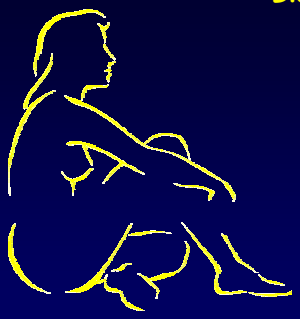
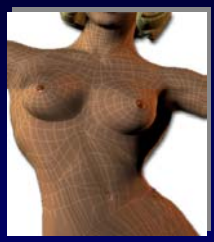
Biology of reproduction
Female Cancers



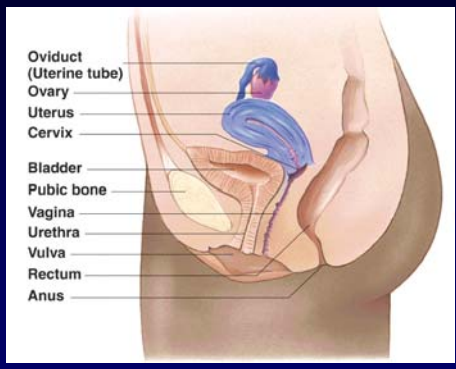


Achim Rody, M.D.

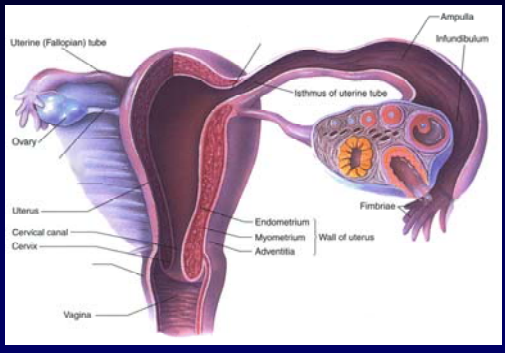
Department of Obstetrics and Gynecology

J. W. Goethe-University Frankfurt

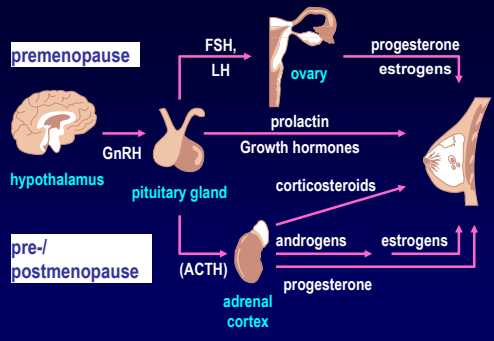
The Female Reproductive System



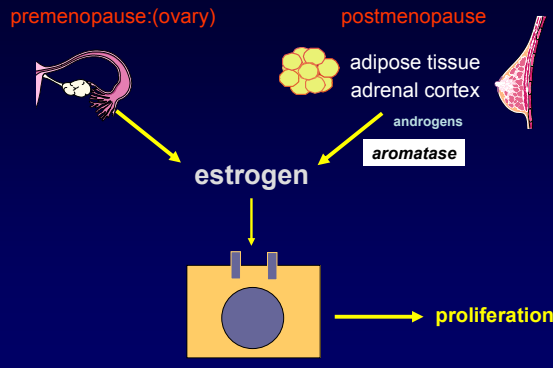
The Female Reproductive System



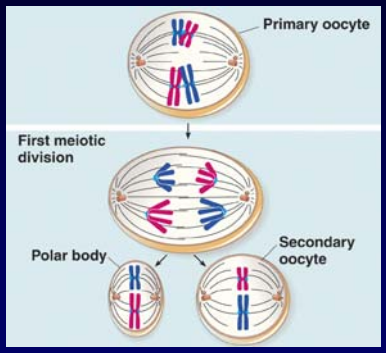
Endocrine regulation of female organs



Estrogens: where do they come from ?



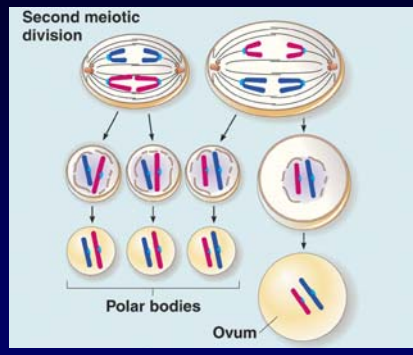
Oogenesis: Meiosis I



Meiosis II of Oogenesis

- The first polar body may undergo a further division or not; in either event, the polar bodies ultimately disintegrate
- The secondary oocyte remains in meiosis II until fertilization
- Oogenesis results in one haploid ovum

Oogenesis: Meiosis II

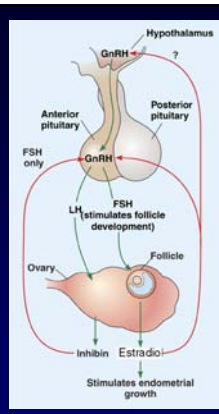


Production of the 2^{O} Oocyte

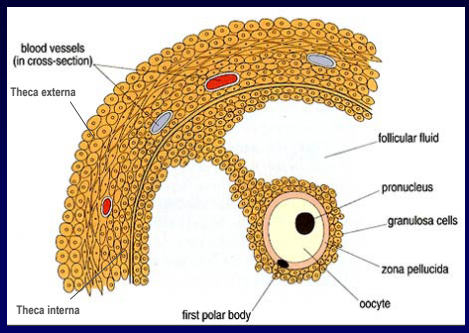
- The cells of the follicle secrete fluid, as well as estrogens
- Typically, one follicle matures fully each month
- The secondary oocyte is ejected from the follicle during ovulation
- The remaining follicular cells form the corpus luteum
  - The *corpus luteum* is a temporal endocrine organ that secretes progesterone and estrogens

Hormones, Follicle, and Endometrial Development

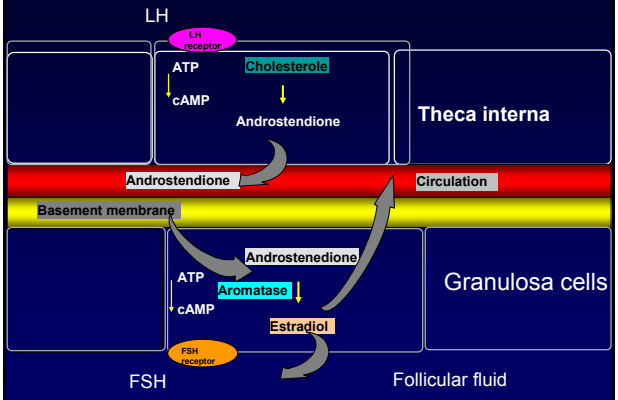
- During the menstrual phase, in which the *endometrium* is shed, GnRH is released, which stimulates the *anterior pituitary* to release FSH and LH
- FSH stimulates the development of a few *follicles* in the ovary
- During the *preovulatory phase*, the developing follicles secrete *estrogens*
- *Estradiol* stimulates the development of the *endometrium* and the follicular cells



Ovulatory follicle

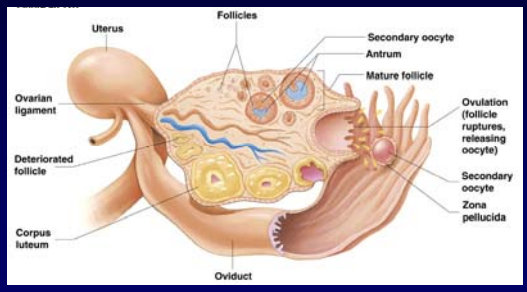


Steroidogenesis in ovary

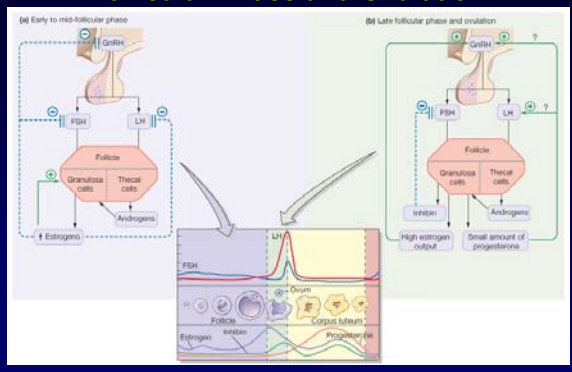


The Oviduct

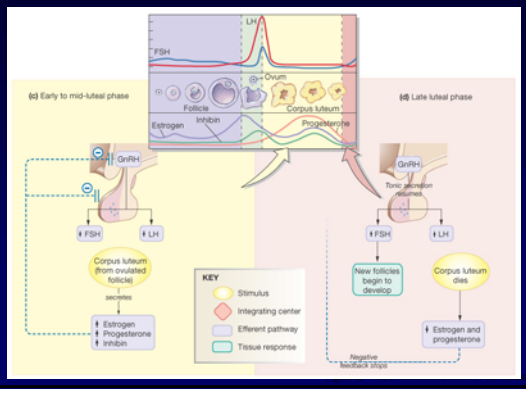
- The oviduct receives the secondary oocyte,which moves by peristalsis and ciliary beating down the oviduct toward the uterus
  - A successful fertilization occurs in the oviduct



Endocrine Control of Menstrual Cycle: Follicular Phase and Ovulation

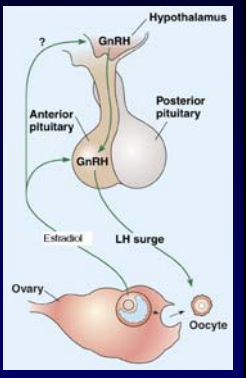


Endocrine Control of Menstrual Cycle: Luteal phase and Late Luteal phase



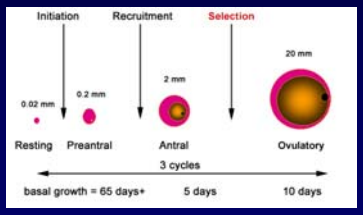
Hormones and the Menstrual Cycle

- LH stimulates theca cells to grow & produce androgens
- One dominant follicle continues to grow
- Granulosa cells of that follicle respond to LH & FSH & secrete estrogen
- Estradiol peaks in the late preovulatory stage & causes a surge in LH because it stimulates the anterior pituitary
- Granulosa cells secrete inhibin and finally have effect on FSH blood concentrations so FSH drop off just prior to ovulation



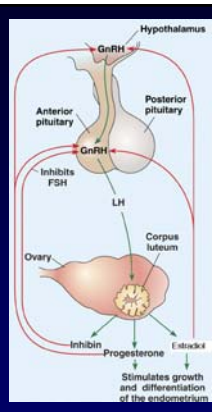
Selection of dominant follicle

1. The smaller the follicle, the lower the aromatase activity
   A) Androgens ↑
   B) Estrogens ↓
- Growing follicle has a high aromatase activity by FSH-Stimulation
   A) Estrogens ↑
   B) Inhibin ↑ (suppresses FSH release)
1. Follicles, which do not have further growth accumulate androgens (follicular arrest, atresia)



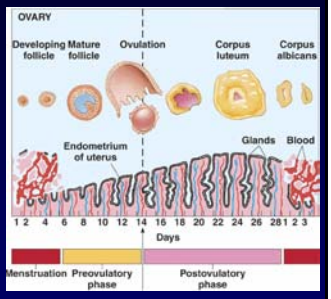
Late Postovulatory

- The LH-surge causes ovulation & supports development of the follicle residual, the *corpus luteum*
- The postovulatory phase occurs after ovulation
- The corpus luteum is itself a gland and secretes progesterone and estrogen as well as inhibin

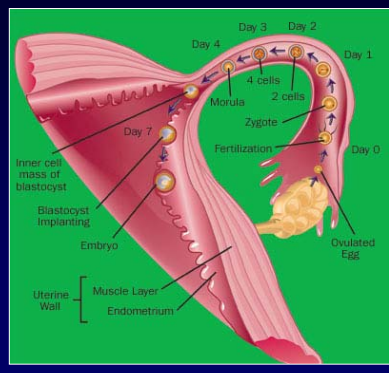


The Menstrual Cycle

- The corpus luteum begins to degrade after ~8 days. Progesterone support falls off, and the endometrium arteries constrict
- Menstruation begins; anterior pituitary inhibition drops and it begins to secrete LH and FSH again
- This cycle repeats every ~ 28 days

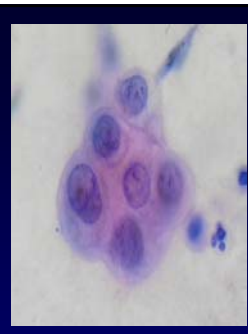


Fertilization and early pregnancy



Case report # 1

- 58 aged women
- Obstipation and feeling of fullness
- Shortage of breath during activity
- Increase of abdominal circumference
- Office-based gynecologist performed a PAP-smear
  - papillary tumor cells



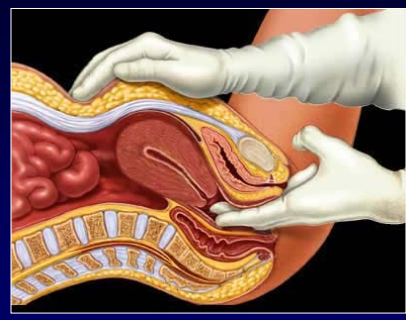
Blood check

- Anemia
- Slightly elevated infection parameters
- Elevated liver enzymes
- Tumor marker CA-125 ↑↑

Ultrasound

cystic-solid masses + ascites

palpation



Adnexal masses: diagnostic procedure

preoperative: palpation, TVS, CA 125
menopausal status

- evident malignant
- suspicious
  - Large mass, solid → **Transfer to oncologic center** laparotomy + staging
  - **laparoscopy:** diagnostic, lavage
    - suspicious → **Break off laparoscopy** ! **Laparotomy + Staging with optimal conditions !**
    - not suspicious → **Continue laparoscopy !** Cystectomy/ Oophorectomy
- minor suspicious → **laparoscopy:** diagnostic, lavage

Ovarian cancer - Germany (2003)

incidence / year		**7,400 Pat**
	sporadic type (Stage I-IV)	6,800 Pat
	hereditary type (Stage I-IV)	600 Pat
Stage and diagnosis	Stage I-IIa	1,700 Pat (25%)
	Stage IIb-IV	5,700 Pat (75 %)
response to primary therapy		70-80%
	Stage IIb-IV	(4,400 Pat)
recurrences during course of disease		75- 80 %
	Stage I - IV	(5,800 Pat)
median surival	Stadium IIb-IV	45 Mo.
5-year overall survival	Stadium I-IV	52 %

Stages of ovarian cancer

related to 100 patients

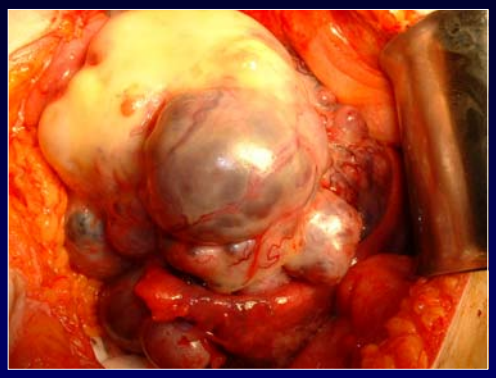
25 „early"		75 „advanced"	
Low Risk	High Risk	optimal	suboptimal
5	20	50	25
- Borderline - Stage Ia /Ib (G 1)	- Stage Ia/Ib (G2 + G3) - Ic - IIa (Ø Tu)	- Stage IIb IIIc (< 1cm)	- Stage III (> 1cm) - Stage IV
> 90%	56-88%	20-40%	< 20%

Chance of 5-year survival

surgical treatment of ovarian cancer

1. laparotomy by vertical incision
2. Aspiration of abdominal fluids (for detection of tumor cells)
3. Exploration of the whole abdominal cavity
4. Biopsy of all suspicious lesions
5. Hysterectomy + bilateral salpingoovarectomy
6. omentectomy
7. Blind-biopsy : ≥ 2 peritoneum of the bladder and the douglas
   ≥ 2 peritoneum of the pelvis
   ≥ 3 paracolic
   ≥ 2 diaphragma
8. Pelvic/ paraortal lymphadenectomy

Trimbos J. et al. : *Obstet Gynecol Surv 1994 49: 814-16*



Surgery of ovarian cancer

goal: tumor residuals 0 - ≤ 1 cm

Ovarian Cancer

„early Stage Disease“

Prognostic factors:

- Stage/ tumor dissemination
- differentiation
- histological subtyp
- extension/ quality of staging procedure
- ascites
- adhesions
- age
- general condition

Helpful markers:

- DNA Ploidie
- S-phase fraction
- PDGF and PDGFR-α
- Ki 67
- p53 protein
- Bcl2
- disseminated tumor cells

Dembo AJ et al (1990) *Obstet Gynecol 75: 263*

Tropé C. et al (2000)

Treatment of early stage ovarian cancer

25 Pat „early stage“ Ov-Ca

„advanced“ Ov-Ca 75 Pat

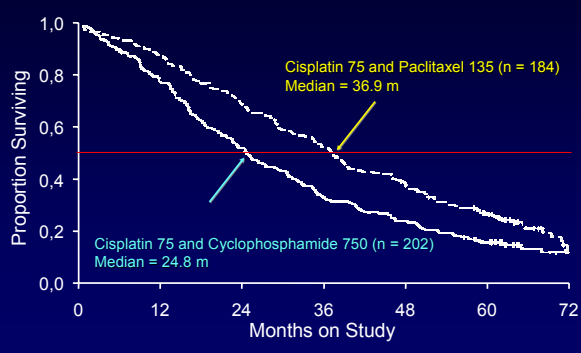
Surgical staging

Low Risk	High Risk
- Stadium : Ia (Ib) - grade: G 1	- Stadium Ia/Ib (G2 + G3) Ic -IIa (Ø Tu)
observation	adjuvant Chemotherapy (Taxane/ Platinum)
> 95%	56-88%

disease-free survival (5 years)

GOG111

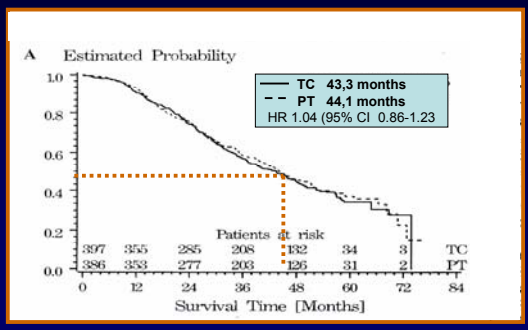
(Suboptimal debulking, stage III/IV)



McGuire, et al. *N Engl J Med* 334:1-6, 1996

Journal of the National Cancer Institute, Vol. 95, No. 17, 1320-1329, September 3, 2003

A Randomized Clinical Trial of Cisplatin/ Paclitaxel Versus Carboplatin/ Paclitaxel as First-Line Treatment of Ovarian Cancer (AGO-*OVAR* 3)



Case report #2

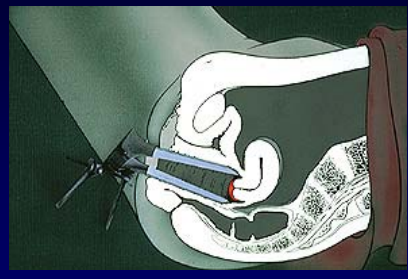
- 45 aged women
- Bloody vaginal discharge for three weeks
- Weight loss (10 kg within 2 months)
- Uncontrolled loss of fluids
- Painful left flank

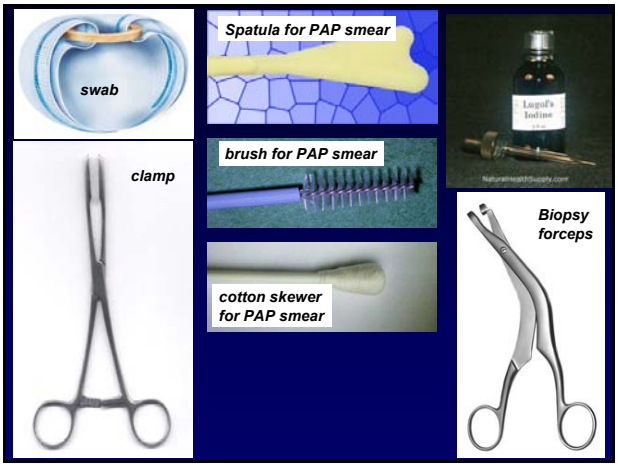
Oncological reasons for vaginal bleeding

- Gynecological carcinomas
  - Cervical cancer
  - Endometrial cancer
  - Vaginal cancer
  - Ovarian cancer
  - Cancer of the fallopian tube
- Urological carcinomas
  - Bladder cancer
  - Urethral cancer
  - Renal cancer
- Colorectal cancer

these organs are in close relationship to the vagina !

Clinical examination





Acetic acid test – mode of action

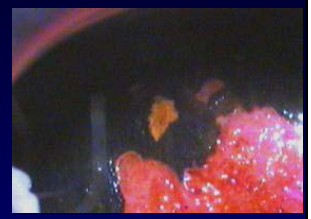
- Acetic acid
  - Dissolves mucus
  - Induction of intracellular dehydratation
  - causes coagulation of proteins
- Visible cells with:
  - nucleus-plasma-relation
  - nuclear density
  - chromosomal aneuploidies
- sensitivity: 70-92%
- positive predictive value: 15-20 %

Acidic white zones visible – test is positive

Lugol´s jodine test

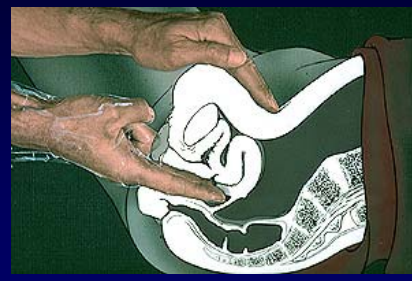
- Squamous cells contain glycogen, dysplasias or invasive cancer contain low or no glycogen
- iodine associates with glycogen – brown staining
- Glandular cells of transformation zone do not contain glycogen

acidic white zone



jodine negative zone

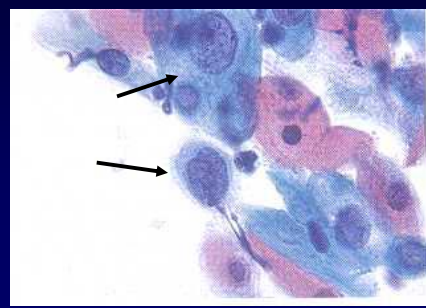
Clinical examination



nomenclature cytological diagnosis

Classi-fication	Cytological findings	WHO-nomenclature	recommendation
I	normal		checkup after 1 y.
II	Inflammatory, degenerative or metaplastic changes Hyper-/paraceratosis		checkup
III	dubious finding: • severe inflammation • suspect glandular cells		Suspect colposcopy: histology Otherwise checkup within 3 months
III D	slight or moderate dysplasia	CIN1/2	Suspect colposcopy: histology Otherwise checkup within 3 months
IV A	severe dysplasia or Ca in situ	CIN 3	Histology
IV B	severe dysplasia, Ca in situ, invasive Ca can not be excluded		Histology
V	invasive cancer		Histology

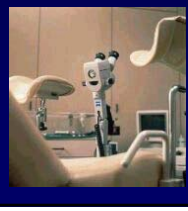
PAP smear with dysplastic cells

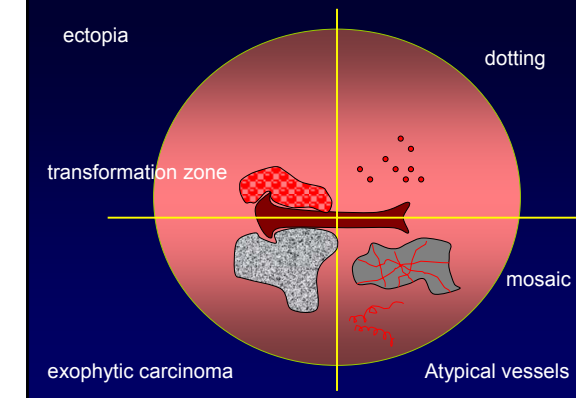


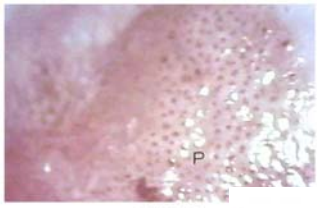
colposcopy

colposcopy:

- examination of cervix and vagina by loup (6 to 40 fold magnification)
- 3 % acetic acid (30 sec.)
- Lugol´s iodine

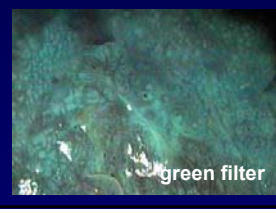






Transformation zone can not be evaluated

transformation zone can be evaluated



Epidemiology

- 6.580 women/year (Germany)
- 3,4 % of all female cancers
- 1,9 % of all female cancer deaths
- 5-year OAS 65 % (stagnation)

Inzidence and mortality according to age

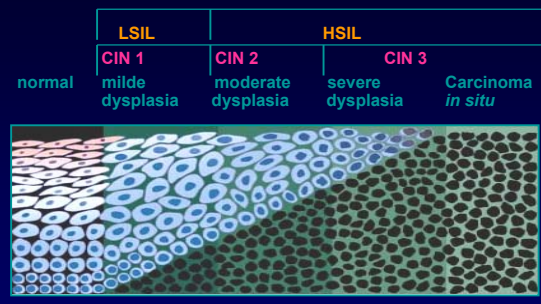
cases per 100.000 women (Germany)

age		
	incidence	mortality
< 45	11,5	1,3
45 to 60	23,8	5,7
60 to 75	16,4	7,7
> 75	22,0	14,3
total	15,7	4,5

risk factors

- early sexual activity
- promiscuous behaviour
- oral contraceptives
- nicotine abuse
- HPV-infection
  - verification in >85% of all cancers of the cervix
  - High risk type – 16, 18, 31, 33 (DNA-bound)
  - Low risk type – 6, 11, 42-44 (free DNA)
  - Oncogenes E6 (p53) & E7 (Rb)
- Immunodeficiency (e.g. HIV)

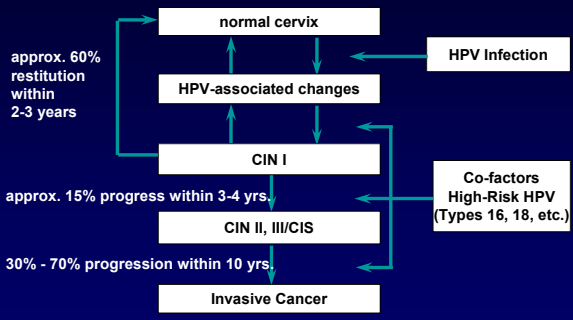
precursor lesions of cancer of the cervix



Wright TC, Kurman RJ, Ferenczy A: Precancerous Lesions of the Cervix. In Kurman RJ, ed: *Blaustein's Pathology of the Female Genital Tract*. 4th ed. New York: Springer-Verlag NY Inc, 1994.

LSIL = Low Grade Squamous Intraepithelial Lesion CIN = Cervical Intraepithelial Neoplasia
HSIL = High Grade Squamous Intraepithelial Lesion

pathophysiology



treatment options of CIN

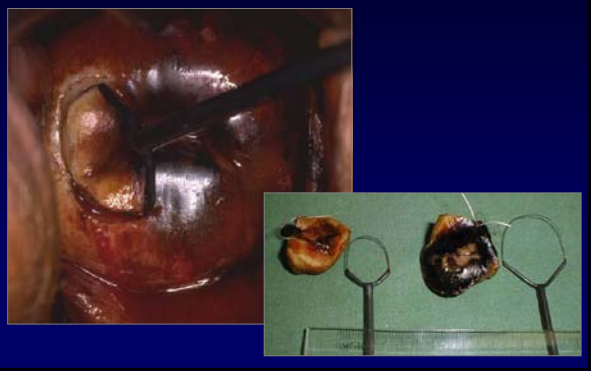
- **LEEP** (**L**oop **e**lectrosurgical **e**xcision **p**rocedure)
- **laser vaporization**
- **cryotherapy**

no histology !

- **conization**
- **in special cases: hysterectomy**

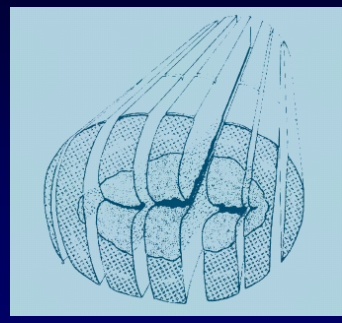
LEEP

= loop electrosurgical excision procedure

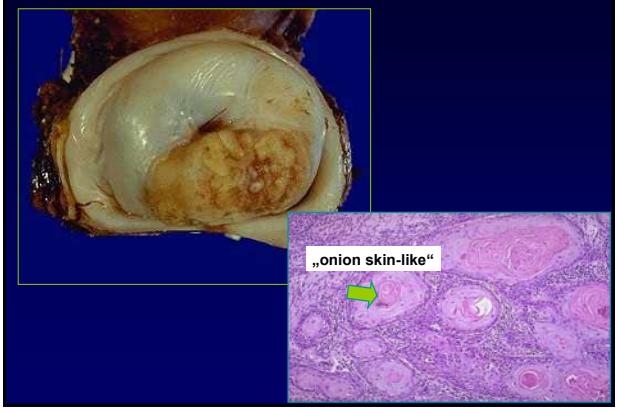


conization

histological assessment



exulcerated cancer of the cervix



histology

- squamous cell carcinoma 80-95%
  - keratinizing
  - non-keratinizing
- Adenocarcinoma 5-20%
- others:
  - clear cell carcinoma
  - sarcoma
  - glandulär-villous

symptoms

- **abnormal bleeding**
  - **meno-/metrorrhagia**
  - **after intercourse**
  - **postmenopausal bleeding**
- **Vaginal discharge**
- **other symptoms**
  - **deep venous thrombosis (leg)**
  - **pelvical pain**
  - **rectal/ vesical bleeding**
  - **incontinence**
- **asymptomatic !**

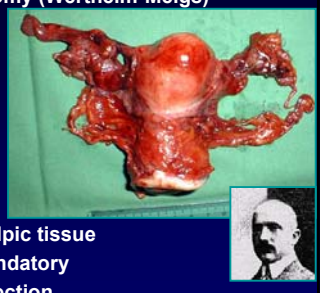
cancer spread

- continuously:
  - vagina
  - adnexae, ureter, ovary, pelvic wall
  - bladder
  - rectum
- lymphatic:
  - paracervical, obturatory, external and internal iliac artery, paraaortic
- hematogen: liver, lung, ….

surgical treatment

radical hysterectomy (Wertheim-Meigs)

Indication:
stage Ia2 to IIa (IIb)



En-bloc-resection of

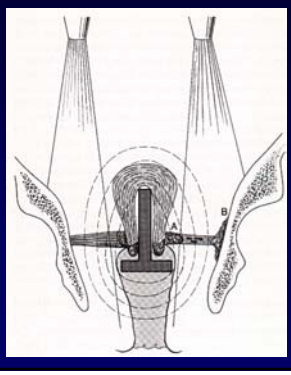
- **Uterus**
- **Parametria**
- **Sacrouterine ligaments**
- **vaginal cuff and paracolpic tissue**
- **adnexectomy is not mandatory**
- **pelvic lymph node dissection**
- **if necessary paraaortic lymph node dissection**

survival rates

FIGO stage	5-yrs. OAS
Stage I	81-96%
Stage II	65-87%
Stage III	35-50%
Stage IVA	15-20%

combined radiotherapy

inoperable stages (> IIB)

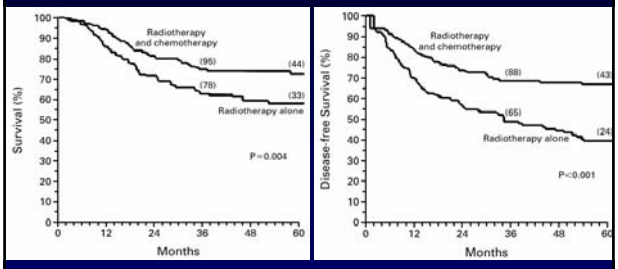


radiochemotherapy

- standard for treatment of advanced stages (> FIGO IIB)
- basics:
  1. percutaneous radiation
  2. afterloading radiation
  3. Low dose chemotherapy simultaneously (radiosensitizer, e.g. cisplatin)

combined radiochemotherapy

FIGO > IIb

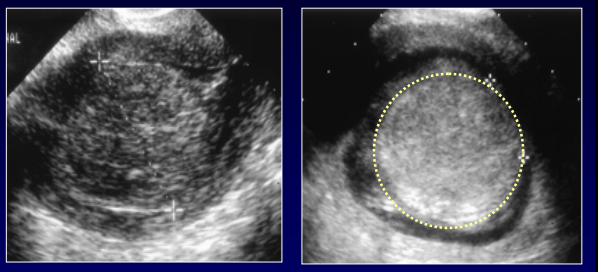


Morris et al., NEJM, Vol. 340, No.15, 1137-43, 1999

case report #3

- 62 year old nullipara
- vaginal bleeding since 5 days
- adiposity
- Insuline-dependent Diabetes mellitus
- Cytology: PAP IV A

Transvaginal ultrasound

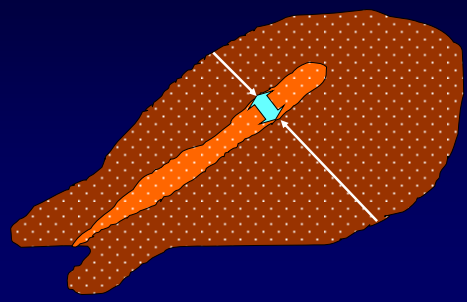


thickened endometrial layer (> 10 mm)

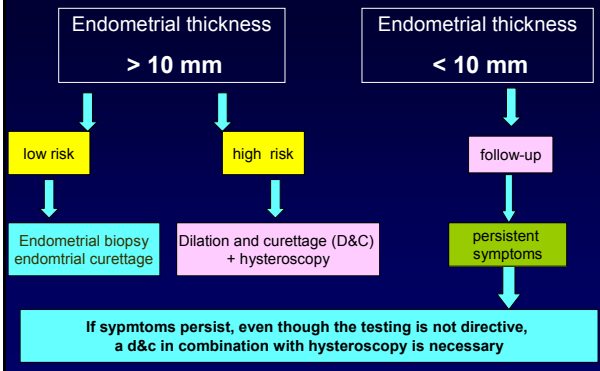
postmenopause

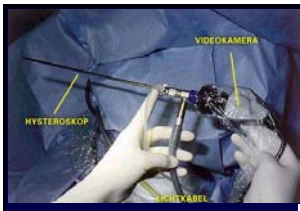
- time after occurence of menopause
  - amenorrhoea 12 months after the occurence of the last spontaneous menstrual bleeding
- often difficult to indicate
  - "hormone replacement therapy"
  - 80 % of all women over the age of 54 J. are postmenopausal (McKinlay et al, 1992)

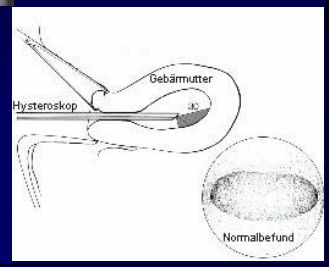
TVS

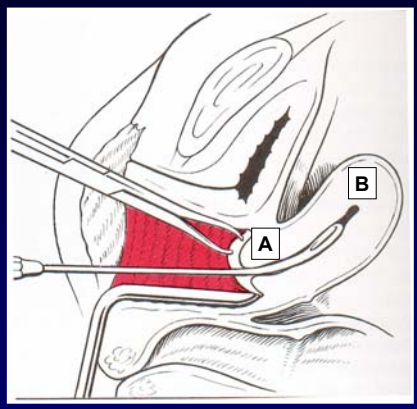


transvaginal ultrasound





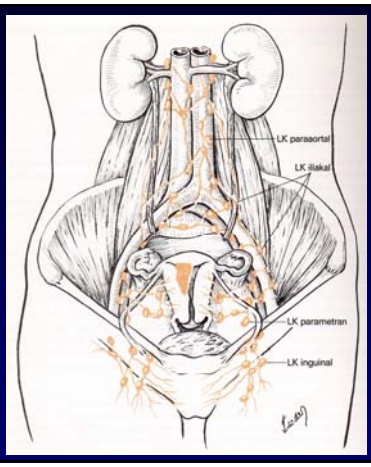




„endometrial cancer"
-classification-

Type I
- In pre- and perimenopausal women
- History of unopposed estrogen exposure
- Endometrial hyperplasia
- Minimally invasive
- low-grade endometrioid
- Good prognosis

Type II
- In older, postmenopausal women
- Not associated with estrogen exposure
- High grade endometrioid
- Papillary serous or clear cell carcinoma
- Poor prognosis



Endometrial cancer
- incidence -

- 30-35 incidences per 100.000 women/year
- 11.000 women in Germany per year
- median age: 66,4 years

endometrial cancer
- risk factors -

- age
- adiposity (RR 3.0 – 10.0)
- nulliparous (RR 2.0 – 5.0)
- late menopause (RR 2.4)
- diabetes mellitus (RR 2.8)
- estrogen exposure (RR 6.0 – 9.6)
- use of tamoxifen (RR 3.0 – 6.0)

endometrial cancer
- precursor lesions -

histology	risk of malignancy
Simple hyperplasia	< 2 %
complex hyperplasia without atypia	4 %
atypical hyperplasia	23 %

R.J.Kurman et al 1985

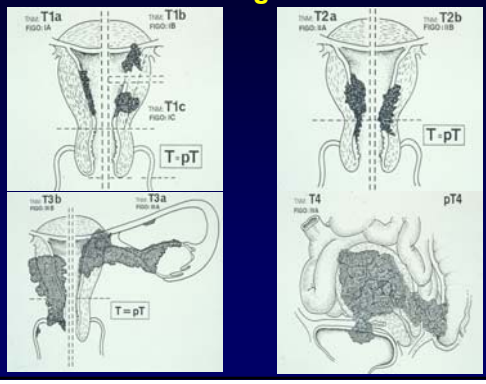
Endometrial cancer
- symptoms -

- bleeding –peri/postmenopausal-
- (bloody) discharge
- pain
- ***No screening has proved of value***

Endometrial cancer
- diagnostics -

- Dilation & Curettage
- hysteroscopy
- ultrasound (?)

Endometrial cancer
- stages -



endometrial cancer
- prognostic factors -

- stage
- histological type
- differentiation
- depth of myometrial invasion
- Lymph node involvement
- Hormonal receptors (ER, PR)

Endometrial cancer
stage and prognosis
FIGO, Annual Report 1994 Vol.22

Stage	Pat.(n)	5 – year overall survival
I	8.603	86 %
II	1.650	66 %
III	1.181	44 %
IV	399	16 %

Endometrial cancer
depth of myometrial invasion and prognosis
Figo, Annual Report, 1994, VOL22

Depth of invasion	5-year overall survival
< 1/3	82,4 % (n=3.224)
1/3 –1/2	78,0 % (n=974)
> 1/2	66,8 % (n=1.144)

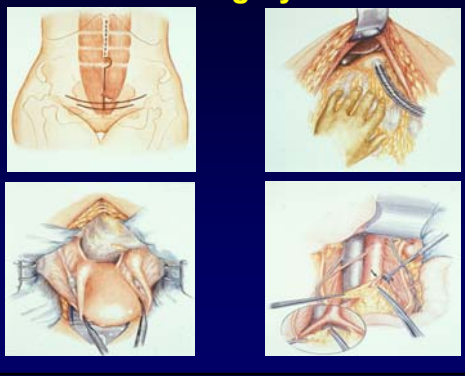
endometrial cancer
-nodal involvement-
(Creasman et. Al., Cancer 60:2035)

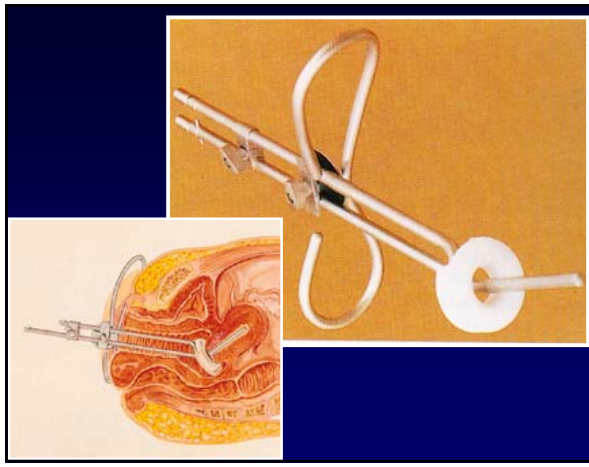
Invasion depth	pelvic nodes	paraaortal nodes
< 1/3	5 %	3 %
1/3 – 2/3	6 %	1 %
> 2/3	25 %	17 %
grading		
G 1	3 %	2 %
G2	9 %	5 %
G 3	18 %	11 %

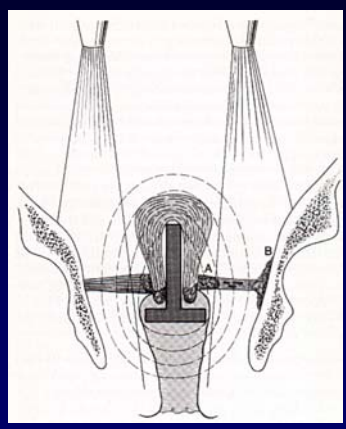
Endometrial cancer
-surgery-

- Laparotomy by vertical incision
- total exploration of the abdomen
- peritoneal lavage
- hysterectomy and salpingoopherectomy
- (vaginal cuff)
- Lymph node dissection, Stage I, high risk
- „Debulking“-surgery Stage III and IV

Endometrial cancer
-surgery-







Endometrial cancer
- localization of recurrences –
(UFK Freiburg, 1984-1995, n=165)

vagina	38,8 %
pelvis	25,5 %
lung	22,5 %
intraperitoneal	21,8 %
Liver	12,1 %

Endomtrial cancer
- treatment of recurrence -

- surgery (debulking)
- radiation
- Endocrine treatment (progestins)
- Cytotoxic treatment

Risk for breast cancer
age-dependent

25 years	1:19608
30 years	1:2525
35 years	1:622
40 years	1:217
45 years	1:93
50 years	1:50
55 years	1:33
60 years	1:24
65 years	1:17
70 years	1:14
75 years	1:11
80 years	1:10
85 years	1:9
>85 years	1:8

Risk factors for breast cancer

age

Genetic alterations

childlessness

family history of breast cancer

Age at first birth

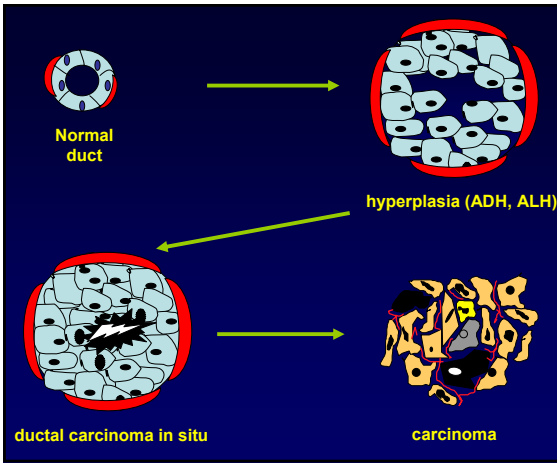
estrogen exposure

adiposity

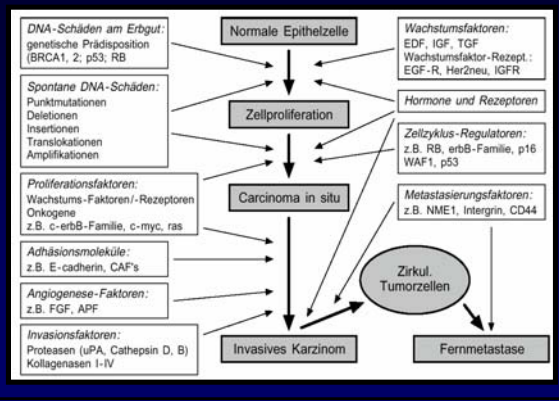
alcohol

fatty alimentation

exposure to irradiation



tumour initiation



prognosis of advanced breast cancer

- median survival according to localisation of metastases:
  - bone metastases only ~ 30 months
  - visceral metastases ~ 17 months
  - multiple metastases ~ 11 months
- favourite prognosis: ER+ / PR+
- poor prognosis: DFI < 2 years
  Her2-neu overexpression

hereditary breast cancer

epidemiology

- incidence: 5-10 % of all breast cancers
- BRCA-1/2 associated: 40 - 50 % of all hereditary breast cancers
- hereditary gene mutations: 36 % at the age < 30 years

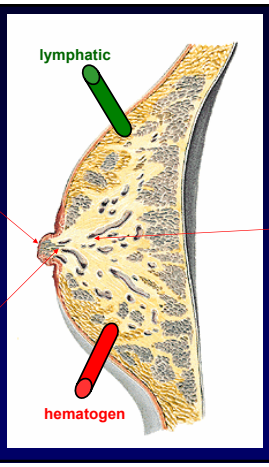
Claus E et al.,Hum Genet, 48:232-42, 1991

BRCA-mutation

risk of breast/ ovarian cancer

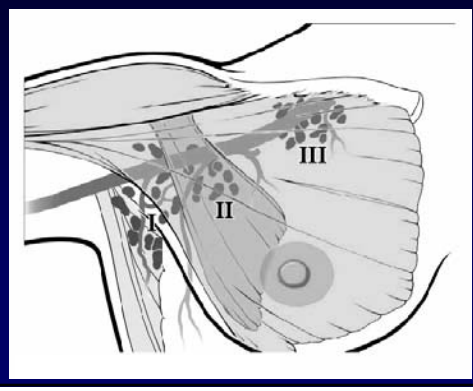
BRCA-1-mutation
breast:
19,1 % risk at the age of < 40 yrs
70 % risk at the age of < 70 yrs.
ovary:
45 % risk at the age of < 70 yrs.

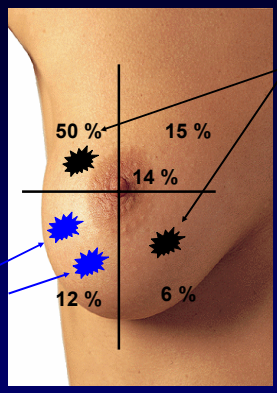
BRCA-2-mutation
breast:
according to BRCA-1 mutation
ovary:
15-20 % risk at the age of < 70 yrs.



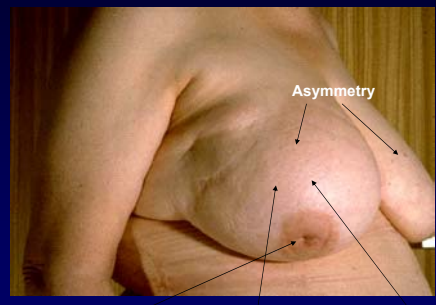
Lymphatic drainage of the breast

level classification according to Berg et al.



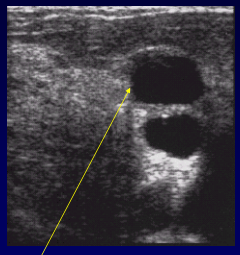


Signs and symptoms

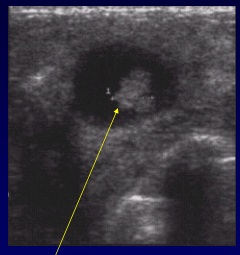


ultrasound

benign cyst



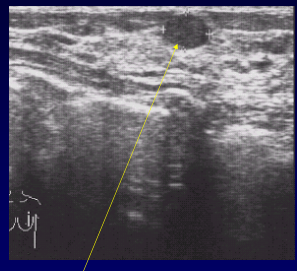
smooth bordered, without echoes
dorsal enhancement of echoes



intracystic papillary structure

Ultrasound

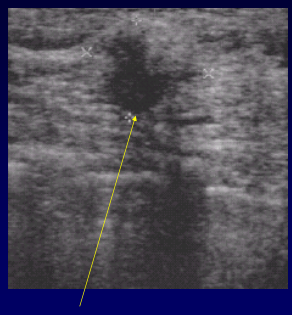
fibroadenoma



Smooth bordered, with poor echoes,
dorsal enhancement of echoes

Ultrasound

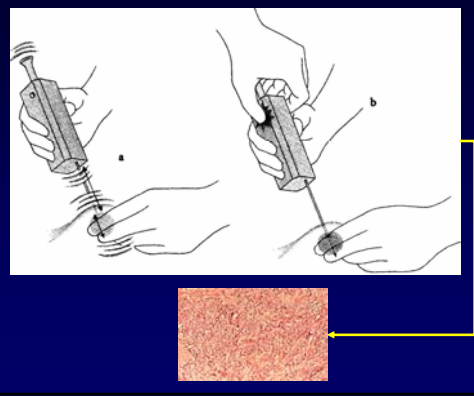
breast cancer



Irregular shape, diffuse, poor echoes
Dorsal attenuation, structural disrupture
vertical growth pattern

diagnosis

core-cut biopsy

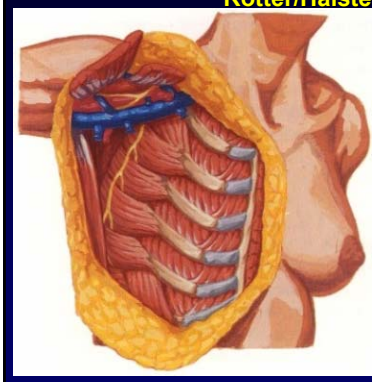


Theory of the disease

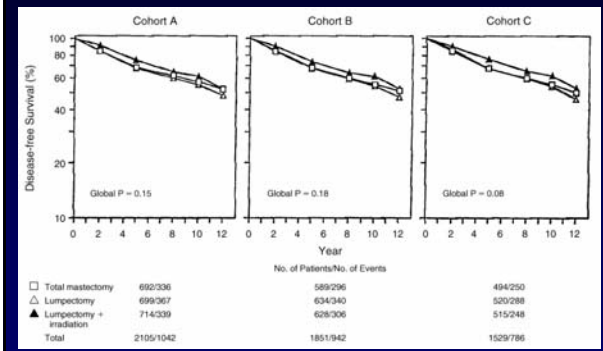
Halstedtian doctrine

Breast cancer is a locoregional disease

Radical mastectomy according to Rotter/Halstedt

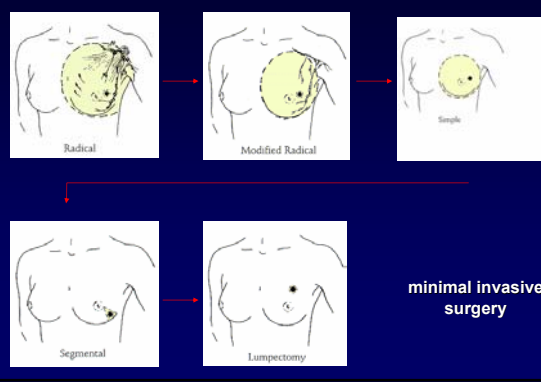


breast conserving surgery vs. mastectomy



Fisher B. et al., NEJM 1995, 333: 1456-61

Reduction of surgical radicalness



minimal invasive surgery

Principles of surgical treatment

- breast conservation in ~ 70 %
- mastectomy

(± autologous/ heterologous reconstruction)

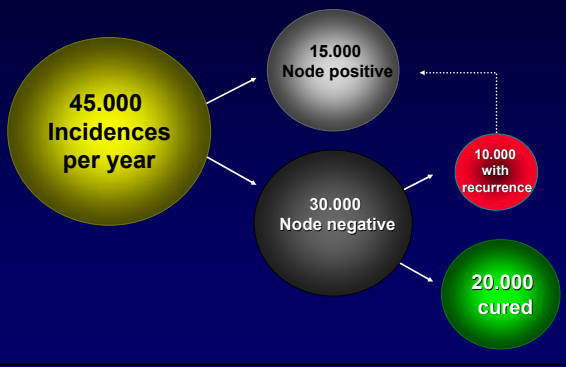
- reduction mammoplasty
- skin sparing mastectomy
- subcutaneous mastectomy
- axillary lymph node dissection (> 10 nodes)
- sentinel node biopsy

Complications of axillary clearance

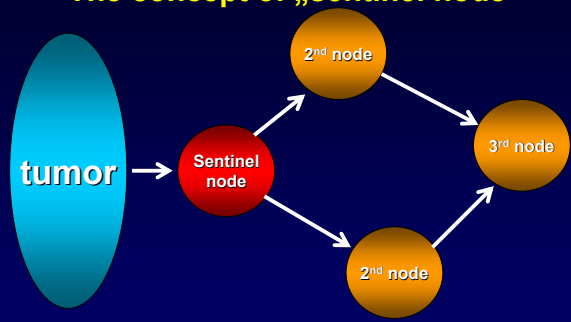
- seroma 10 %
- lymphedema 5 - 6 %
- Livelong protection of the affected arm
- Injury of vessels and/ or nerves
- postoperative pain
- unfavorable scar

The reduction of surgical radicalness is associated with an improved quality of life

Incidences per year
Germany

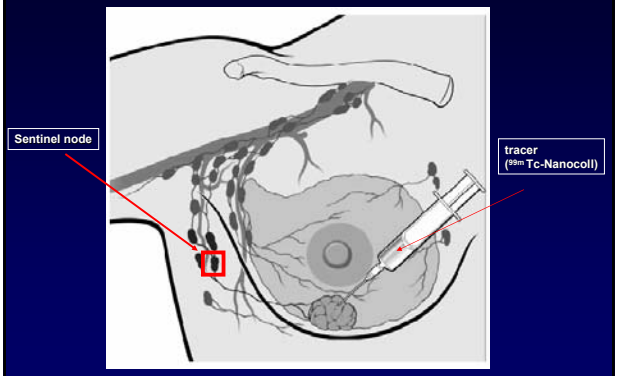


The concept of „sentinel node“



rationale: metastasis occurs in a continuous fashion without skipping of lymph nodes

detection of „sentinel node“



sentinel node assessment

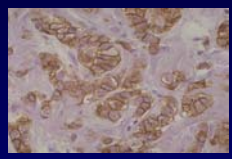
identification: 86%

- sensitivity 94% ⟶ FN 6%
- specificity 100%

Surgical staging

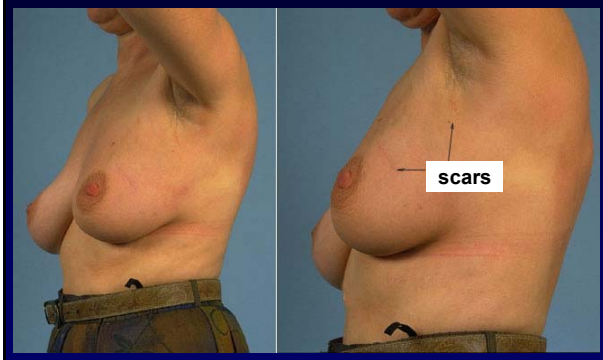
necessary informations

- Tumor size
- margins
- Nodal status (at least 10 Ln)
- hormonal receptor status
- HER-2/neu
- grading



mastectomy

Breast conserving surgery



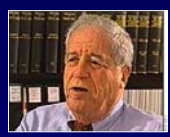
Contraindications for breast conservation

- incomplete tumor resection
- multicenter carcinoma or DCIS
- extensive lymphatic/ vessel invasion
- Unfavourable breast/ tumor relation
- inflammatory breast cancer
- Intramammary local recurrence after BCS

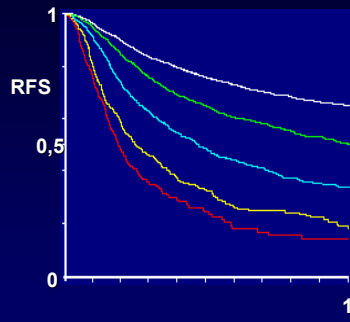
Theory of the disease

Fisher-doctrine

Breast cancer is a systemic disease



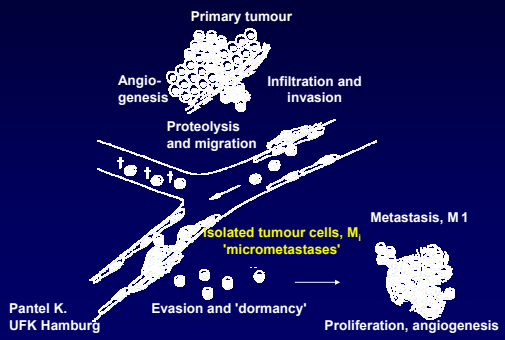
Risk assessment



0 LN (n = 5.403)
1-3 LN (n = 2.348)
4-10 LN (n = 1.404)
11-20 LN (n = 591)
> 20 LN (n = 251)

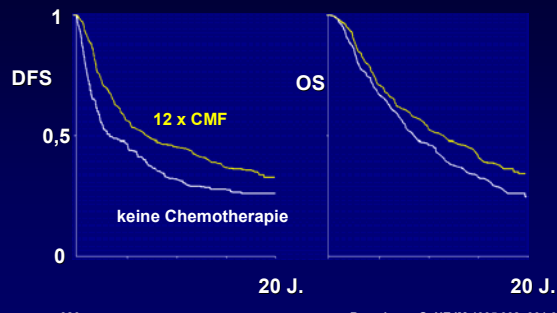
Clark GM in Harris (ed.), diseases of the breast, Lippincott 1996

Disseminated tumor cells



Pantel K.
UFK Hamburg

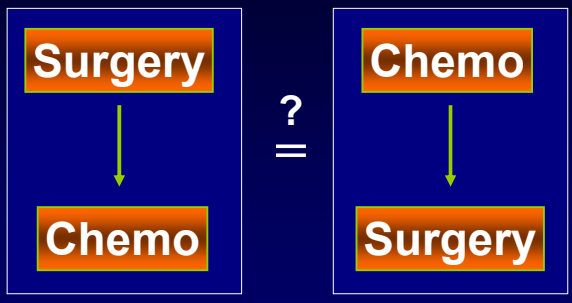
Adjuvant chemotherapy



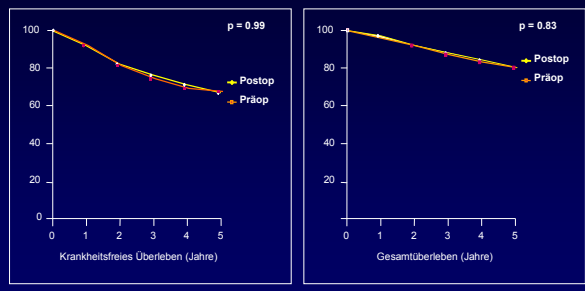
n = 386

Bonadonna G. NEJM 1995 332; 901-906

primary chemotherapy

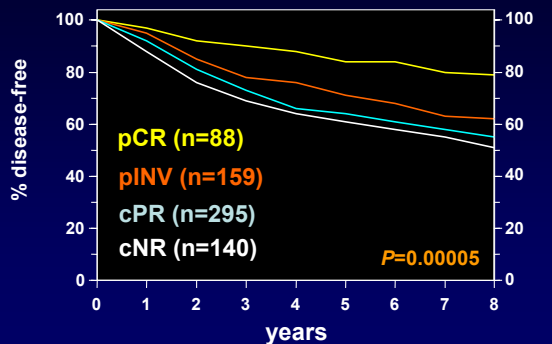


comparison between pre- and postoperative chemotherapy



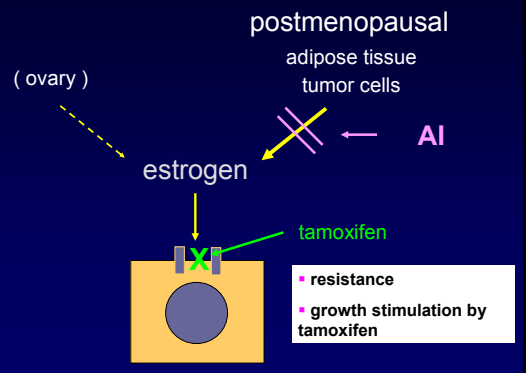
Fisher et al. JCO,16: 2672-85 1998

Pathological complete remission (pCR) is a prognostic indicator

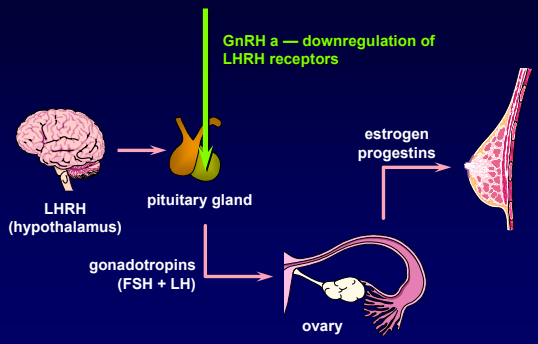


Fisher et al. J Clin Oncol 1999

Principles of endocrine treatment

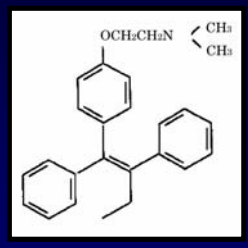


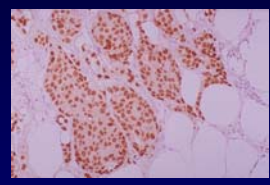
GnRH-analogues – mode of action



tamoxifen

selective estrogen receptor modulator

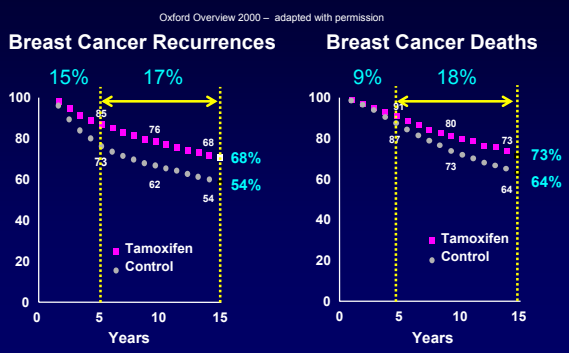




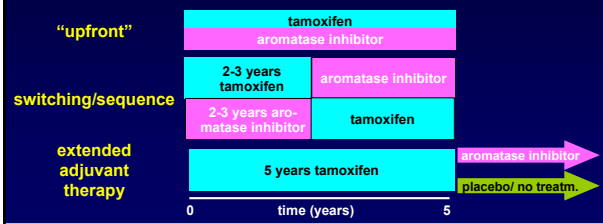
ER-positive breast cancer

Benefits of 5 Years of Adjuvant Tamoxifen - Hormone Receptor Positive

Oxford Overview 2000 – adapted with permission



Inhibition of aromatase activity

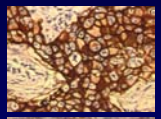


Klinik für Gynäkologie und Geburtshilfe

J. W. Goethe-Universität Frankfurt

HER2-overexpression

- HER-2 positive breast cancer patients have an impaired prognosis in terms of overall survival



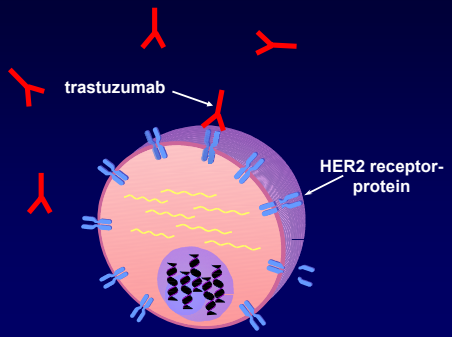
median survival

HER2-positive 3 years

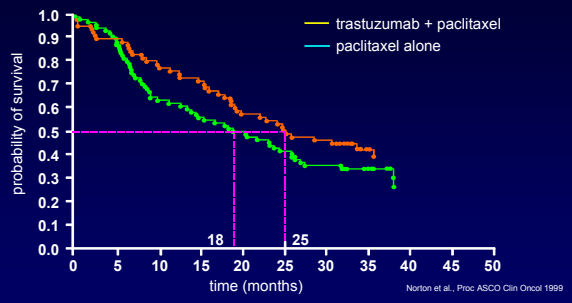
HER2-negative 6–7 years

Slamon et al. 1987

Molecular targeting



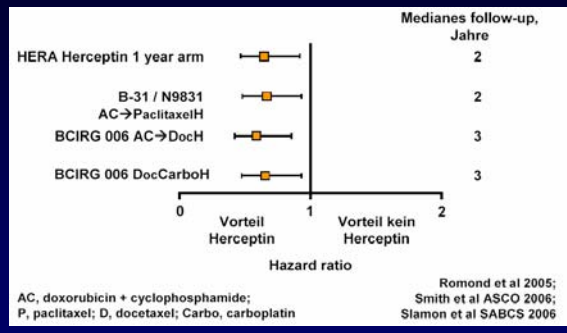
chemotherapy +/- trastuzumab in 1st-line therapy of Her-2 positive breast cancer



Norton et al., Proc ASCO Clin Oncol 1999

trastuzumab in the adjuvant setting

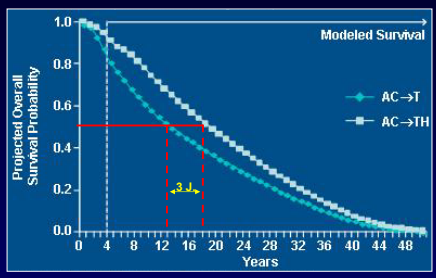
overall survival



AC, doxorubicin + cyclophosphamide;
P, paclitaxel; D, docetaxel; Carbo, carboplatin

Romond et al 2005;
Smith et al ASCO 2006;
Slamon et al SABCS 2006

projected long time effect of trastuzumab



projected long time survival is 3 years longer in the trastuzumab arm (19,4 vs. 16,4 Jahre)

Garrison et al., ASCO 2006, #6023

treatment of breast cancer

locally
surgery
irradiation

systemic
chemotherapy
endocrine therapy
antibody therapy