mutazioni
- Morte cellulare
- Danno sistema NER (nucleotide excision repair)

Radiazioni ionizzanti

Sources of ionizing radiation exposure

Source	Amount (mSv per year)
Natural	
Radon	3.0
Cosmic	2.0
Terrestrial	0.3
Internal	0.3
Artificial	
Medical	0.4
Consumer	0.6
Other	0.5
Work, nuclear power generation, fallou	0.1
Total	<0.01
	3.6

Agenti cancerogeni

radiazioni

Radiazioni **corpuscolate** (α,β, protoni, neutroni)

Radiazioni elettromagnetiche (x, γ)

Leucemie
Carcinoma tiroide
Carcinoma mammella
Carcinoma polmone
Carcinoma ghiandole salivari

Agenti cancerogeni

chimici

Important occupational agents or work processes considered by IARC (WHO) as being human carcinogens

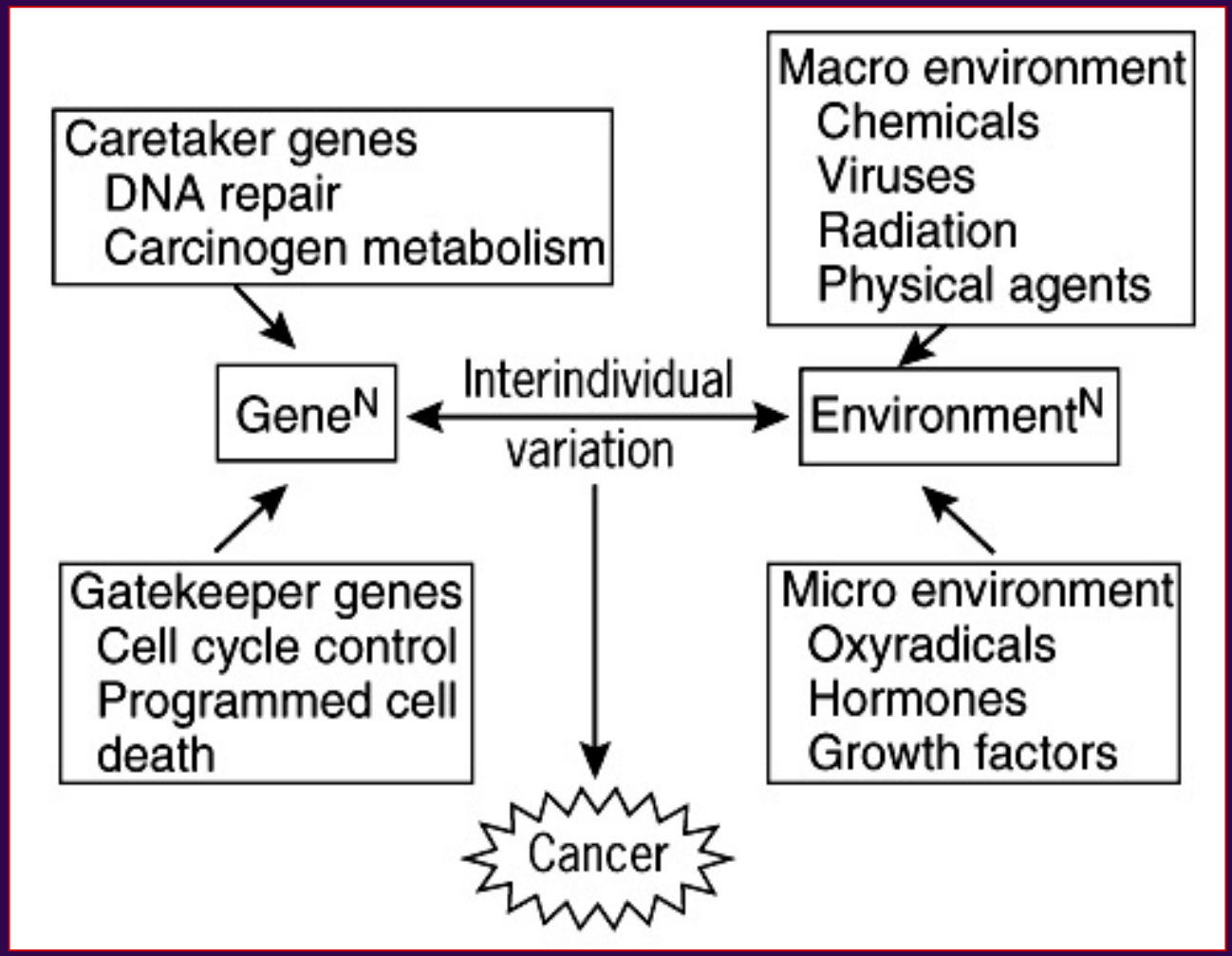
Substance of process	Site(s) of cancer
Acrylonitrile	Lung
Aluminum production	Lung, bladder
4-Aminobiphenyl	Bladder
Arsenic and certain arsenic compounds	Lung, skin
Asbestos	Gasto-intestinal tract, mesothelioma of pleura and peritoneum, lung, larynx
Auramine manufacture	Bladder
Benzene	Haemopoietic tissue
Benzidine	Bladder
Beryllium and beryllium compounds	Lung
Bis(chloromethyl) ether and chloromethyl methyl ether	Lung
Boot and shoe manufacture and repair	Nasal cavity
1,3-Butadiene	Haemopoietic tissue
Cadmium and cadmium compounds	Lung
Coal gasification	Lung
Coal-tars and pitches	Skin
Coke production	Lung
Chromium and certain chromium compounds	Lung
Diesel exhaust	Lung
Dioxins	Soft-tissue sarcoma, non-Hodgkin's lymphoma
Ethylene oxide	Haemopoietic tissue
Formaldehyde	Nose and nasopharynx
Glass manufacture	Lung
Hairdresser or barber	Bladder
Underground hematite mining	Lung
Iron and steel founding	Lung
Magenta, manufacture of	Bladder
Mineral oils, treated and mildly treated	Skin
Mustard gas	Pharynx, lung
2-Naphthylamine	Bladder
Nickel and nickel compounds	Nose and nasal sinus
Nonarsenical pesticides, spraying of	Lung
Painter	Lung
Petroleum refining, occupational exposure	Skin, haemopoietic tissue
Polychlorinated biphenyls	Liver, skin
Radon	Lung
Rubber industry	Bladder, haemopoietic tissue
Shale-oils	Skin
Silica	Lung
Soots	Skin
Sulphuric acid mist	Nasal cavity, larynx, lung
Talc-containing asbestiform fibres	Lung
Trichloroethylene	Liver, biliary tract
Vinyl chloride	Liver
Wood dust	Nasal cavity

Agenti cancerogeni

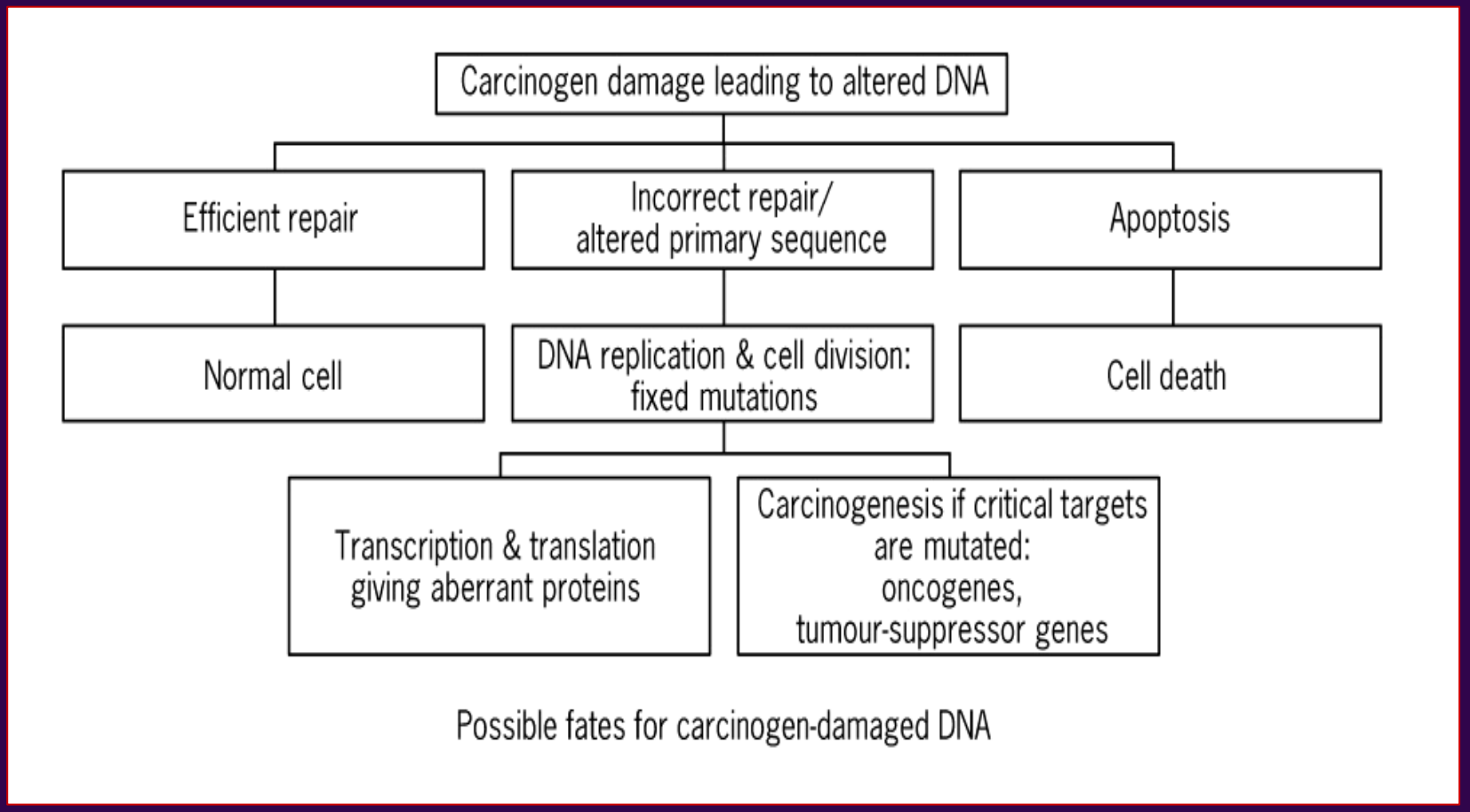
Agents evaluated in vols. 1–77 of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans and the classification of their carcinogenicity to humans (http://www.iarc.fr)

Group 1	
Carcinogenic to humans	78
Group 2A	
Probably carcinogenic to humans	63
Group 2B	
Possibly carcinogenic to humans	235
Group 3	
Not classifiable as to its carcinogenicity to humans	483
Group 4	
Probably not carcinogenic to humans	1
Total	860

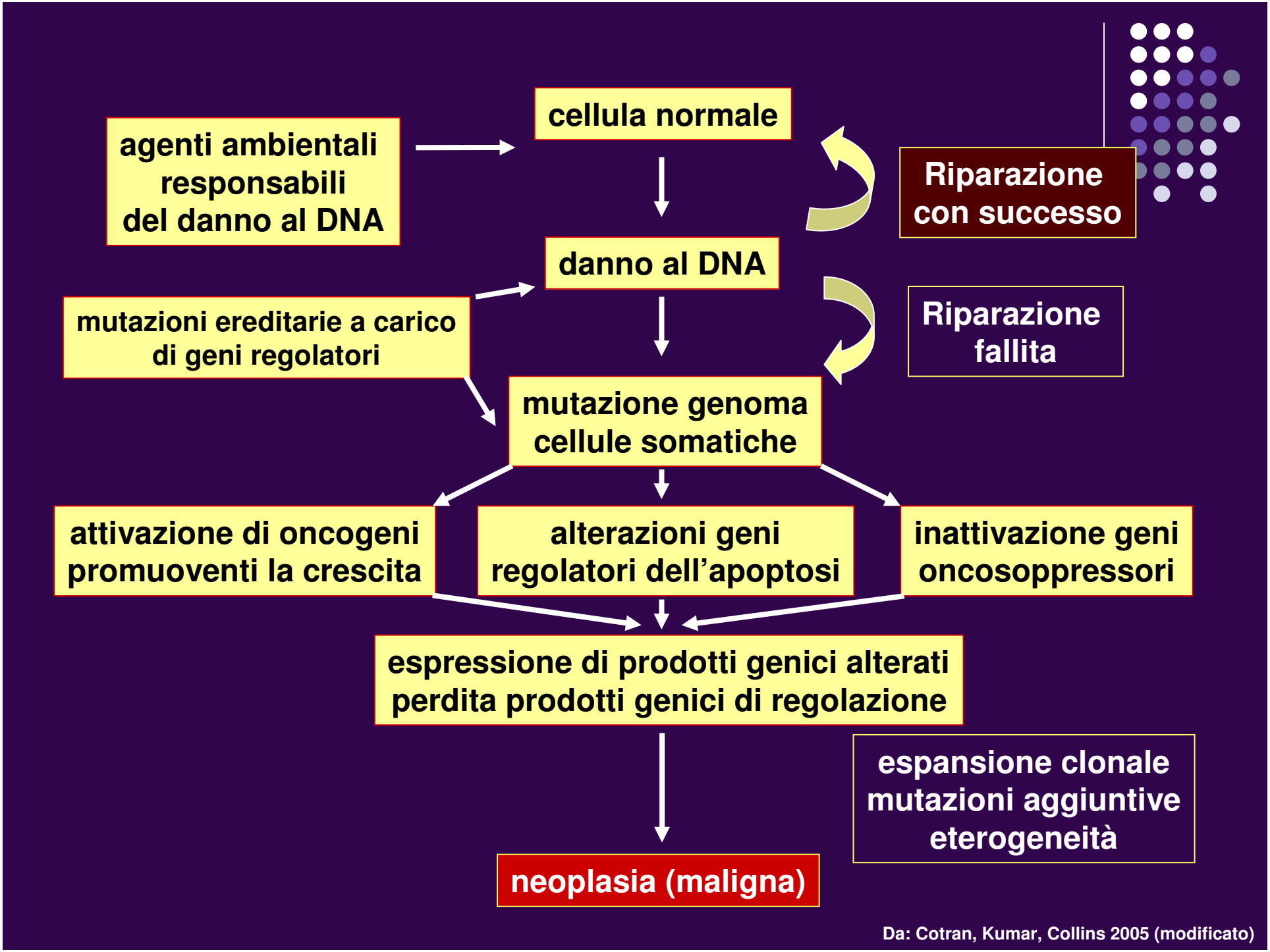
Vie cancerogenetiche



Vie cancerogenetiche

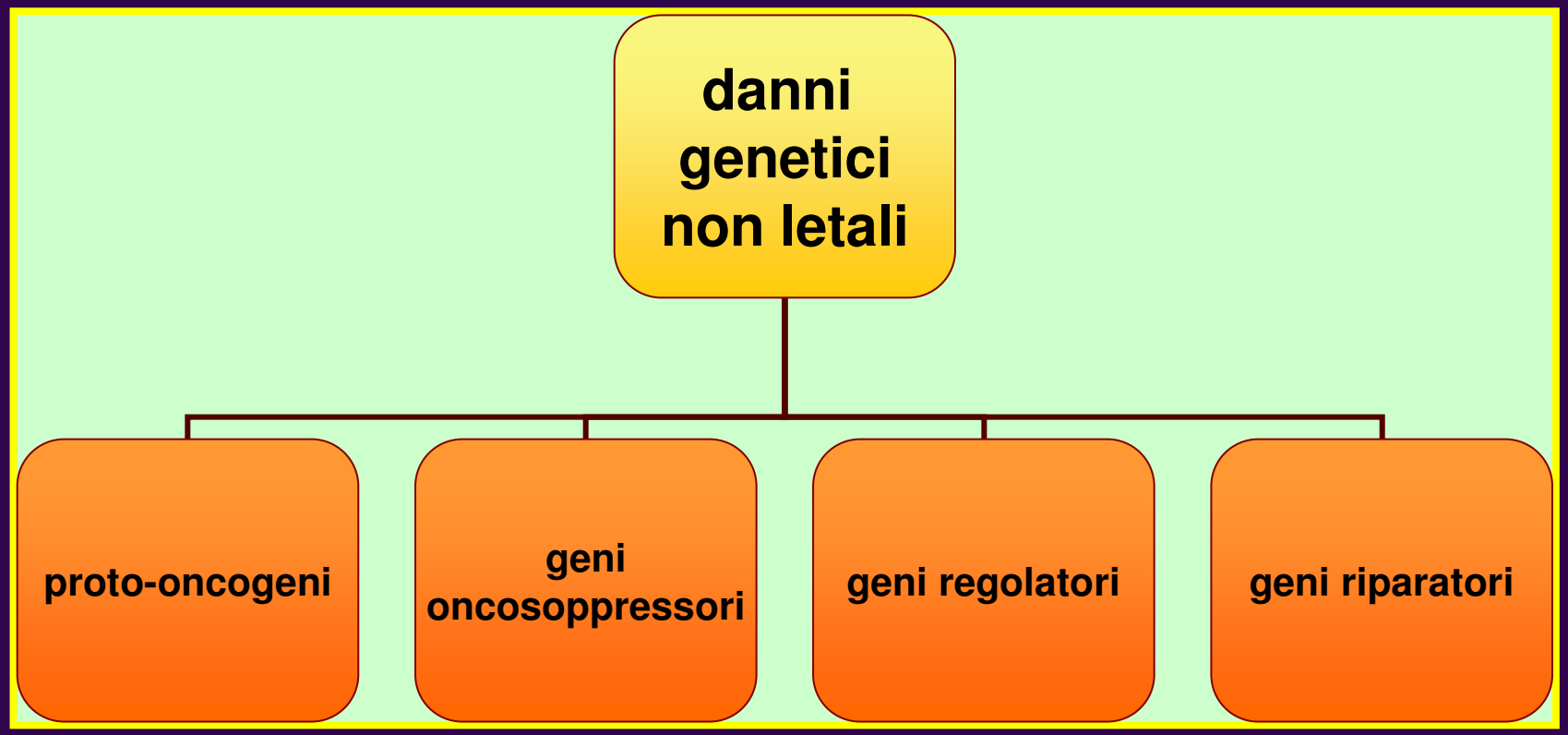


Possible fates for carcinogen-damaged DNA

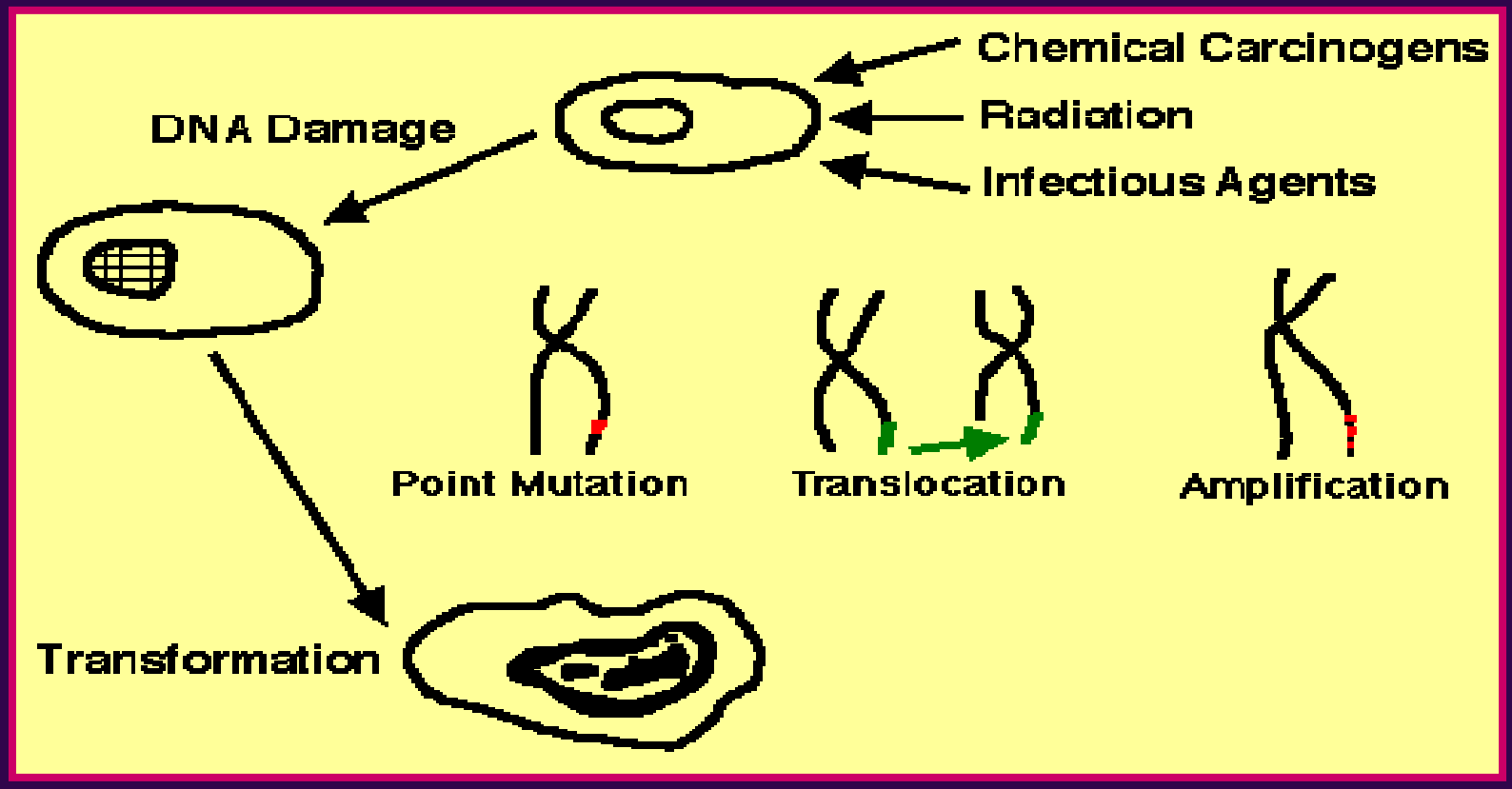


Da: Cotran, Kumar, Collins 2005 (modificato)

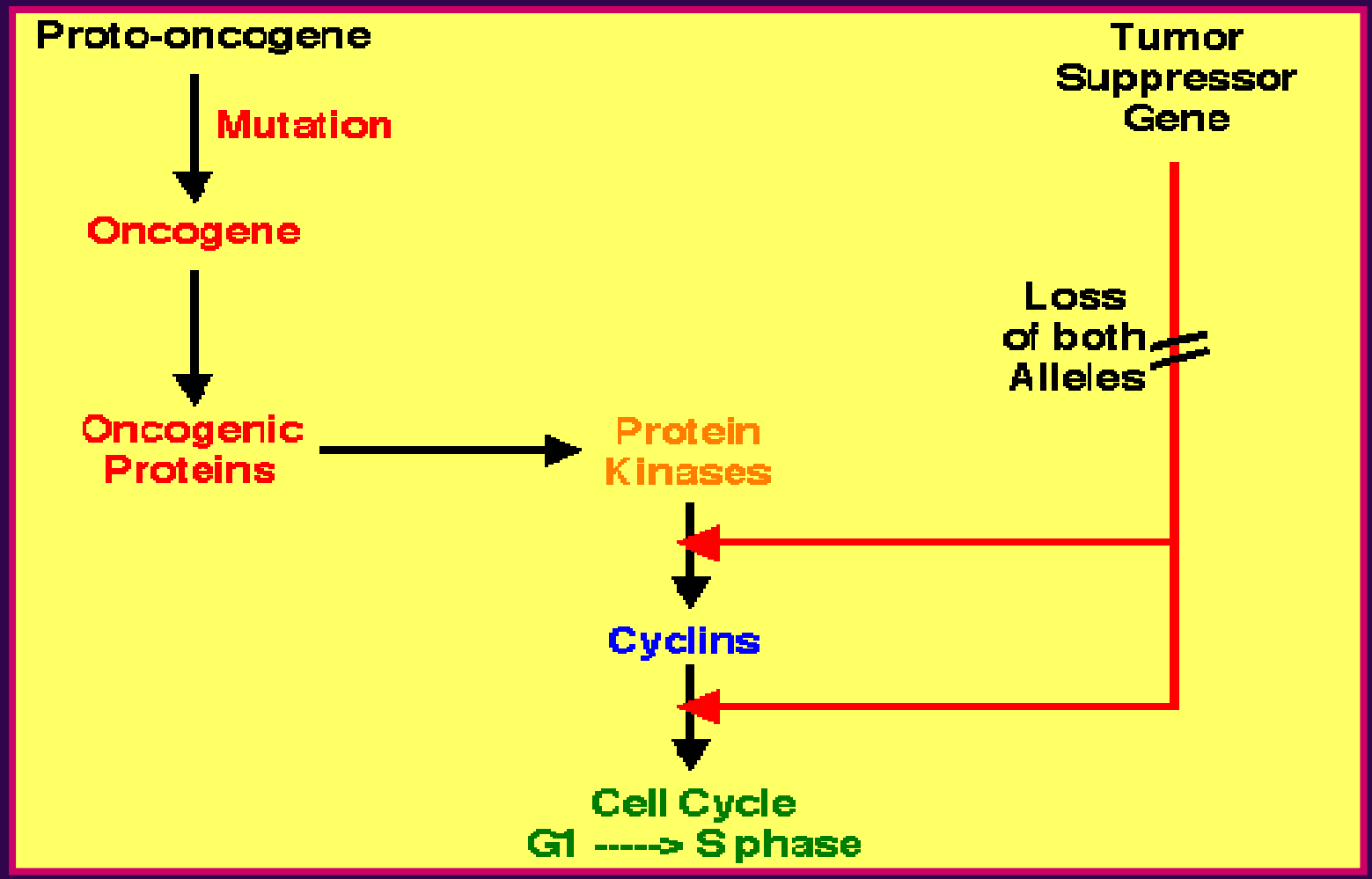
Basi molecolari del cancro



Basi molecolari del cancro



Basi molecolari del cancro



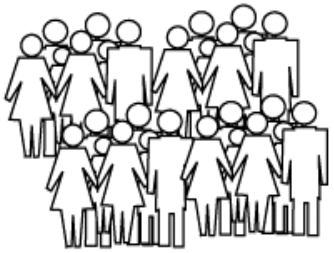
Geni e cancro

Examples of critical genes involved in carcinogenesis

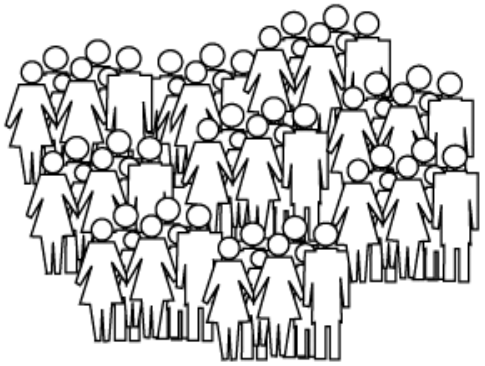
Gene	Function	Localization
Oncogenes		
SIS, FGF, INT2, WNT1	Growth factors	Extracellular
MET, NEU, EPH, EGRF, FMS, KIT, HER2, RET, ROS,	Receptor/protein tyrosine kinases	Extracellular/cell membrane
SRC, ABL1, FPS, FGR, FYN, HCK, LCK, YES	Nonreceptor tyrosine kinases	Cell membrane/cytoplasmic
MAS	Receptors lacking protein kinase activity	Cell membrane/cytoplasmic
RAS, GIP2, GSP	Membrane-associated G proteins	Cell membrane/cytoplasmic
BCR, DBL, ECT2	RHO/RAC-binding proteins	Cytoplasmic
RAF, PIM1, BCR, EST, MOS, STY	Cytoplasmic protein serine kinases Protein serine, threonine and tyrosine kinase	Cytoplasmic Nuclear
BCL1, CRK, ODC, NCK	Cytoplasmic regulators	Cytoplasmic
MYC, FOS, JUN, BCL3, CBL ERBA, ETS, HOX, MYB, MYCL, REL, TAL1, SKI	Nuclear transcription factors	Nuclear
BCL-2	Mitochondrial membrane factor	Mitochondrial/cytoplasmic
Tumour-suppressor genes		
NF1	GTPase activation	Cell membrane/cytoplasmic
RB-1	Cell cycle-regulated nuclear transcription repressor	Nuclear
P53	Cell cycle-regulated nuclear transcription repressor	Nuclear
WT1	Zinc finger transcription factor	Nuclear
HMLH1	Mismatch DNA repair	Nuclear
BRCA1	DNA repair enzyme	Nuclear
APC	Regulates cytoskeletal networks	Cytoplasmic
DCC	Cell adhesion molecule	Plasm membrane
VHL	Signal transduction or cell–cell contact	Plasm membrane
NME	Cell receptor	Plasm membrane
CMAR/CAR	Cell attachment	Plasm membrane
WNT	Growth factor	Extracellular matrix
YES1	Tyrosine kinase	Plasm membrane

Livelli di rischio

High risk:
FAP, HNPCC
Lifetime risk ~ 80–100%



Moderate risk:
Current/prior adenoma, cancer survivor, inflammatory bowel disease
Lifetime risk ~ 10–20%



General population (US):
50% incidence of adenomas by age 50;
130 000 colorectal cancer cases/yr
Lifetime risk = 5.6% (2000)

Agent testing along a risk gradient: colorectal neoplasia as a model

Livelli di rischio

Predisposizione genetica

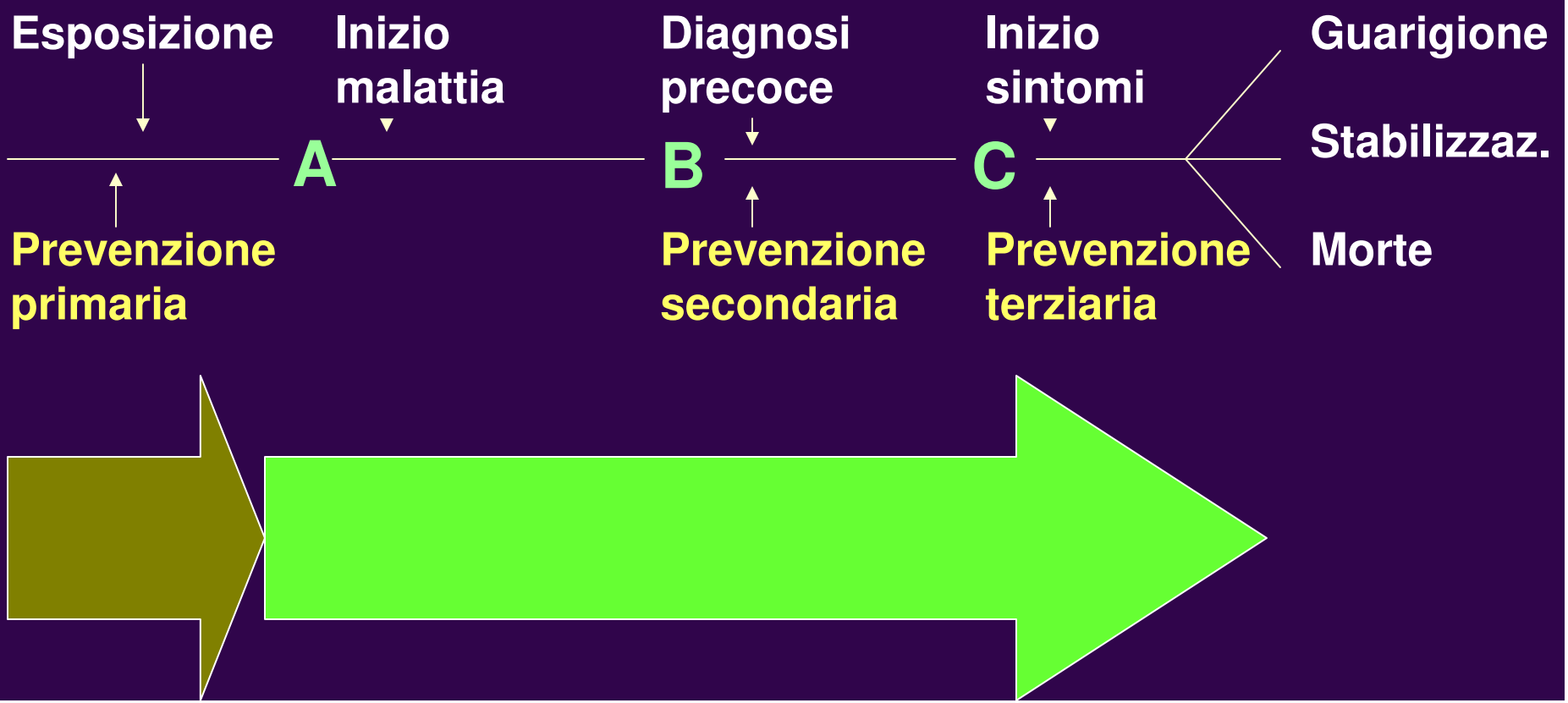
(mutazioni ereditarie: < 10% dei pazienti)

1. Forme autosomiche dominanti
2. Sindrome del "mismatch repair"
3. Forme familiari
   - *Insorgenza precoce*
   - *Tumori multipli/bilaterali*
   - *Coinvolgimento di più parenti*
   - *Modalità di trasmissione non chiara*

Condizioni non ereditarie e predisponenti

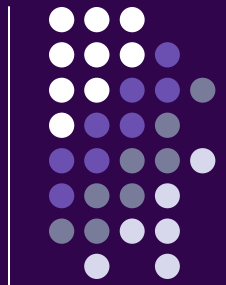
- Fattori geografici ed ambientali
- Età
- Infiammazione cronica
- Condizioni precancerose

La storia naturale del cancro



Biologia della crescita cellulare

La cinetica di crescita



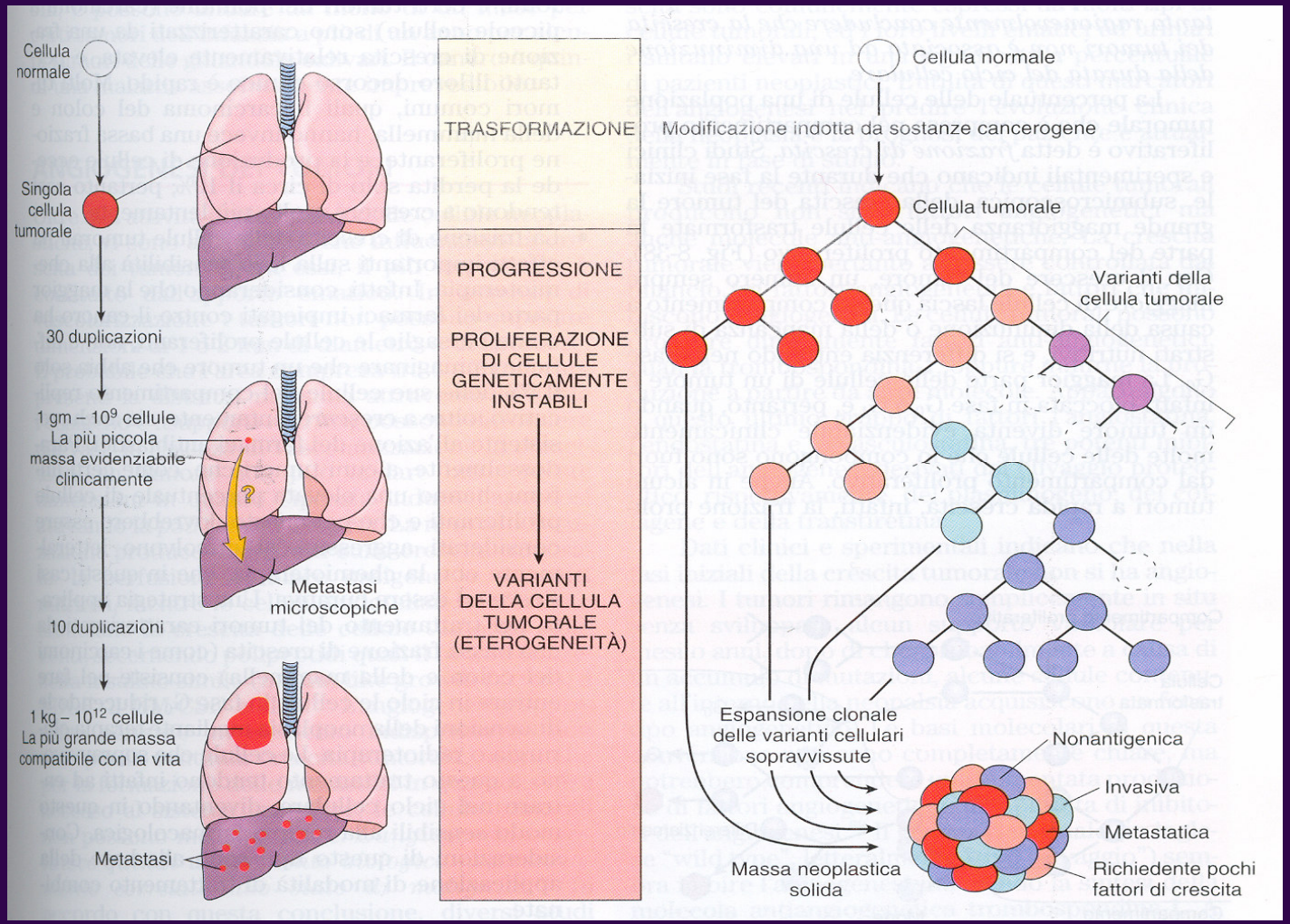
Da una cellula ad un grammo = 30 duplicazioni (10^9 cellule)

Da 1 g a 1.000g = 40 duplicazioni (10^{12} cellule)

Fattori:

1. Tempo di duplicazione
   - Tempo di crescita teorico e reale (latenza)
2. Frazione di crescita
   - Decorso clinico
   - Sensibilità alla terapia
3. Frazione di perdita
4. Risposta immunitaria

Progressione della malattia



Angiogenesi nei tumori

Funzioni:

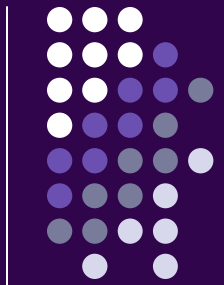
1. Perfusione (ossigeno e fattori nutritivi)
2. Stimolo alla crescita
   - Fattori crescita prodotti dagli endoteli
   - Sensibilità alla terapia
3. Processo di metastasi

Progressione ed eterogeneità

Determinanti:

1. Fenotipo tumorale
2. Instabilità genetica
3. Rapporto cellula/ospite

Il grado di differenziazione



Grado 1 (G1): tumore (bene) differenziato

Grado 2 (G2): tumore moderatamente differenziato

Grado 3 (G3): tumore scarsamente differenziato

Grado 4 (G4): tumore indifferenziato

Grading (mammella)

Formazione tubuli

> 75%	- Score 1
10 - 75%	- Score 2
<10%	- Score 3

Pleomorfismo nucleare

minimo	- Score 1
moderato	- Score 2
marcato	- Score 3

Mitosi (hpf=0,50 mm)

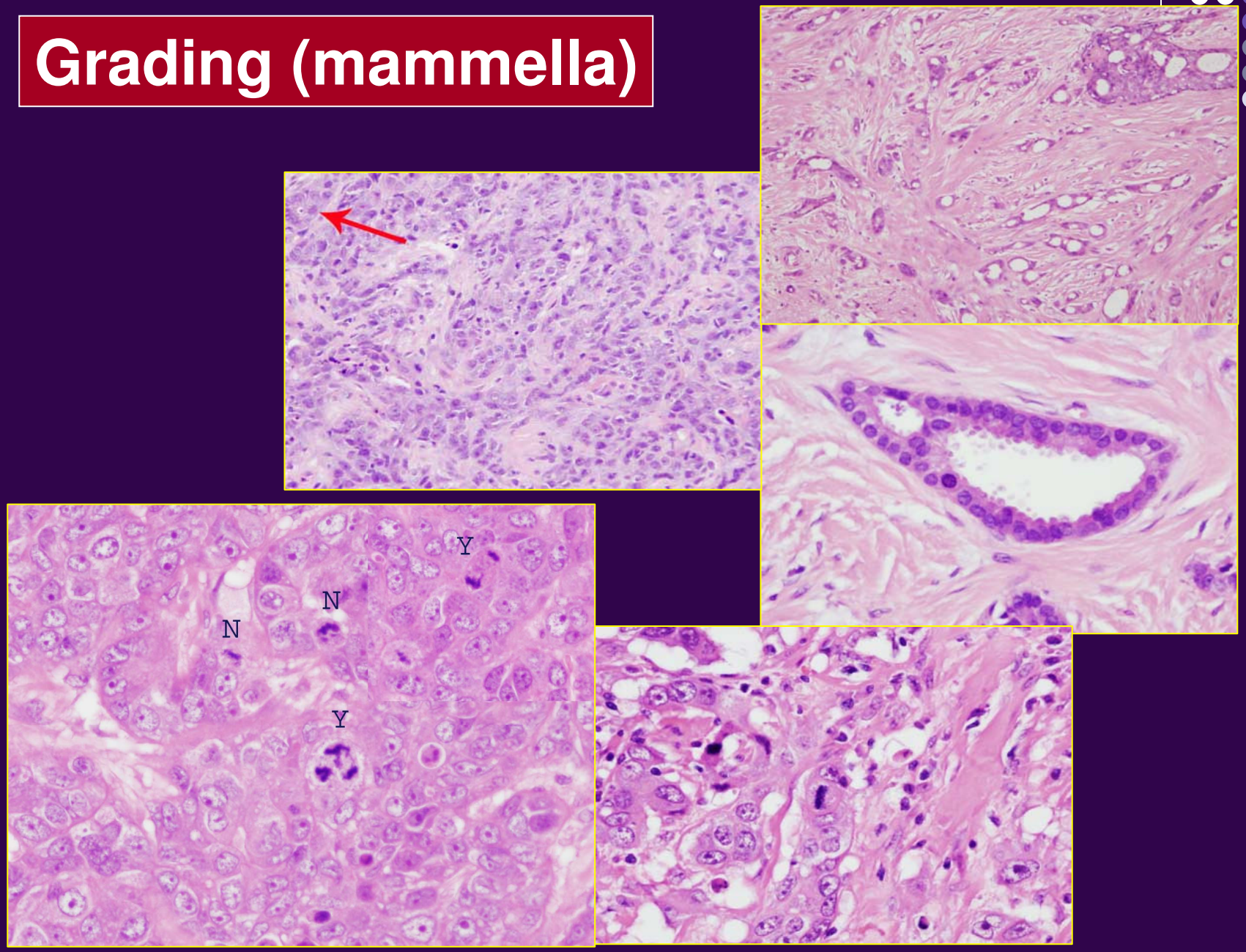
fino a 7 x10 hpf	- Score 1
da 8 a 14 x10hpf	- Score 2
15 ed oltre x10 hpf	- Score 3

TUB+
NUC+
MIT=

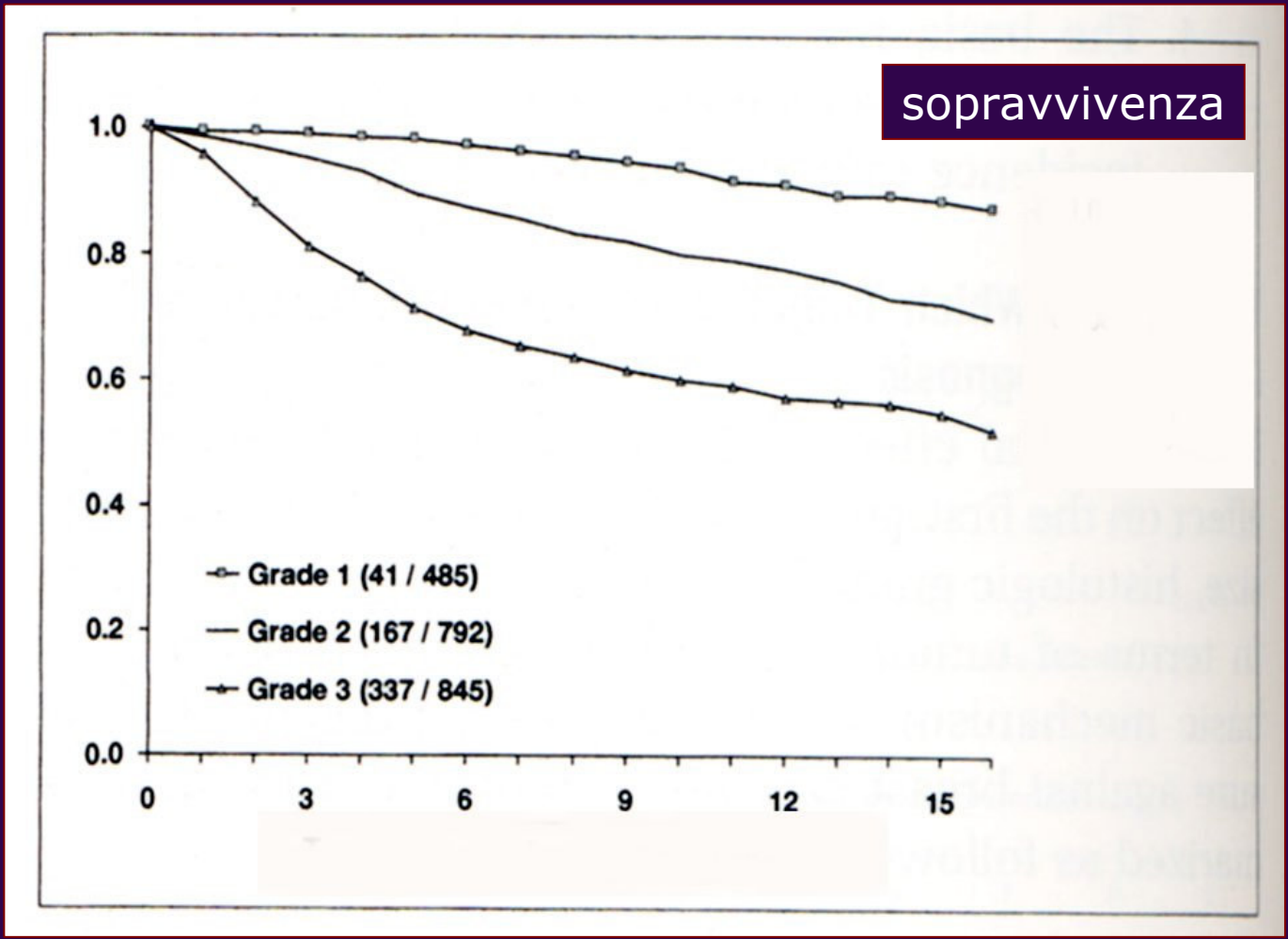
3-5: G1
6-7: G2
8-9: G3

Elston, Ellis 1991

Grading (mammella)

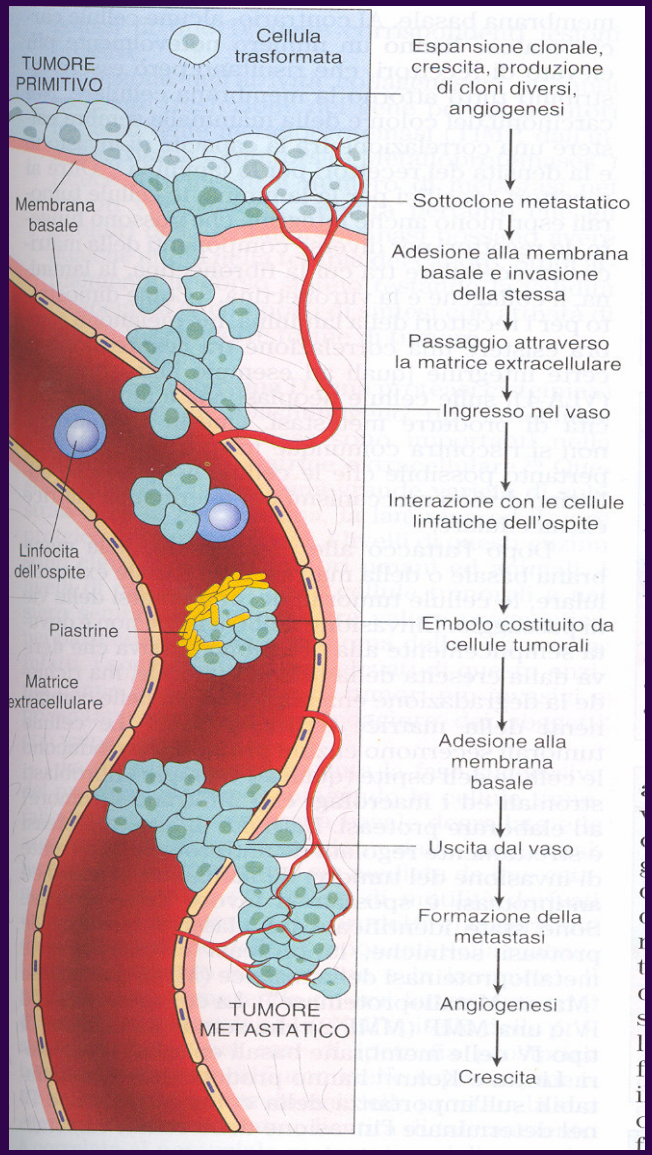


Grading (mammella)



disseminazione e metastasi

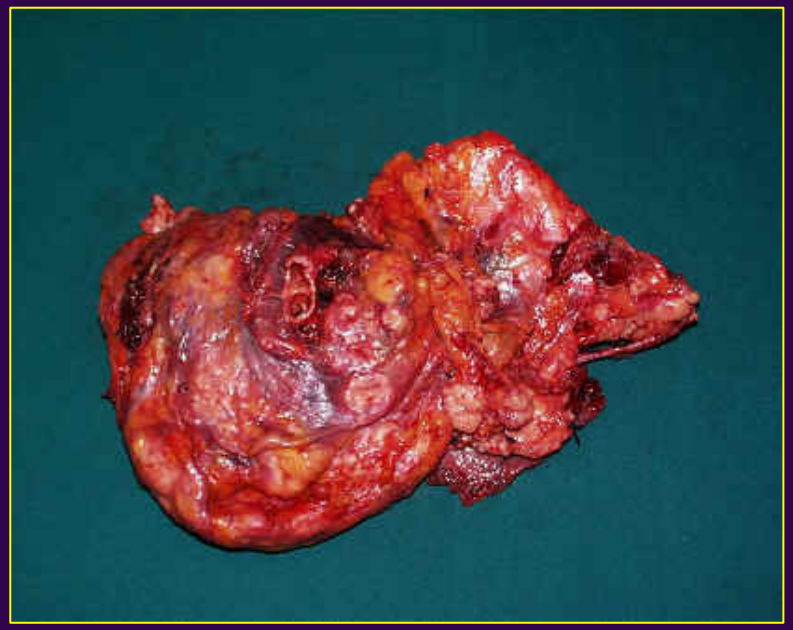
Invasione e metastasi

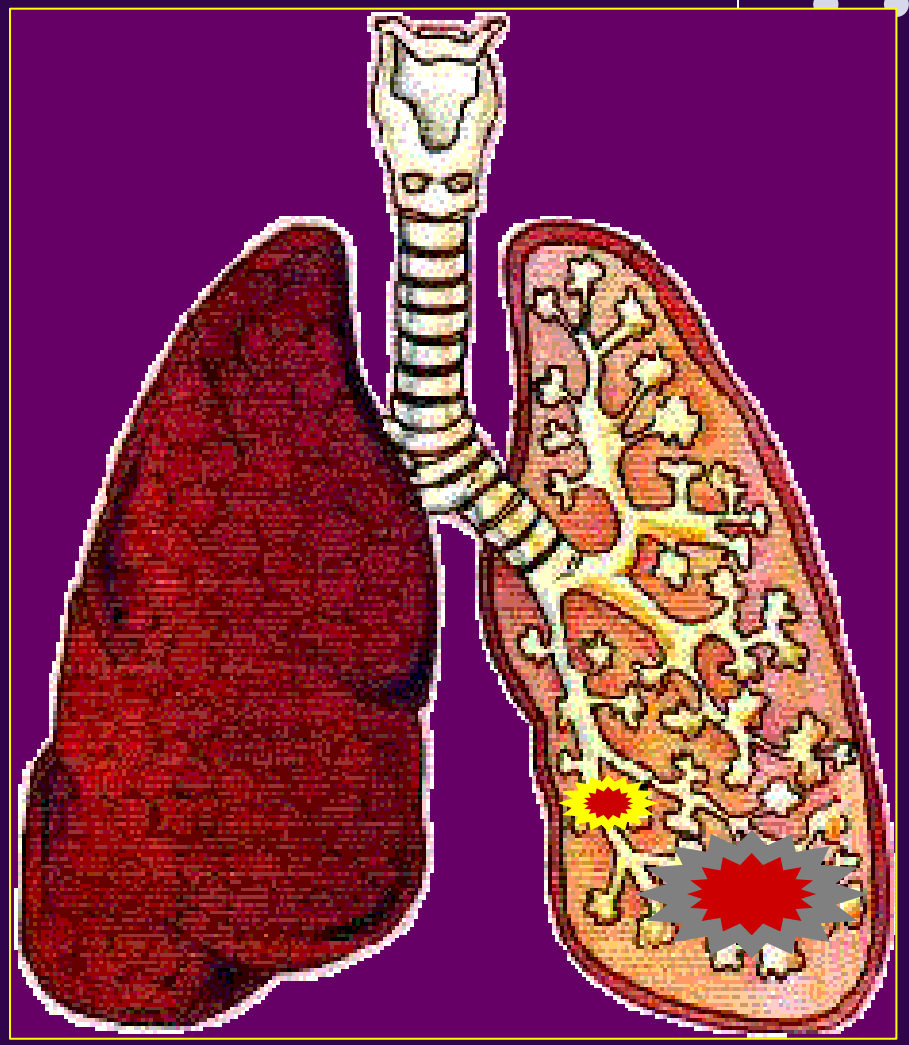


- **Distacco delle cellule tumorali**
- **Attacco alle componenti della matrice**
- **Degradazione della matrice**
- **Migrazione delle cellule tumorali**

Vie metastatiche

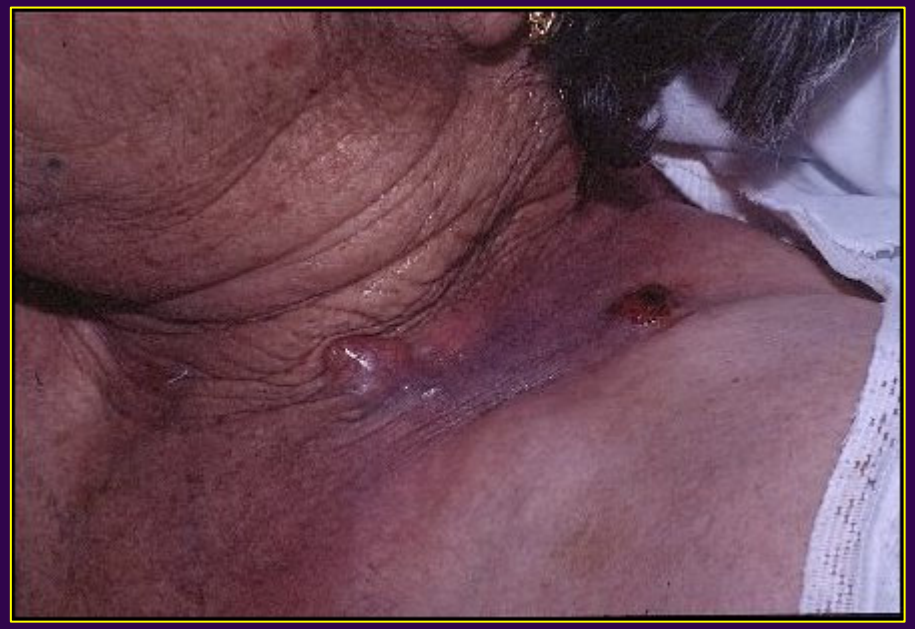
1. Continuità

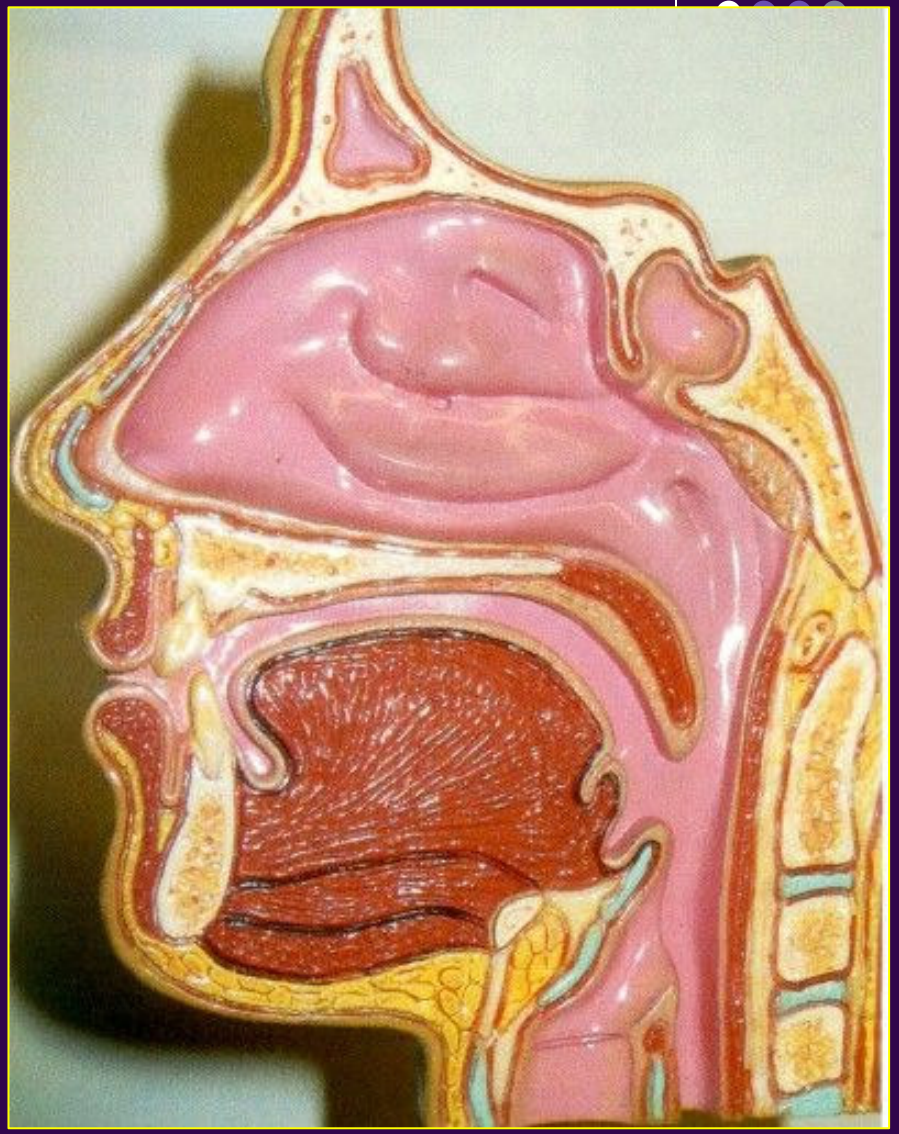




Vie metastatiche

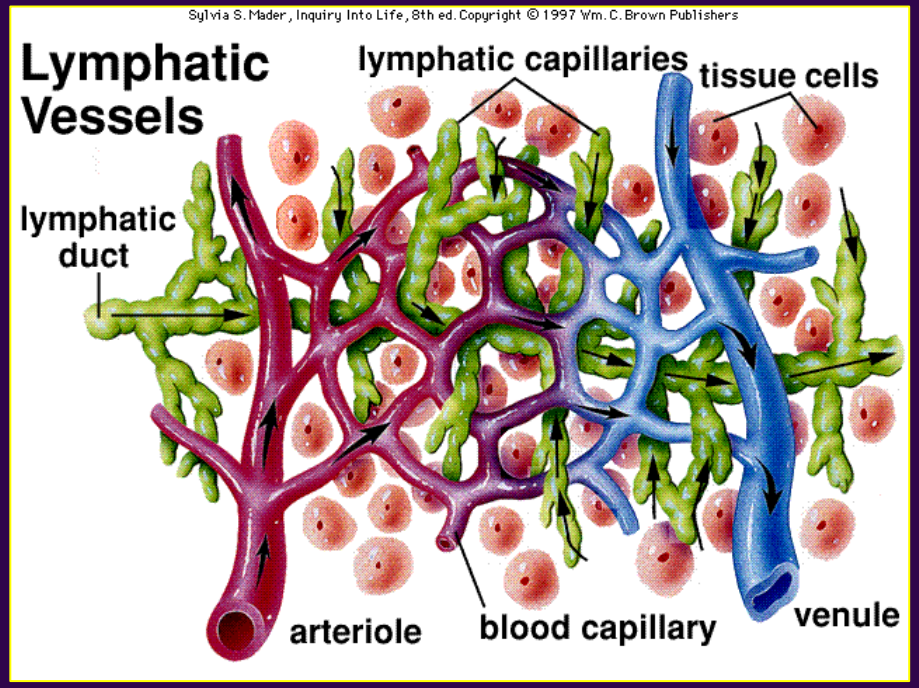
2. Contiguità

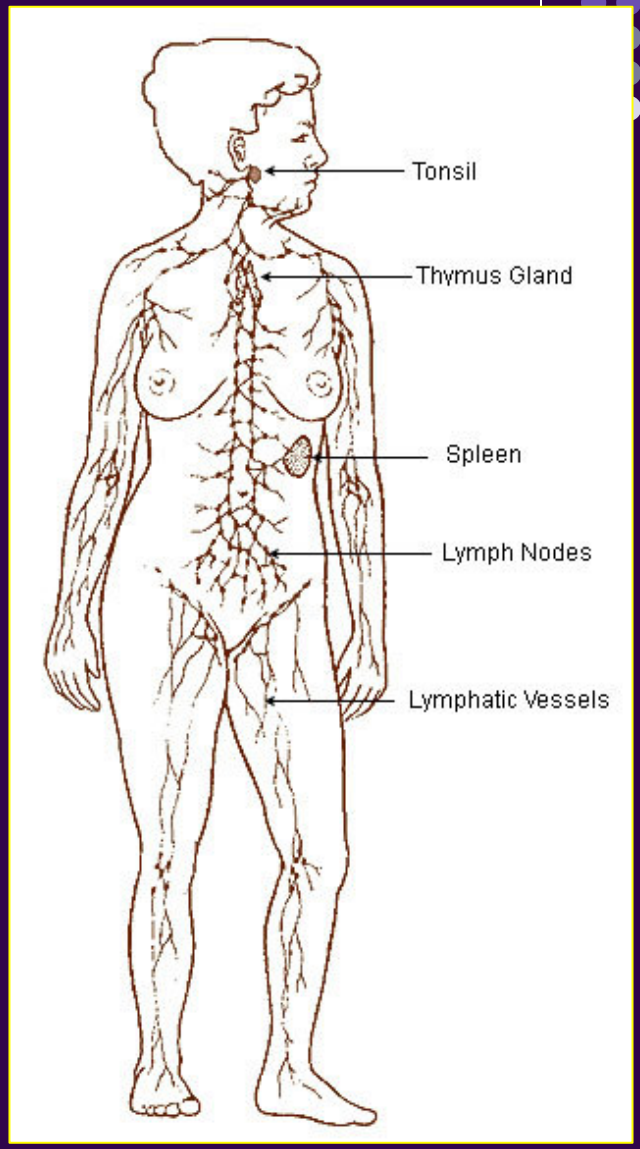




Vie metastatiche

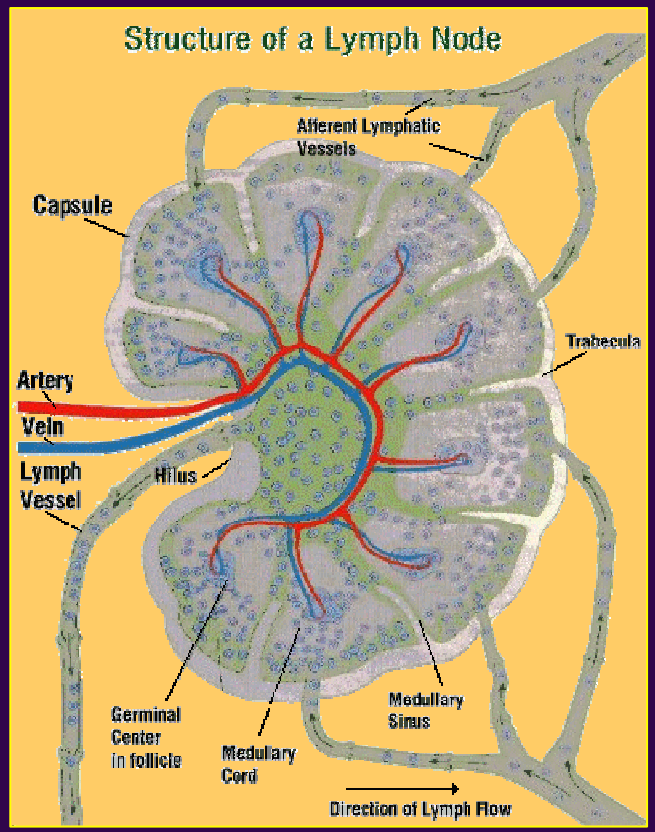
1. Via linfatica

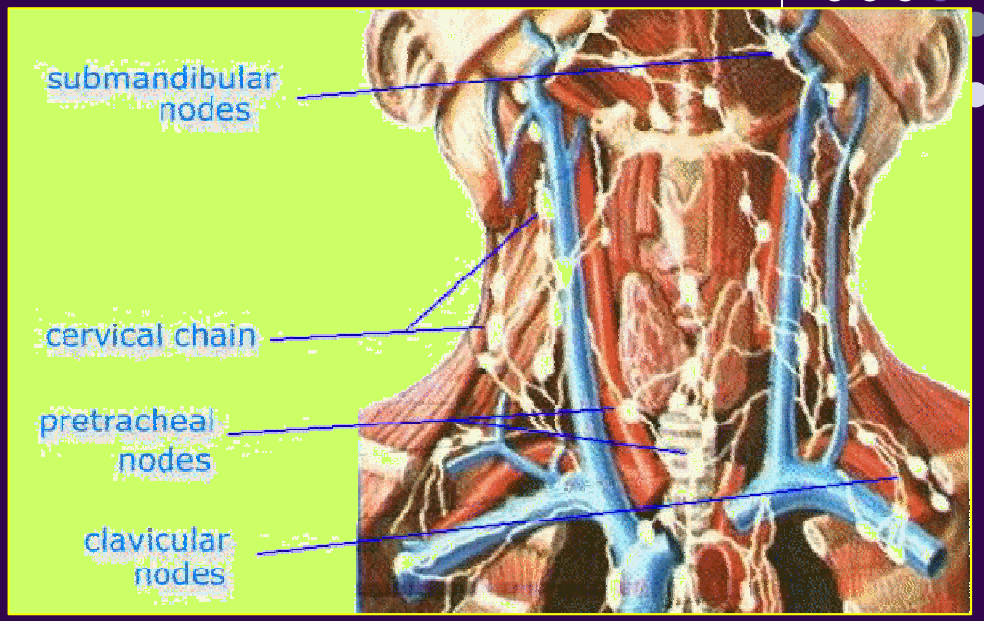


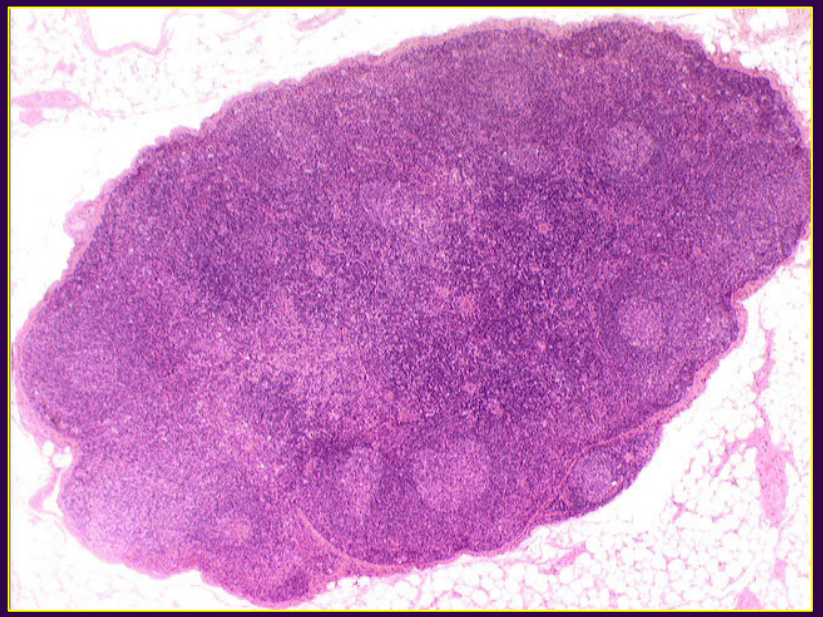


Vie metastatiche

2. Via linfatica

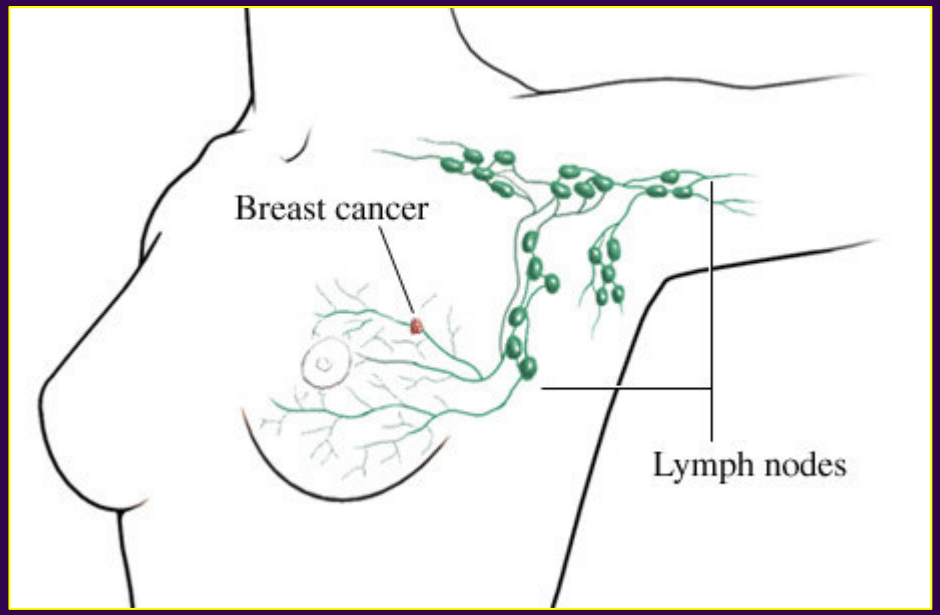


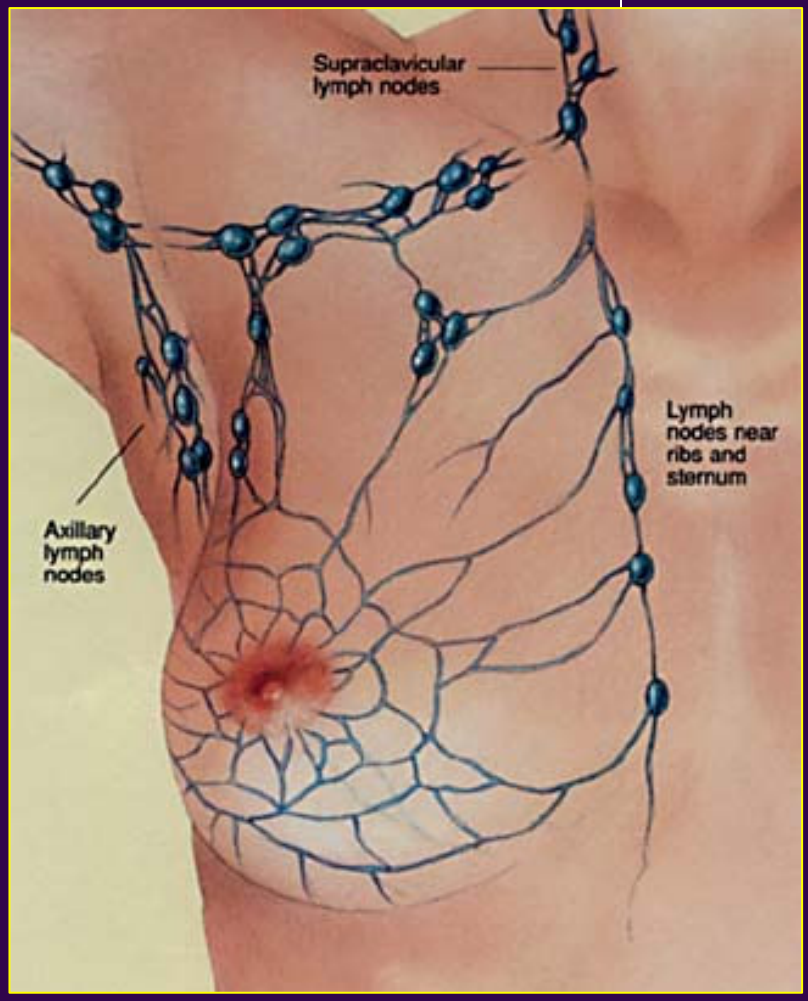




Vie metastatiche

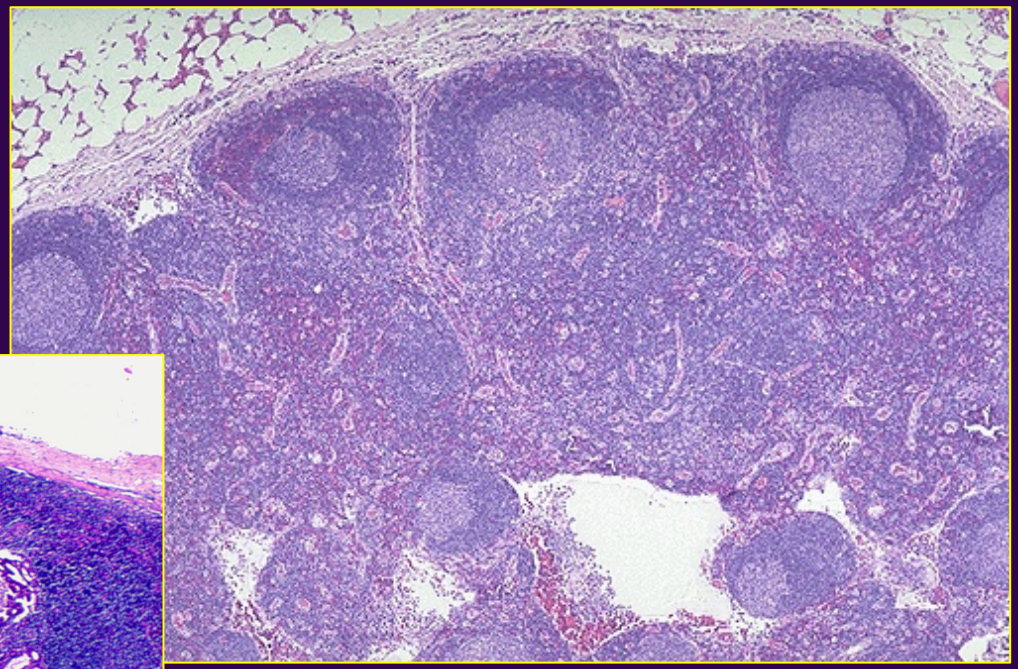
3. Via linfatica

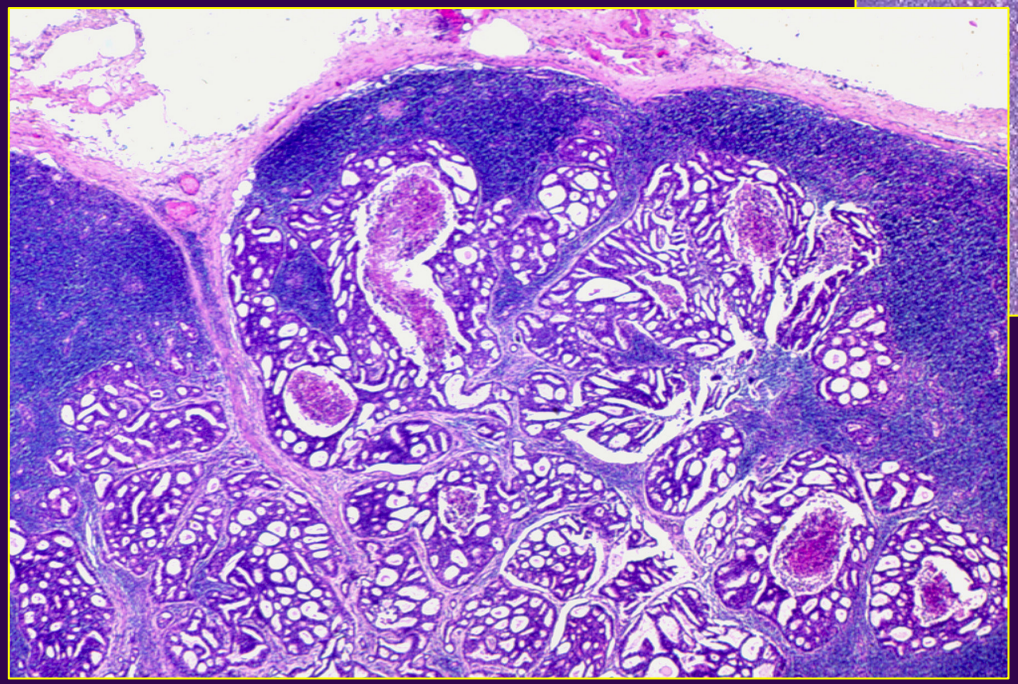




Vie metastatiche

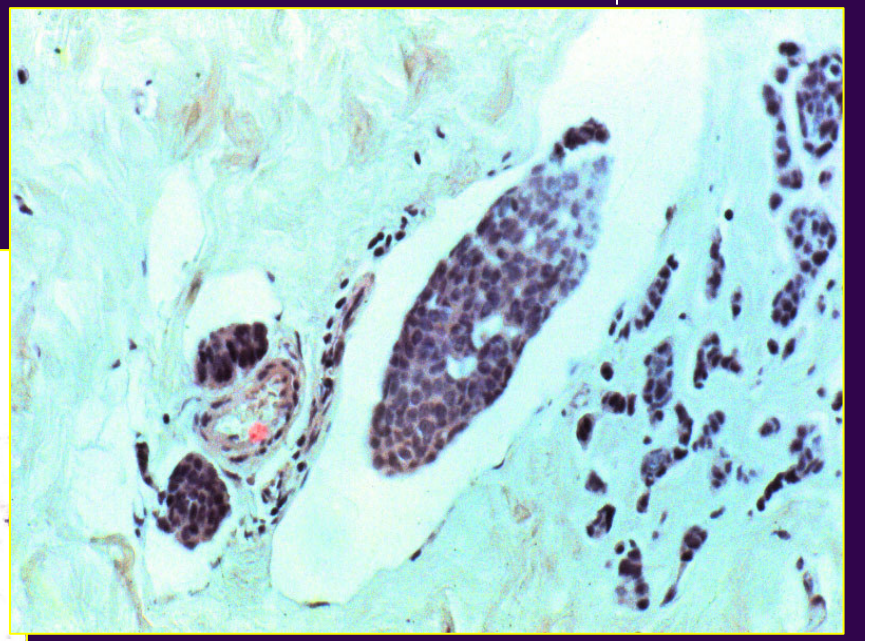
4. Via linfatica



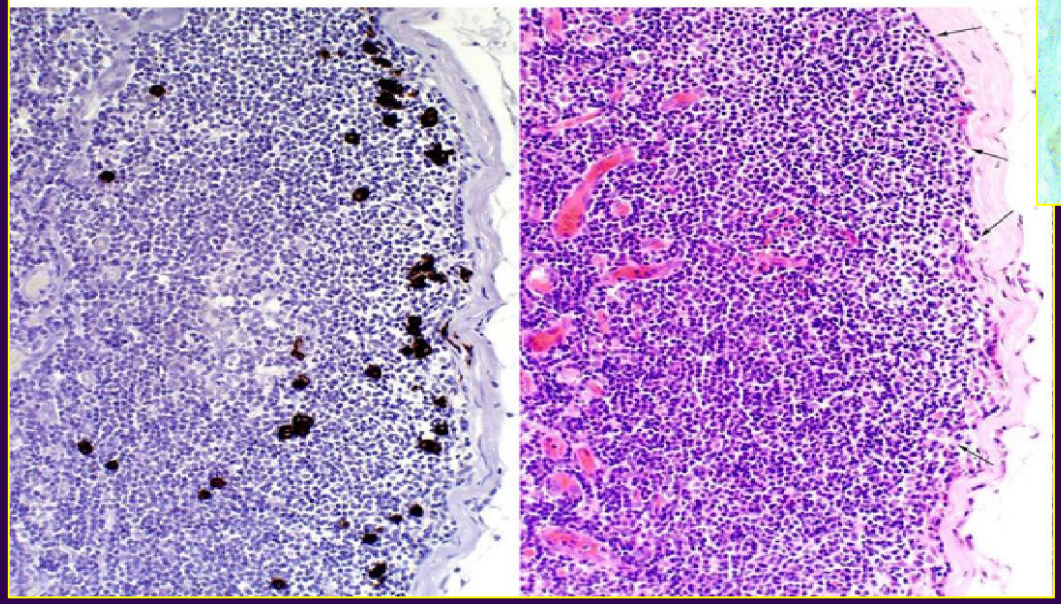


Vie metastatiche

5. Via linfatica

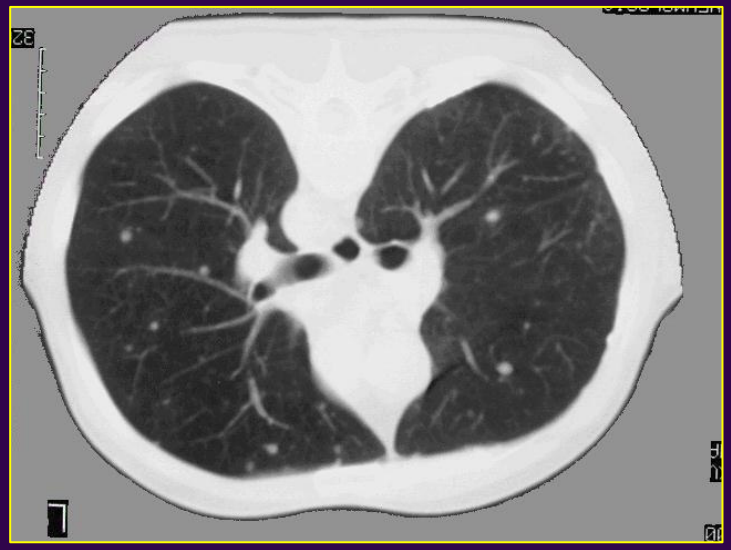


MICROMETASTASI LINFONODALE
CARCINOMA LOBULARE (N0Im+)



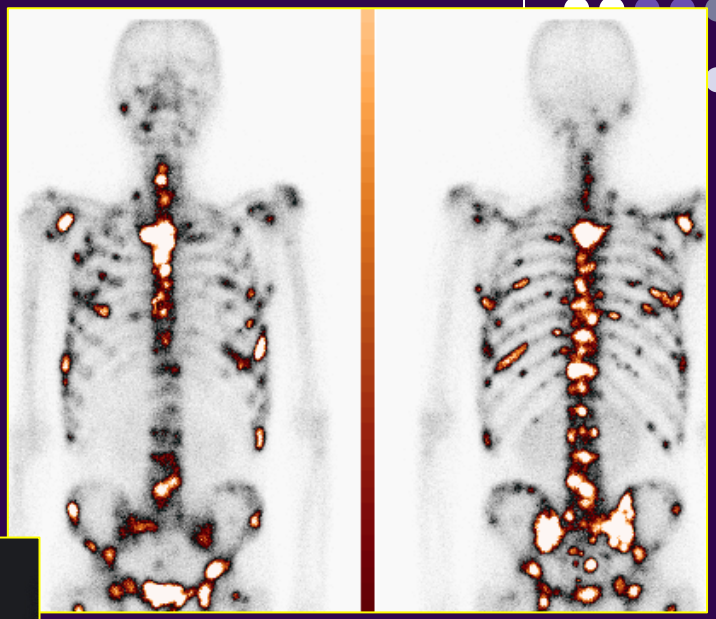
Vie metastatiche

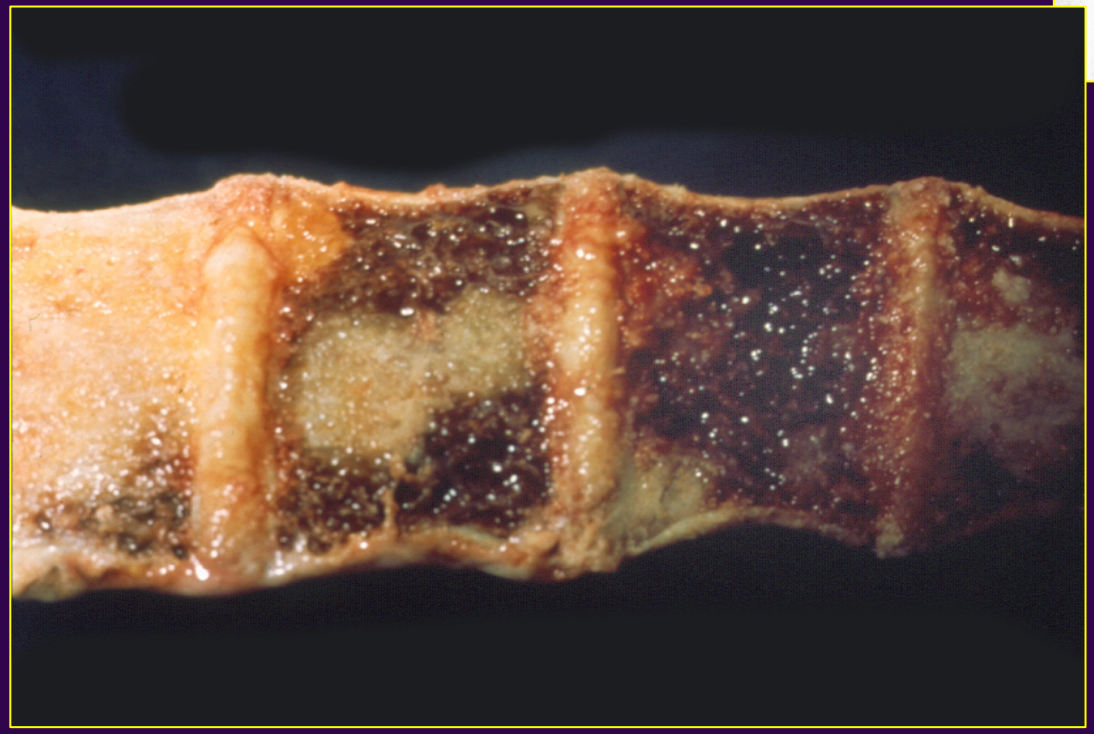
1. Via ematica



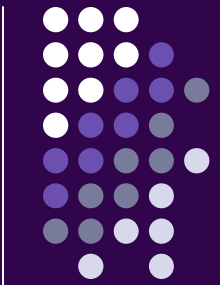
Vie metastatiche

2. Via ematica





Tropismo d'organo (meccanismi)



- rapporto tumore-ligandi degli organi bersaglio
- chemiotassi d'organo
- fattori "ambientali" favorevoli/sfavorevoli

Caratterizzazione biologica

Caratterizzazione biologica delle neoplasie

Individuazione di marcatori molecolari considerati:

- **potenziali fattori prognostici**
- **bersaglio terapie mirate**

Caratterizzazione biologica: esempi

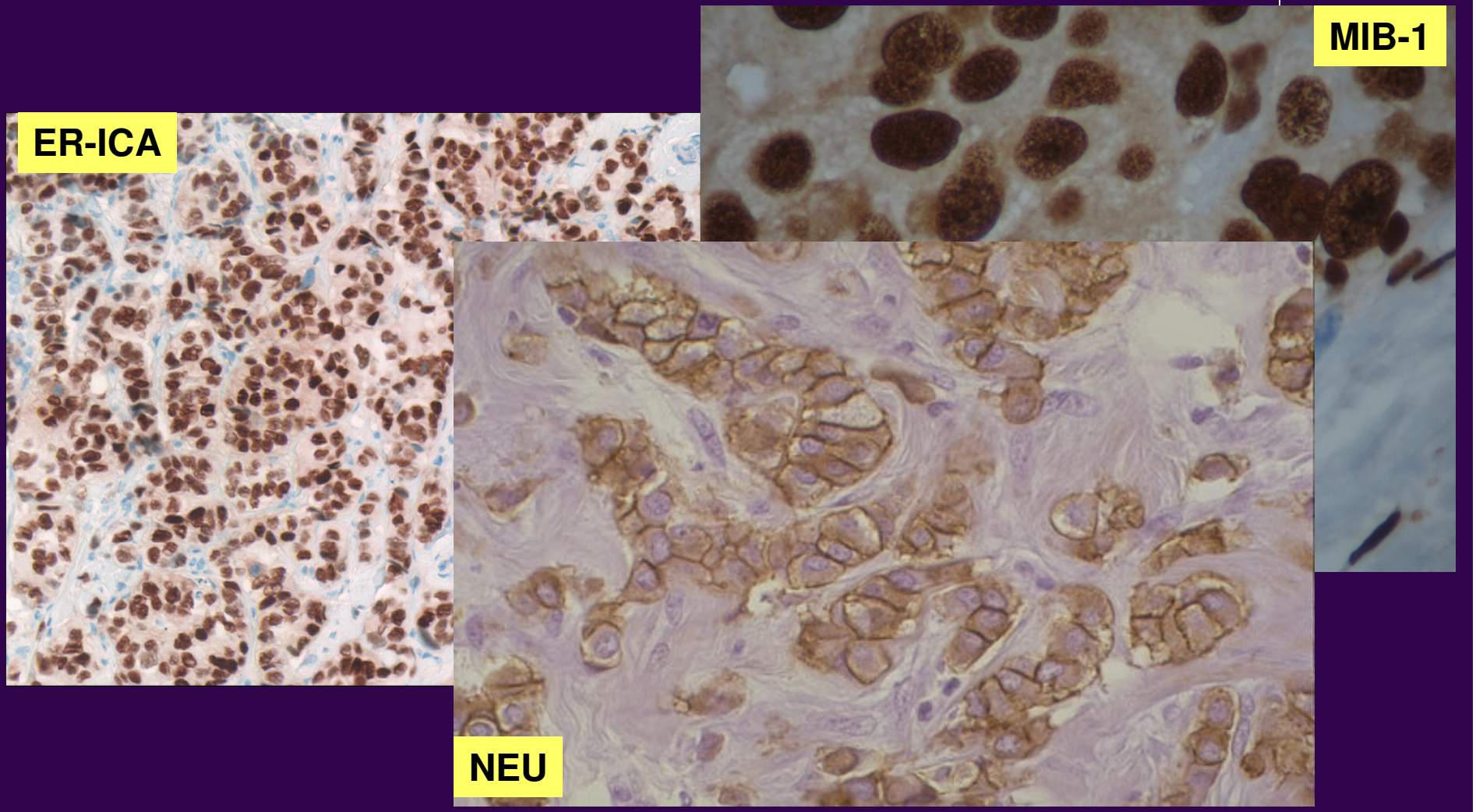
Carcinoma mammario:

- Recettori estroprogestinici (ER, PR)
- Attività proliferativa (MIB-1)
- Oncogeni (HER2/neu)
- Oncosoppressori (p53)

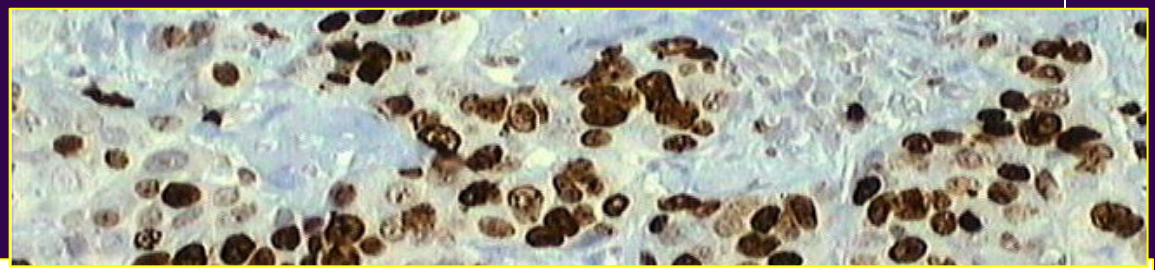
Carcinoma colorettale:

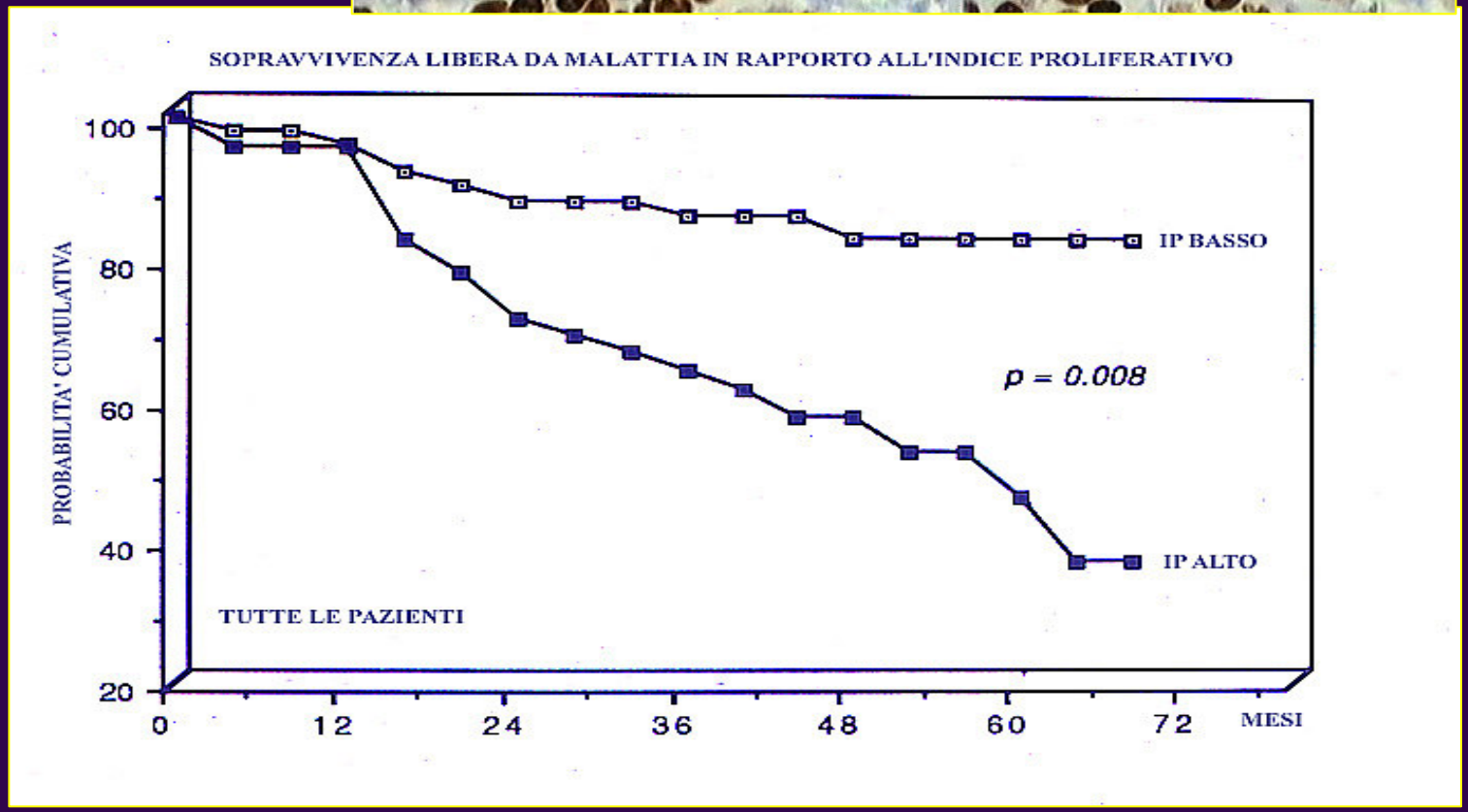
- Indicatori di DNA repair
- Instabilità microsatelliti (MSI)
- Oncogeni/oncosoppressori
- Proliferazione cellulare
- Angiogenesi
- Markers di invasione

Caratterizzazione biologica: esempi



Caratterizzazione biologica: esempi





Checklists di refertazione

Azienda Ospedale-Università di Ferrara
ANATOMIA, ISTOLOGIA E CITOLOGIA PATOLOGICA

PATOLOGIA MAMMARIA - SCHEDA DIAGNOSTICA

Paziente MAM/ 2001/ 14 — N° Caso ..... — Data compilazione 31/1/2001
N° MAM PREC/ ..... — N° Prec .....
Screening ☒ SI ☐ NO

Cognome — Nome
Luogo di nascita FERRARA — Data di nascita 09/09/1925
Reparto CLINICA CHIRURGICA

Campione

Procedura: Y5405 QUADRANTECTOMIA + LINFONODO SENTINELLA
Sede del Prelievo: 04034 MAMMELLA SINISTRA QSE
Radiografia: ☒ SI ☐ NO ☒ LESIONE PRESENTE ☐ LESIONE ASSENTE

Reperto Macroscopico

Dimensioni:
- ☒ CAMPIONE mm 60 x 50
- ☒ CUTE mm 40 x 20
- ☒ TUMORE mm 8 x 4

Margini: ☒ ESENTI ☐ INTERESSATI
Marcatura ☒ SI ☐ NO

DIAGNOSI

Calcificazioni: ☐ ASSENTI ☐ BENIGNE ☐ MALIGNE ☐ ENTRAMBE

Lesioni benigne:
☐ LESIONE SCLERO-ELASTOSICA ☐ ADENOSI ☐ ADENOMA DUTTALE ☐ Altro...
☒ MASTOPATIA FIBROCISTICA ☐ ADENOSI SCLEROSANTE ☐ FIBROADENOMA
☐ ECTASIA DUTTALE ☐ PAPILLOMA SOLITARIO ☐ PAPILLOMI

Proliferazione epiteliale:
☐ ASSENTE ☐ PRESENTE CON ATIPIA (DUTTALE)
☒ PRESENTE SENZA ATIPIA ☐ PRESENTE CON ATIPIA (LOBULARE)

Carcinomi in situ:
☐ ASSENTE ☐ LOBULARE
☐ DUTTALE ALTO GRADO NUCLEARE ☐ MALATTIA DI PAGET
☒ DUTTALE GRADO BASSO/INTERMEDIO ☐ DIMENSIONI (solo duttale) mm 5

Tipo: ☒ BEN DIFFERENZIATO ☐ INTERMEDIO ☐ SCARSAMENTE DIFFERENZIATO

Istotipo:
☐ COMEDO ☒ CRIBRIFORME ☐ PAPILLARE ☐ CISTICO IPERSECRETORIO
☐ SOLIDO ☐ MICROPAPILLARE ☐ APOCRINO ☐ ALTRO .....

Microinvasione: ☐ ASSENTE ☐ PRESENTE ☐ POSSIBILE

Carcinomi invasivo:
☐ ASSENTE ☐ CARCINOMA PAPILLARE
☒ CARCINOMA DUTTALE NAS ☐ CARCINOMA MIDOLLARE
☐ CARCINOMA TUBULARE ☐ CARCINOMA LOBULARE
☐ CARCINOMA CRIBRIFORME ☐ ALTRO .....
☐ CARCINOMA MUCINOSO ☐ NON TUMORE RESIDUO

STADIAZIONE

Diametro max tumore invasivo mm 3 — Diametro complessivo con DCIS esterno mm 5

Linfonodi ascellari: ☒ SI ☐ NO — N° metastatici 0 — N° totale 1 — Extracapsulare ☐ SI ☐ NO

Altri linfonodi: ☐ SI ☒ NO — Sede ..... — N° metastatici ..... — N° totale .....

Margini: ☐ INTERESSATI ☐ INCERTI/NON VALUTABILI ☒ NON INTERESSATI — distanza mm .....

Grado: ☒ I ☐ II ☐ III ☐ NON CLASSIFICABILE

Invasione vascolare (ematica o linfatica) ☐ SI ☒ NO — Cute ☒ INDENNE ☐ INFILTRATA

DIAGNOSI ISTOLOGICA ☐ NORMALE ☐ BENIGNA ☒ MALIGNA — pT T1a — pN N0(sn)(I-)

NOTE/COMMENTI/INFORMAZIONI SUPPLEMENTARI

VEDI BT/2001/00170

PATOLOGO Prof.ssa PATRIZIA QUERZOLI

Ricadute operative

- tutela dell'informazione
- indagini "high resolution"
- valutazioni cliniche, percorsi assistenziali


grazie!