Mammakarzinom in der Schwangerschaft

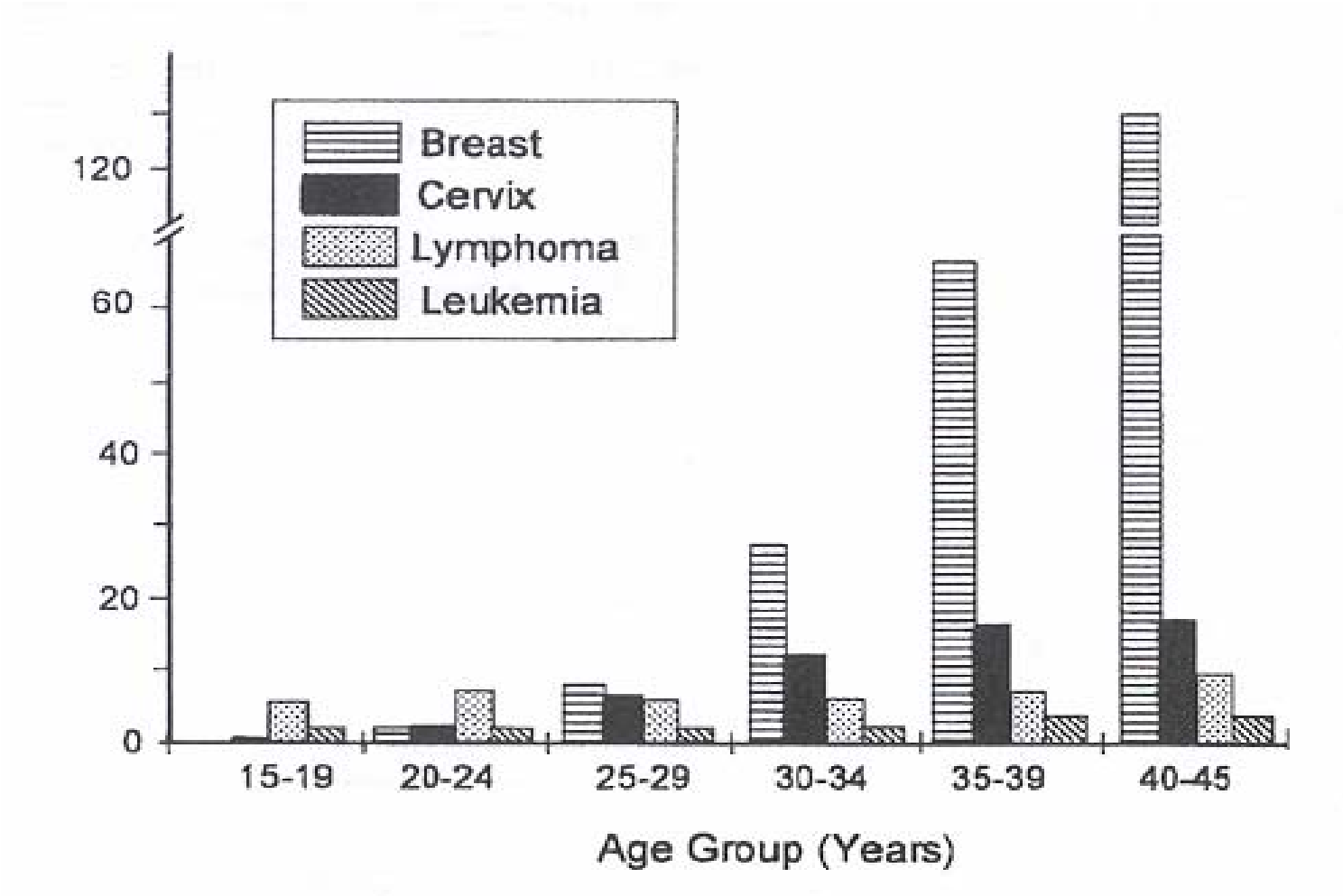
Senologie 2010
14.-16. Oktober
Wien, Museumsquartier

Priv. Doz. Dr. med. Sibylle Loibl

German Breast Group

Frankfurt/Neu-Isenburg

Altersspezifische Inzidenz von Tumorerkrankungen



Berry et al. JCO 17: 855-861,1999

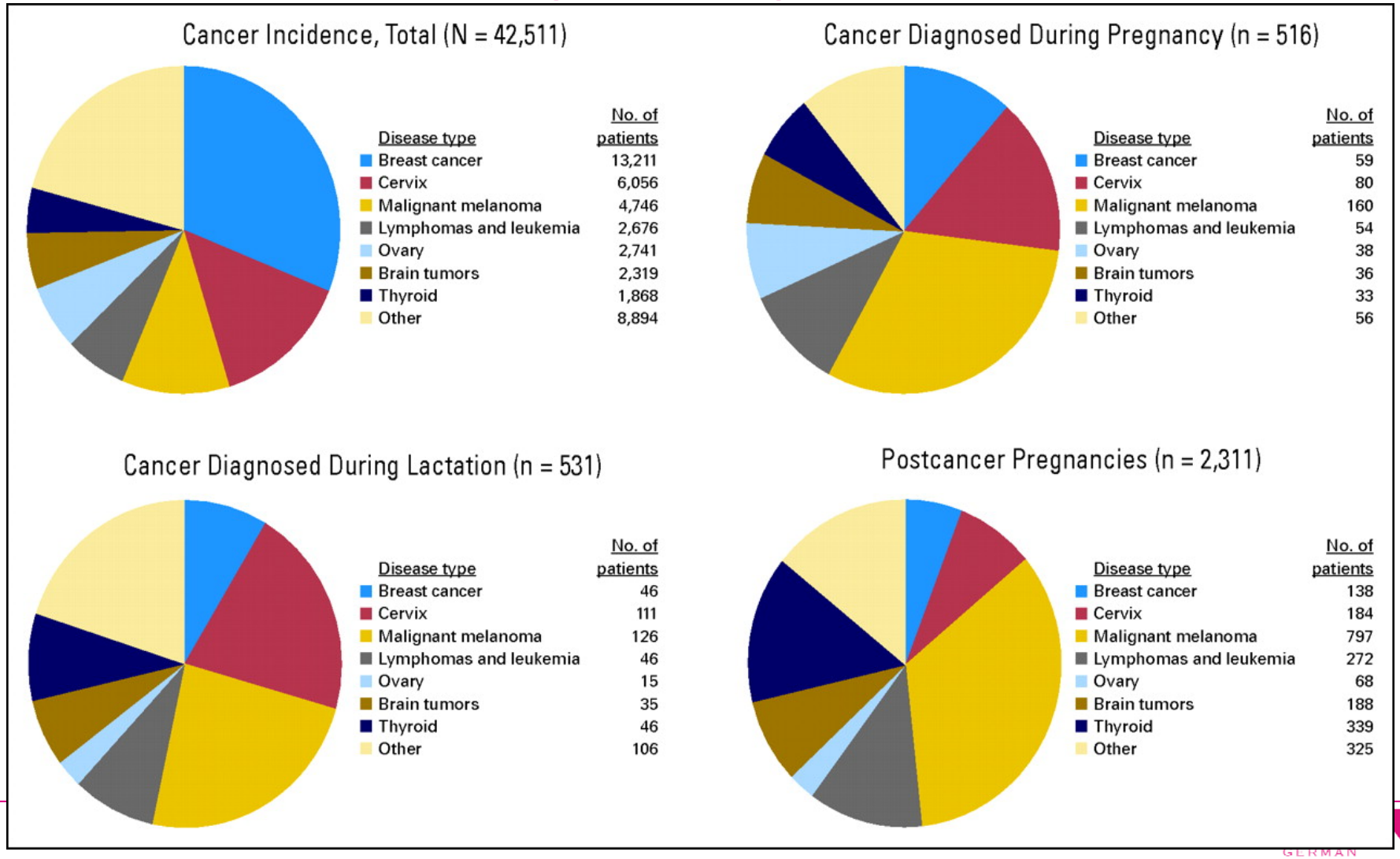
Inzidenz

1 /3.000 – 10.000 Schwangerschaften

< 40J: 15% während der Schwangerschaft

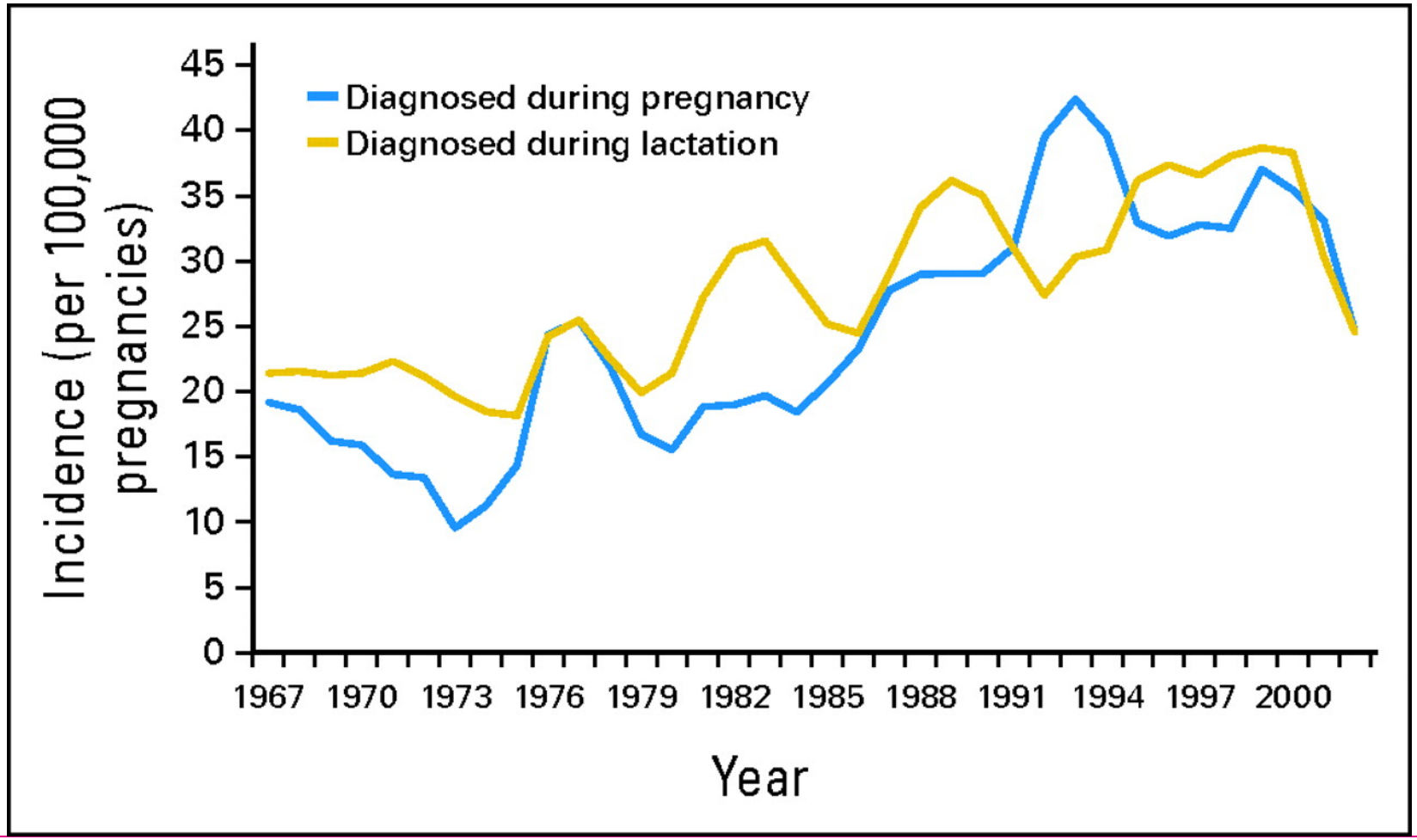
3 -5% pregnancy associated
(bis zu einem Jahr nach der Entbindung)

Cancer Incidence overall, and in the different Subgroups (pregnant, lactating, and postcancer pregnancy group)



Stensheim, H. et al. J Clin Oncol; 2009, 27:45-51

Annual Incidence of Cancer during Pregnancy or Lactation, proportions per year per 100,000 pregnancies



Stensheim, H. et al. J Clin Oncol; 2009; 27:45-51

Ma-Ca in der Schwangerschaft

Längere Zeit bis zur Diagnose zwischen Schwangeren und Nicht-Schwangeren

grav. vs. Nicht-grav = 8,2 m vs. 1,9 m (Liberman et al.)

Gründe für eine Verzögerung der Diagnose

- Brustuntersuchung wird vernachlässigt
- Symptome werden den physiologischen Veränderungen in der Schwangerschaft zugeschrieben
- Mammographie wird aus Angst vor der Strahlenbelastung nicht eingesetzt
- Schwierigkeiten bei der Interpretation der Bildgebung

Mammographie während der Schwangerschaft

Standarddosis einer bds. Mammographie

0.6-3 mGy

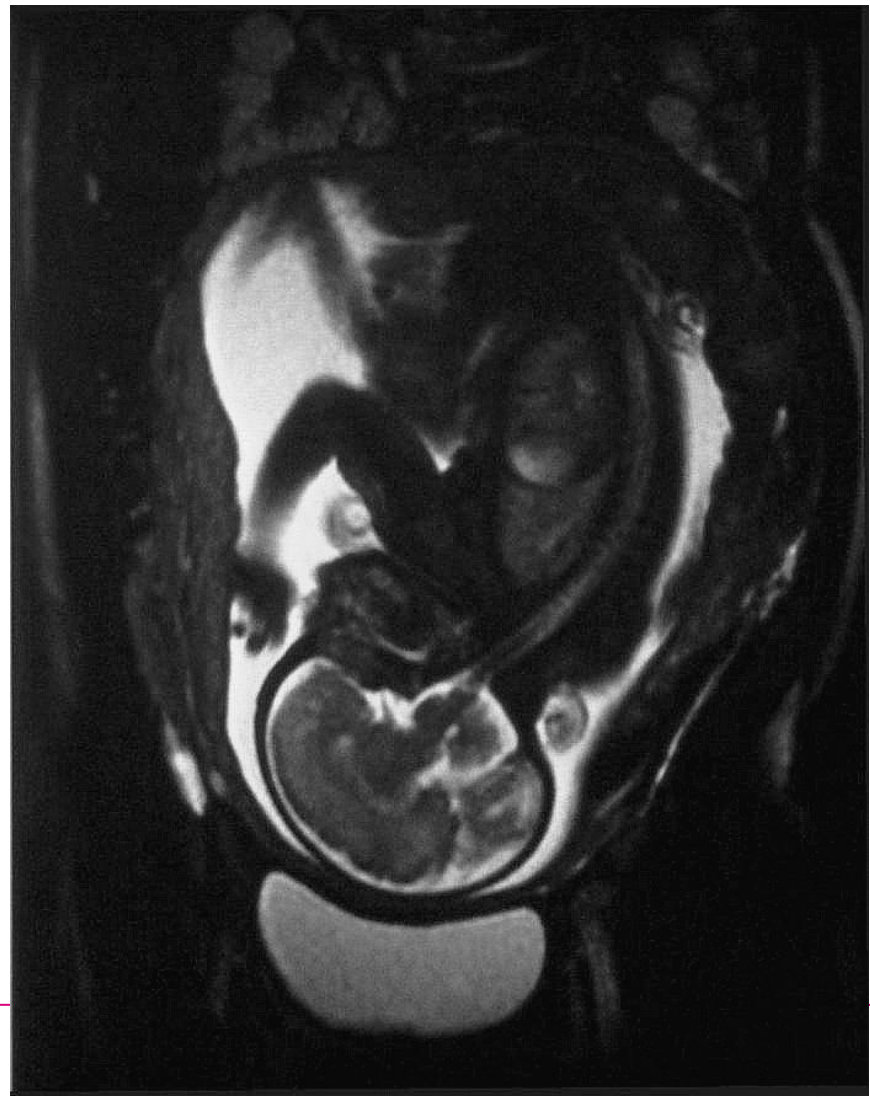
↓

< 0.5 mGy Embryo/Fötus

⇨ 100 mGy erhöhen das Risiko einer Fehlbildung um 1%

MRI in der Schwangerschaft

- **Gadolinum nicht sicher in der Schwangerschaft**
- **Bauchlage**
- **Interpretation de Ergebnisse schwierig**



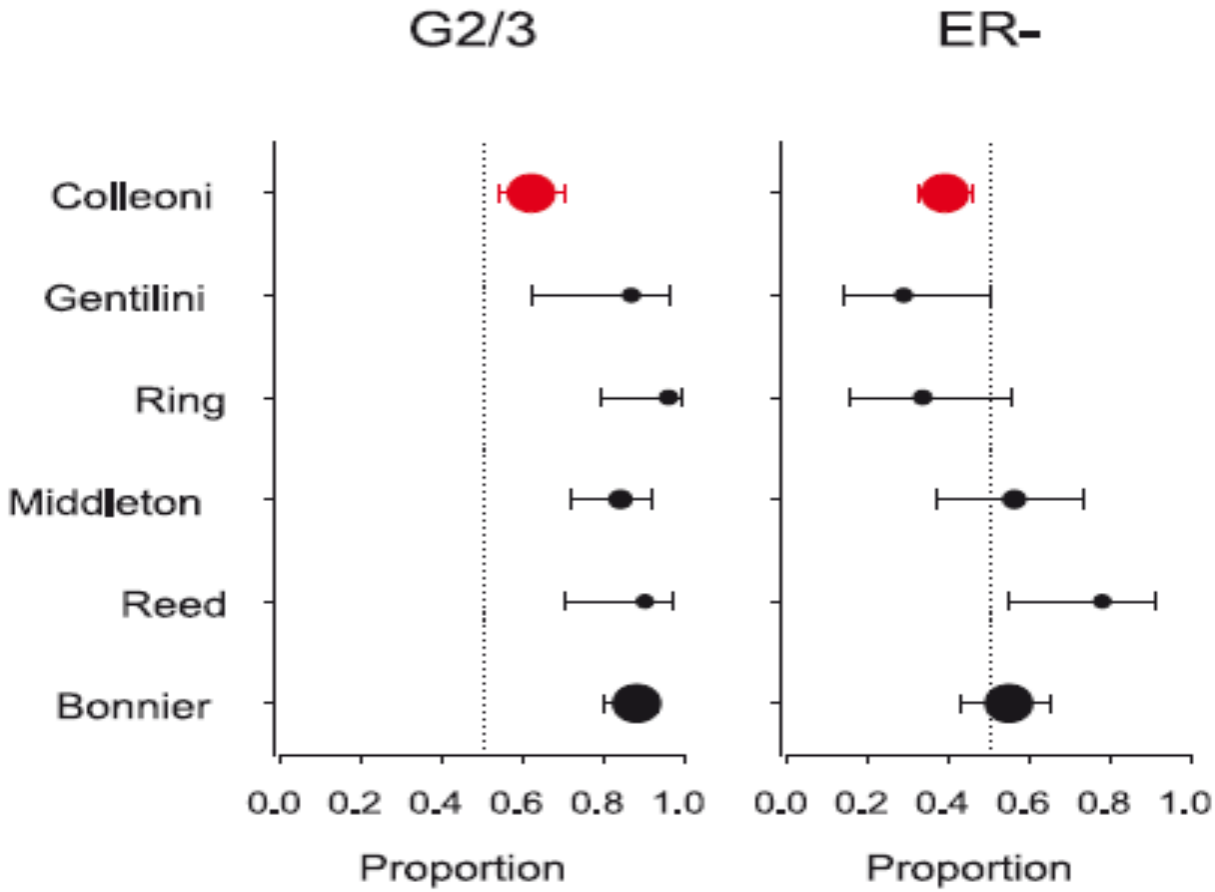
Diagnostik

Examination	Fötale Dosis (mGy)	
	Mean	Maximum
Röntgen		
Thorax	**< 0.01**	**< 0.01**
Abdomen	**1.4**	**4.2**
Becken	**1.1**	**4**
Thorakale WS	**< 0.01**	**< 0.01**
Lumbale WS	**1.7**	**10**
CT		
Abdomen	**8.0**	**49**
Thorax	**0.06**	**0.96**
Kopf	**< 0.005**	**0.005**
Becken	**26**	**79**
Nuclear Medicine		
99m Tc Knochenszinti	**3.3**	**4.6**

Diagnostik

- Mammographie ist sicher – Sensitivität 78-87%
- Ultraschall ist sicher– 100% (Ahn et al. n=22)
- MRT ist nicht evaluiert
  - ! Gadolinum
  - ! Bauchlage

Hormonrezeptoren und Differenzierungsgrad bei Schwangeren und nicht Schwangeren im Vergleich



Aebi S et Loibl S. Recent Results in Cancer Research 2008; 145: 45-55

Her-2/neu Status

	Her-2/neu pos.
Middleton et al. 2003	28%
Reed et al. 2003	44%
Shousha et al. 2000	0%
Elledge et al. 1993	58%

p53 and Ki67

	Middleton et al. 2003 schwanger	**Maru** et al. 2003 nicht-schwanger
p53:	48%	52%
Ki67:	60%	61%

Lymphknotenbefall

Middleton et al.	2003	79%
Reed et al.	2003	50%
King et al.	1985	62%
Holleb and Farrow	1985	72%

Author	Study Desing	Number of patients	Histology	Nuclear Grade	ER/PR	Her2
Middleton	Prospective case series	38 cases (pregnant) and 1 PABC	100% invasive ductal carcinoma	Poorly differentiated: 84%	ER (-): 72% PR (-): 76%	Her-2/neu (+): 28%
Ishida	Case control	72 cases (pregnant); 120 cases (lactating); 191 controls	No difference	Not examined	Fewer ER(+) and PR(+) pregnant and lactating women	Not examined
Reed	Retrospective case series	122 PABC (20 pregnant)	ductal invasive 82%	95% G2-3	ER(-): 66% PR (-): 72%	Her-2/neu (+): 44%
Shousha	Case-control	14 cases PABC; 13 controls	Invasive ductal: 71% PABC vs 69% controls	G3: 80% PABC vs 33% controls	ER (-): 50% PABC vs 9% controls PR(-): 70% PABC vs 36% controls	Her-2/neu (+): 44% PABC vs 18% controls
Tobon and Horowitz	Retrospective case series	14 cases	(93% had invasive ductal carcinoma	Not examined	ER (–) or low in 50%; PR (–) in 64%	Not examined
Elledge	Case-control	15 cases (pregnant); 411 controls	Not examined	Not examined	No difference in ER(+) and PR(+)	58% of cases Her-2/neu (+) vs 16%
Bonnier	Case Control	154 PABC (62 pregnant) 308 controls	No difference	No difference	Pregnant women less likely to be ER or PR positive	Not examined

Loibl et al. Cancer 2006; 106: 237-246

Überleben

Author	Number of patients	Survival type	Subgroup	Survival rate PABC %	Survival rate non PABC %	P-value
Nugent	19 PABC 157 controls	5y OAS	all	56	56	n.s.
Petrek	63 PABC	5 y OAS 10 y OAS	All N0 N+ all N0 N+	61 82 47 45 77 25	73 82 59 62 75 41	n.s. n.s. n.s. n.s. n.s. n.s.
Ishida	192 PABC /191controls	10 y OAS	All N0 N+	55 85 37	79 93 62	0.001 0.05 0.01
Zemlickis	118/102 PABC 269 controls	10y OAS	All	40	48	0.6
Chang	21 PABC 199 controls	5 y OAS	All	57	70	n.s.
Guinee	26 pregnant (66 PABC)	5 y OAS	All	40	70	<0.0001
Anderson	22 PABC 205 controls	10y OAS	I-IIA IIB-IIIA	73 17	74 47	n.s.
Bonnier	154 PABC (62 pregnant) 308 controls	5y RFS 5y MFS 5y OAS	all all N0 N+ all	69 45 63 31 61	81 68 77 63 75	0.01 0.0009 n.s. 0.0001 0.001

Loibl et al. Cancer 2006; 106: 237-246

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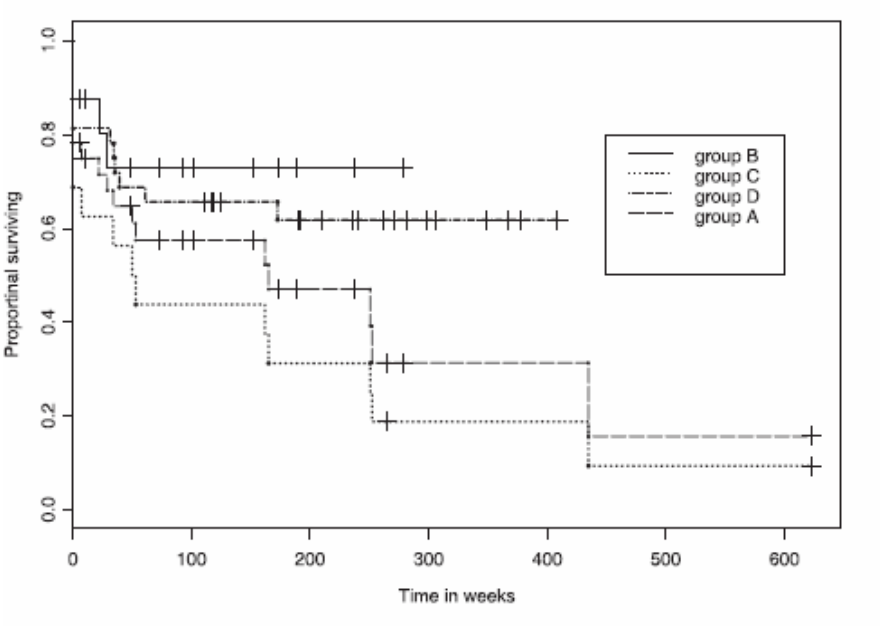
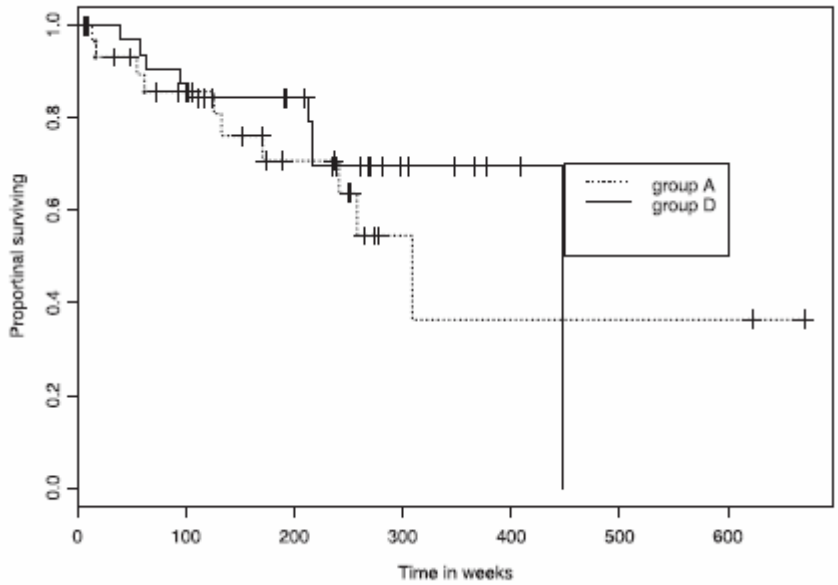
Überleben

DFS



OS



Halaska et al. The Breast 2009; 15: 461-67

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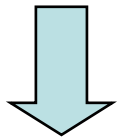
Operation während der Schwangerschaft

- **Brusterhaltung vs. Mastektomie**
  Entscheidung wie außerhalb der Schwangerschaft
- **SNB?**
  Möglich - wahrscheinlich
  Notwendig - wahrscheinlich nicht

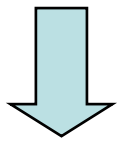
Minimales Risiko für Mutter

Ausgedehntere Op (z.B. Mastektomie)



Abfall der Fibrinolytischen Faktoren

Erhöhung der Koagulationsparameter und Abfall des venösen Blutflusses



5facher Anstieg des Thrombembolierisikos

...und Kind

- Mütterliche Positionierung
- Oxygenierung
- Blutdruck
- fötales Monitoring
- Dauer und Timing der Op

Radiotherapy in pregnant patients Deterministic thresholds as for diagnostic radiology

Radiotherapy to breast/chest wall in pregnant women

Maternal dose (Gy)	Fetal dose (Gy)	Trimester	Reference
50	0.160	3	Van der Geissen, 1997
50	0.140	3	Ngu et al,1992
46	0.039	1	Antypas et al, 1998

Dosisgrenzen für Röntgen oder Gamm strahlen

	Minimum dose (mGy) for:		
Age (weeks)	Death	Malformations	Mental retardation
2-5	250 - 500	200	No effects seen
5-7	500	500	
8-15	>500	Very few observed	IQ decrease 21-30 points per 1 Gy
16-25	>500		IQ decrease 13 points per 1 Gy
To term	>1000		No effects seen

Lokale Therapie

Radiotherapie:

Dosislevel für Schäden: 0,05Gy

Standard-Brust-Bestrahlung: 50Gy

Fötus: 2cGy – 58,6cGy

Keine therapeutische Indikation in der Schwangerschaft

Aktuelle Studien zu CHT während der SS beim primären Ma-Ca

	MD Anderson Cancer Center [Hahn et al. 2006]	Royal Marsden and London Hospitals [Ring et al. 2005]
Number of patients	57	24 [+ 4 stage IV]
Age at diagnosis	33.5 (24–45)	33 (28–42)
Median gestational age at diagnosis	17.4 (2–33)	17 weeks (4–33)
Local therapy		
Mastectomy	42	17
Breast-conserving surgery	15	10
Postpartum radiation therapy	Not reported	17
Gestational age at start of chemotherapy	23 weeks (11–34)	20 weeks (15–33)
Chemotherapy		
Neoadjuvant	25	7
Adjuvant	32	17
[Palliative]		[4]
AC		11
EC		5
CMF		12
FAC	57	
Gestational age at delivery	37 weeks (29–42)	37 weeks (30–40)
Cesarean section	21	6

Aebi et Loibl Recent Results in Cancer Research 2008; 145: 45-55

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Fetal outcome unter Chemotherapie in der Schwangerschaft

	MD Anderson Cancer Center [Hahn et al. 2006]	Royal Marsden and London Hospitals [Ring et al. 2005]
Birth weight	2.89 kg (1.4–4.0)	3.0 kg (1.4–3.5)
		None <10th percentile for gestational age
Fetal/infant follow-up	2–157 months	Not reported
Fetal outcomes	4 required neonatal ventilation	1 abortion after inadvertent first-trimester chemotherapy with CMF
	1 subarachnoid hemorrhage	2 neonatal respiratory distress
	1 Down syndome	1 hemangioma on the abdomen.
	18 school-age children; 2 special attention schooling	
Median maternal follow-up	38.5 months	40.5 months
Maternal outcomes (stages I–III)		
OS	77%	67%
DFS	70%	63%

Aebi et Loibl Recent Results in Cancer Research 2008; 145: 45-55

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	Paclitaxel	Docetaxel	Paclitaxel + docetax
n	21	16	3
Maternal age at initiation of taxanes, years: median (range)	36 (30–42)	34 (26–44)	NR
Gestational age at initiation of taxanes: *n* (T1/T2/T3)	0/17/4	2/10/4	0/3/0
Cumulative dose received during pregnancy, mg/m^2: median (range)	550 (300–1620)	300 (175–570)	NR
Toxicity during pregnancy (*n*)	Grade 1 nausea (2); grade 2 neutropenia (1); alopecia (2); hyperbilirubinemia (2); IUGR (1); preeclampsia (1); anhydramnios[a] (1)	Anhydramnios (1); hand–foot syndrome (1); preeclampsia (1)	NR
Gestational age at delivery, weeks: median (range)	36 (30–38)	35 (32–40)	NR
Type of delivery: *n* (vaginal/ C-section/NR)	2/11/8	5/7/4	0/0/3
Neonatal gender: *n* (Male/ Female/NR)	6/3/12	8/3/5	0/0/3
Neonatal birth weight, g: median (range)	2428 (1460–2800), *n* = 12	2245 (1490–3200), *n* = 9	NR
Neonatal abnormalities (*n*)	Anemia (1), grade NR	Ventriculomegaly[b] not related to docetaxel (2); holoprosencephaly suspected at birth[c] (1)	Pyloric stenosis (1)
Neonatal follow-up, months: median (range)	15 (3–132)	18 (9–36)	0 (0–2)

Mir O et al. Annals Oncol 2010;

Author	Age, years	Therapy	Exposure, weeks of gestation	Delivery, week/mode	Breast cancer	Pregnancy complications	Birth weight, g	Neonatal status
Fanale 2005 [54]	26	vinorelbine 25mg/m^2 weekly + trastuzumab weekly (1 cycle), further postpartum	27–34.50 (1 cycle)	34 + 5/vaginal	liver metastases	oligohydramnios; occasional fetal cardiac decelerations	2,270	male; no sequelae; status APGAR 9/9/-
Watson 2005 [59]	28	trastuzumab 580 mg 3 weekly over 5 months, then STOP	0–23 (7 cycles)	37 + 3/vaginal	primary	reversible anhydramnios at 23 weeks	2,960	female; no sequelae; status APGAR 8/9/-
Waterston and Graham 2006 [60]	30	trastuzumab 736 mg loading, 523 mg 2 cycles, then STOP	before conception, after 2.cycle T pregnant	week of delivery not reported/ vaginal	primary	none	not reported	female; no sequelae; status APGAR not reported
Kelly 2006 [61]	44	lapatinib 750mg/day; stopped at 14 weeks	-0–11	36	metastatic	none	2,600	female; no sequelae; status APGAR 8/9/-
Bader 2007 [62]	38	paclitaxel 175mg/m^2, trastuzumab; stopped after 2 cycles	25^{+6}–26 (2 cycles)	32 + 1/caesarean	metastatic spinal cord compression	oligo-anhydramnios; fetal growth retardation; fetal renal failure at 31 + 6 weeks	1,460	male; bacterial sepsis; hypotension; transient renal and respiratory failure
Sekar 2007 [63]	28	3 docetaxel 190 mg + trastuzumab 2 cycles	23–30	36 + 2 week/ elective caesarean	lung metastases (20th week)	anhydramnios at 30th week; reversible fetal growth restriction (5th percentile)	2,230	male; no sequelae; status APGAR 7/9/5
Shrim 2007 [64]	32	trastuzumab 400 mg, 3 weekly; stopped at 24 weeks	0–24	37/elective caesarean	breast carcinoma, metastatic	reversible maternal heart failure, resolved slowly after discontinuation of trastuzumab	2,600	female; APGAR 9/10/NRD
Witzel 2007 [65]	29	1st line: 24 cycles vinorelbine 25 mg/m^2 + trastuzumab 2 mg/kg weekly, trastuzumab 6 mg/kg 3-weekly 25 cycles; total dose 56 mg/kg	0–25, 23th week pregnancy diagnosis	27/caesarean	invasive ductal, lung metastases, cerebral metastases under trastuzumab alone	oligohydramnios; vaginal bleeding	1,015	female; APGAR 8/7/6; pH = 7.48 umbil. artery; respiratory failure

Loibl; Breast Care 2008; 3:171-76

Platinanaloga in der Schwangerschaft

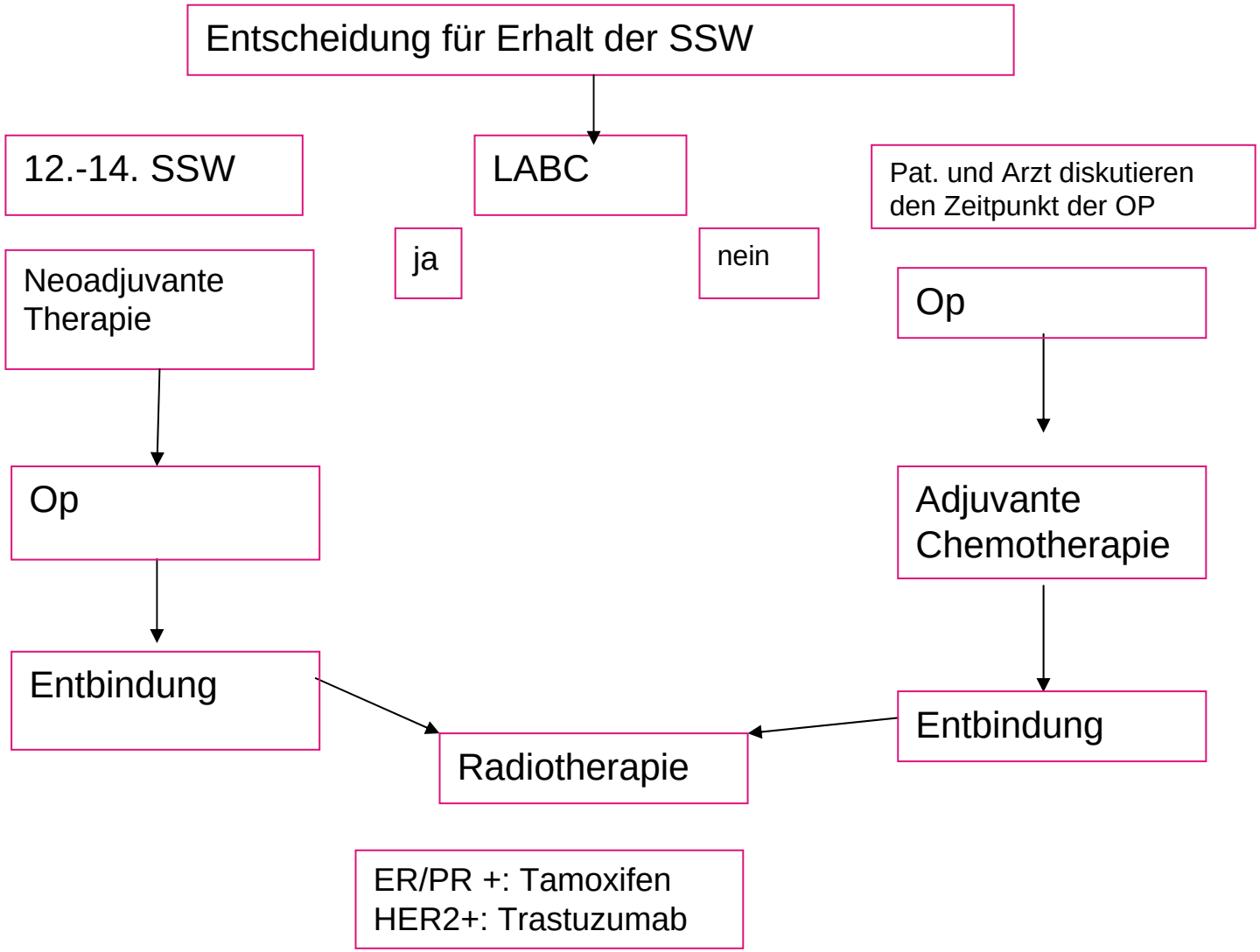
TABLE 3
Evidence of Transplacental Transfer of Platinum Derivatives

Reference	Chemotherapy Regimen	Time Between the Last Cycle and Delivery	Gestational Age at Delivery, wk	Findings at Birth
Henderson 1993[35]	Cisplatin and cyclophosphamide followed by carboplatin (300 mg/m^2) and cyclophosphamide (no. of cycles NR)	NR	36	Platinum-DNA adducts on the placenta and maternal blood; no platinum-DNA adducts noted in the child's blood at 3 mo
Koc 1994[50]	Carboplatin (400 mg/m^2) for 3 cycles	9 wk	37	Normal CBC; normal serum creatinine; platinum-DNA adducts noted in cord blood lymphocytes and maternal lymphocytes
Elit 1999[28]	BEP over 5 d for 1 cycle	16 d	28	Normal leukocyte and platelet counts; cisplatin noted in the cord blood (0.80 μmol/L); cisplatin noted in the maternal blood (1.10 μmol/L)
Arango 1994[33]	Cisplatin (100 mg/m^2), and etoposide, and G-CSF for 4 cycles	3 d	35	Normal CBC; cisplatin noted in the blood of the neonate (40 μmol/L)

NR indicates not reported; CBC, complete blood cell count; BEP, bleomycin, etoposide, and cisplatin; G-CSF, granulocyte-colony-stimulating factor.

Mir et al. Cancer 2008

< 14. (<12.) SSW



Loibl et al. Cancer 2006; 106: 237-246

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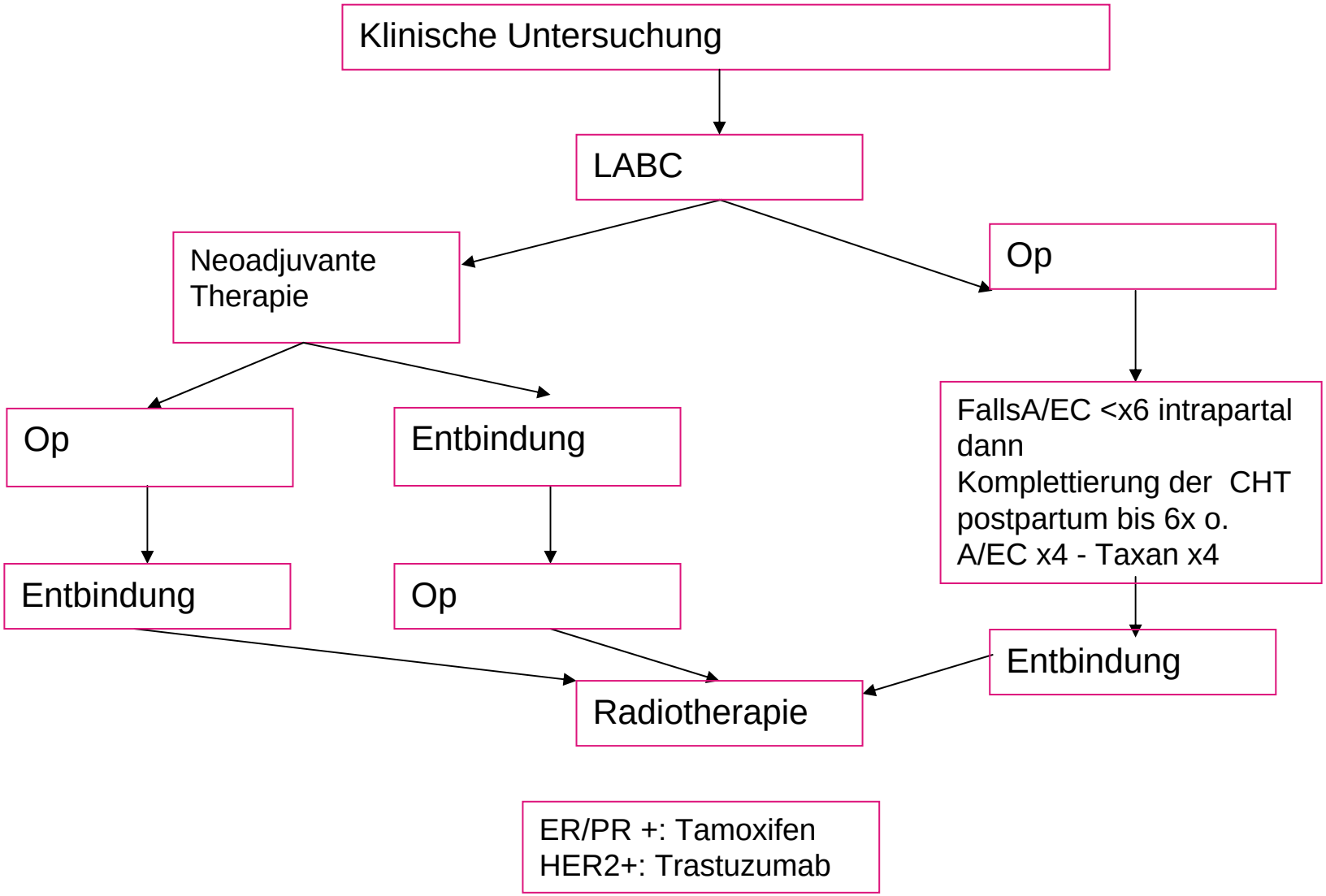
14. – 34. SSW



Loibl et al. Cancer 2006; 106: 237-246

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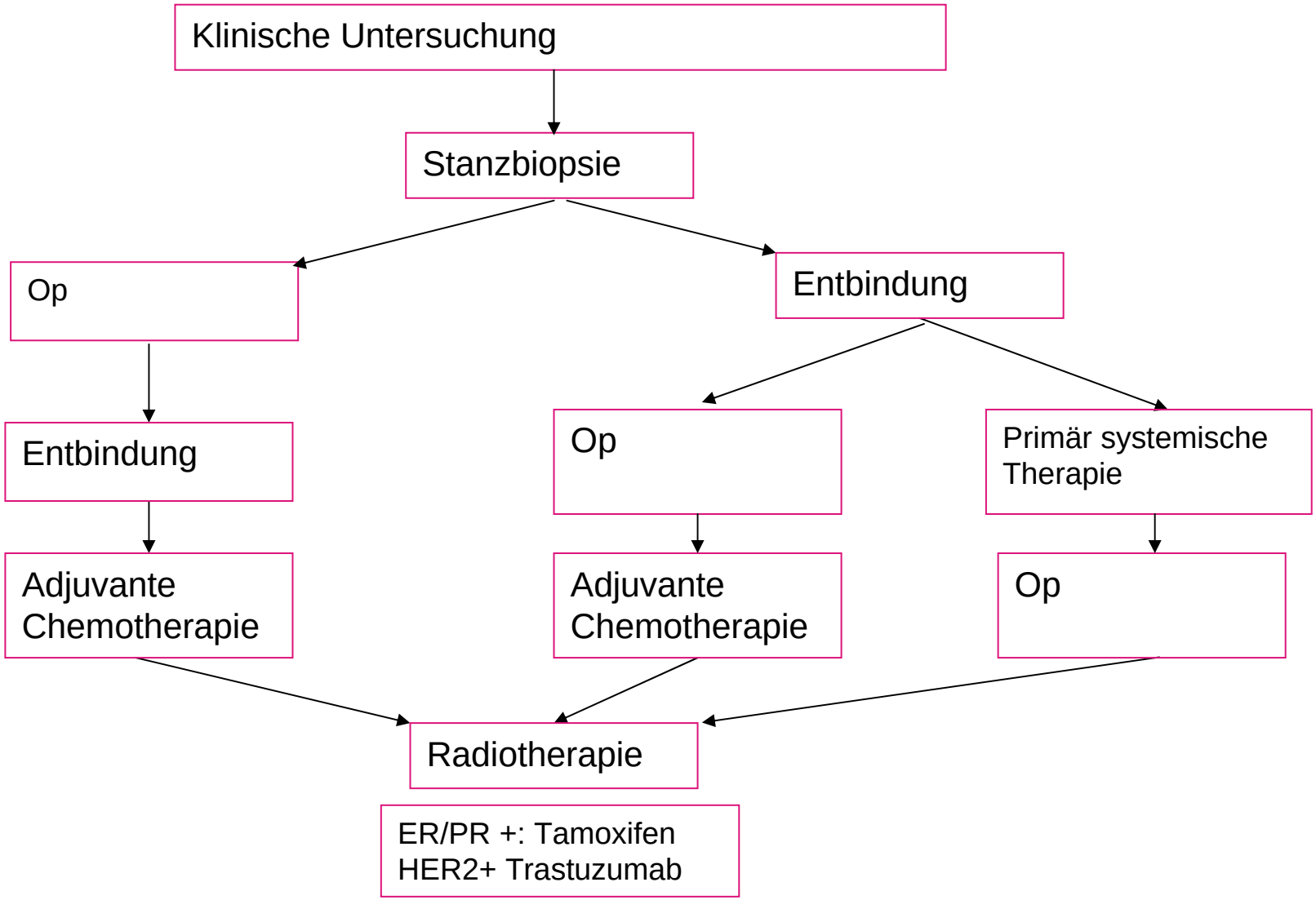
> 34. SSW



Loibl et al. Cancer 2006; 106: 237-246

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Update of guidelines in Leuven 1/2010

- **Role of MRI**
- **Role of Bone Scan**
- **Role of SNB**
- **Role of Radiotherapy**
- **Role of taxanes**
- **Role of Trastuzumab**

As in 2006: treat as closely as possible according to guidelines for non pregnant women

Registerstudie zur Diagnostik und Therapie des Mammakarzinoms in der Schwangerschaft

BCP
Breast Cancer in Pregnancy

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GBG-29
BIG 02-03

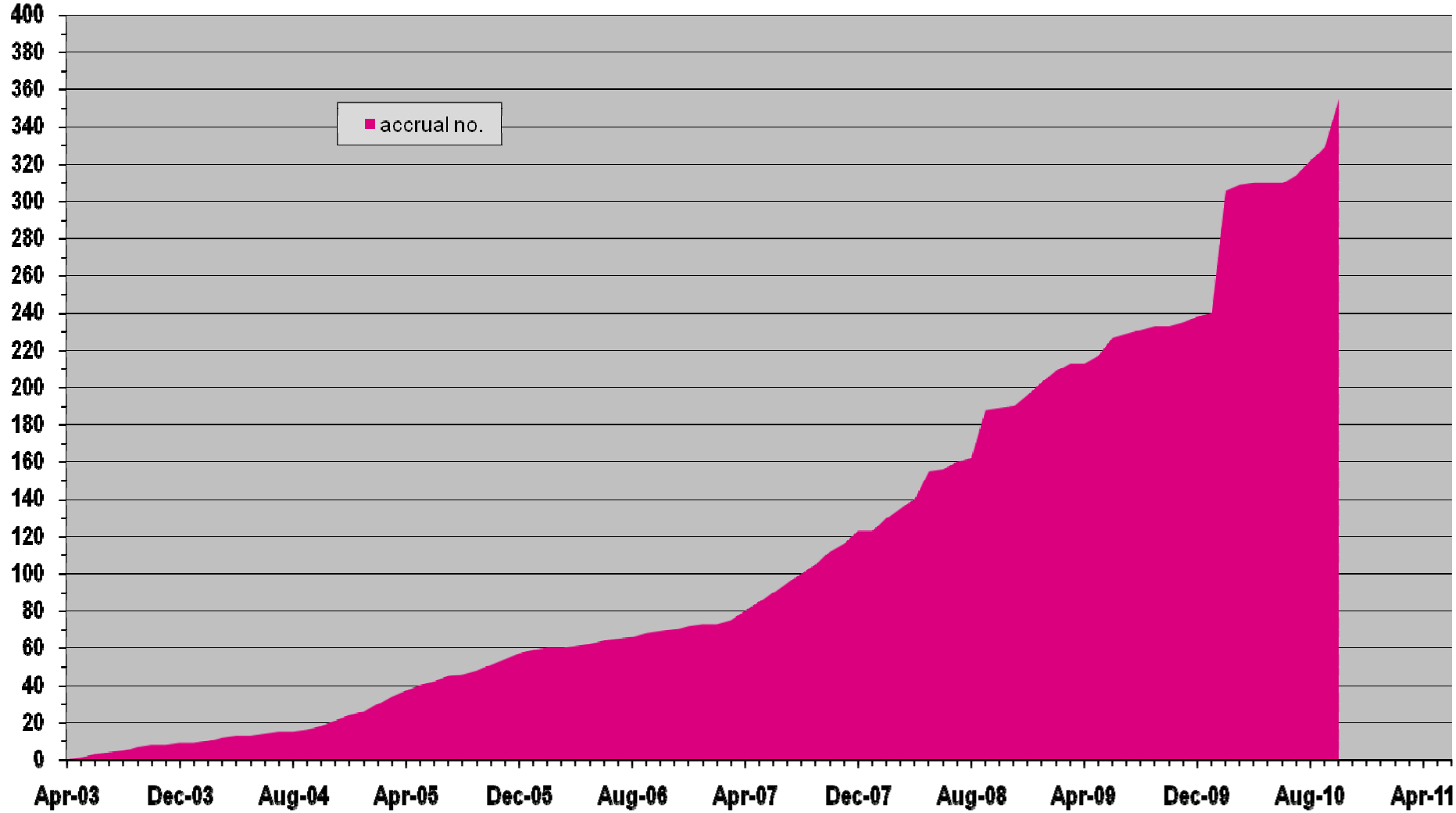
BIG
BREASTINTERNATIONALGROUP

www. germanbreastgroup.de/pregnancy

Mit Unterstützung der BANSS-Stiftung und der Universitätsfrauenklinik Frankfurt/M

BCP
Breast Cancer in Pregnancy

BCP - recruitment at 01.10.2010
n = 355



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Patients and Methods

- The registry is independent of the treatment and gestational age of the patients during pregnancy.

- **Primary endpoint:**
  - Foetal outcome 4 weeks after delivery.

- **Secondary endpoint:**
  - Maternal outcome of pregnancy.
  - Stage of and biological characteristics of breast cancer.
  - Breast cancer therapy, type of surgery.
  - Sensitivity and specifity of diagnostic procedures.
  - Outcome of the newborn after 5 years of therapy.
  - Outcome of breast cancer 5 years after diagnosis.

Patients characteristics (n=235)

T	T1	11.5%
	T2	57.1%
	T3	25.8%
	T4	4.4%
N	N+	50%
M	M1	7.9%
Grading	3	68.6%
ER	Negative	63.5%
Histological type	Ductal invasive/other	93.5%
HER-2	positive	34.8%

Characteristics		%
Time of diagnosis	1st trimester	23.8%
	2nd trimester	39.5%
	3rd trimester	36.8%
Pregnancy outcome	interruptio /misscarriage	13.2%
Mode of delivery	Caesarean section	49.3%
Surgery	mastectomy	47.2%
	breast conservation	45.9%

Delivery and fetal outcome:

The median time of delivery was 36 weeks (range 30-42 weeks). The median overall weight was **2760 g** (range 1260-4295); of babies with intrauterine chemotherapy was **2785g** (range 1270-4050g), the median weight of babies without cytotoxic therapy during pregnancy was **2700g** (range1250-4290g). No significant differences in postpartum haemoglobin were documented. The median haemoglobin in babies receiving systemic treatment was **16.1 g/dl** (range 10.4-21.9) and **17.2 g/dl** (range 14.7-21.4).

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Cytotoxic regimes during pregnancy (n=121)

Regimen	Taxane	Vinca-alkaloids	E/A mono	AC/EC	FEC	CMF
N (121)	**3**	**6**	**4**	**71**	**20**	**17**

Cycles during pregnancy	1	2	3	4	5	6
N (422)	**9**	**22**	**21**	**44**	**11**	**14**

- The 121 patients evaluable received in the median 4 cycles during pregnancy (1-6).
- No significant differences in postpartum haemoglobin were documented.
- The median haemoglobin in babies received intrauterine systemic treatment was 16.7 g/dl (range 10.4-24.9) and 16.9 g/dl (range 13.7-21.4) in babies without intrauterine chemotherapy.

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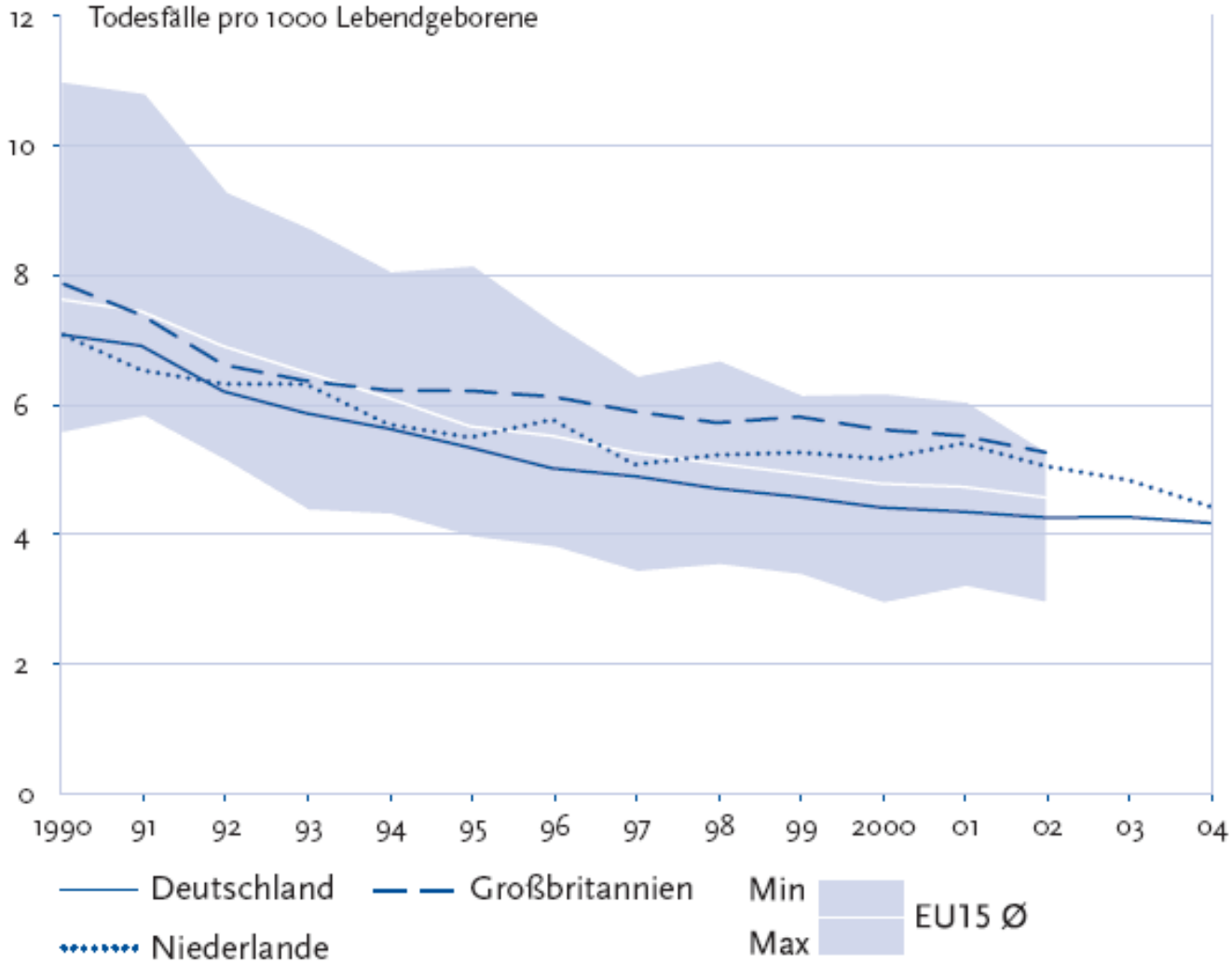
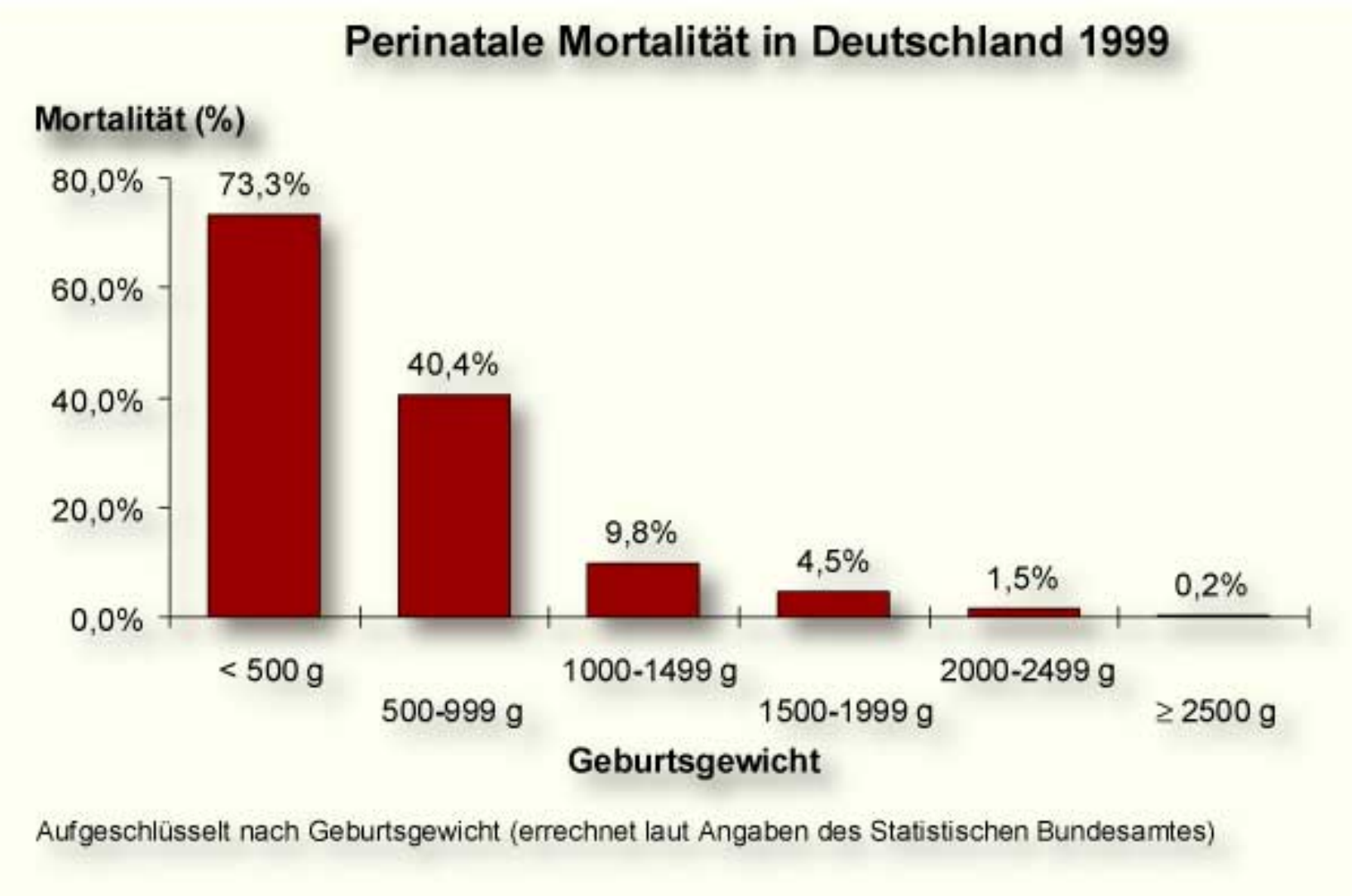
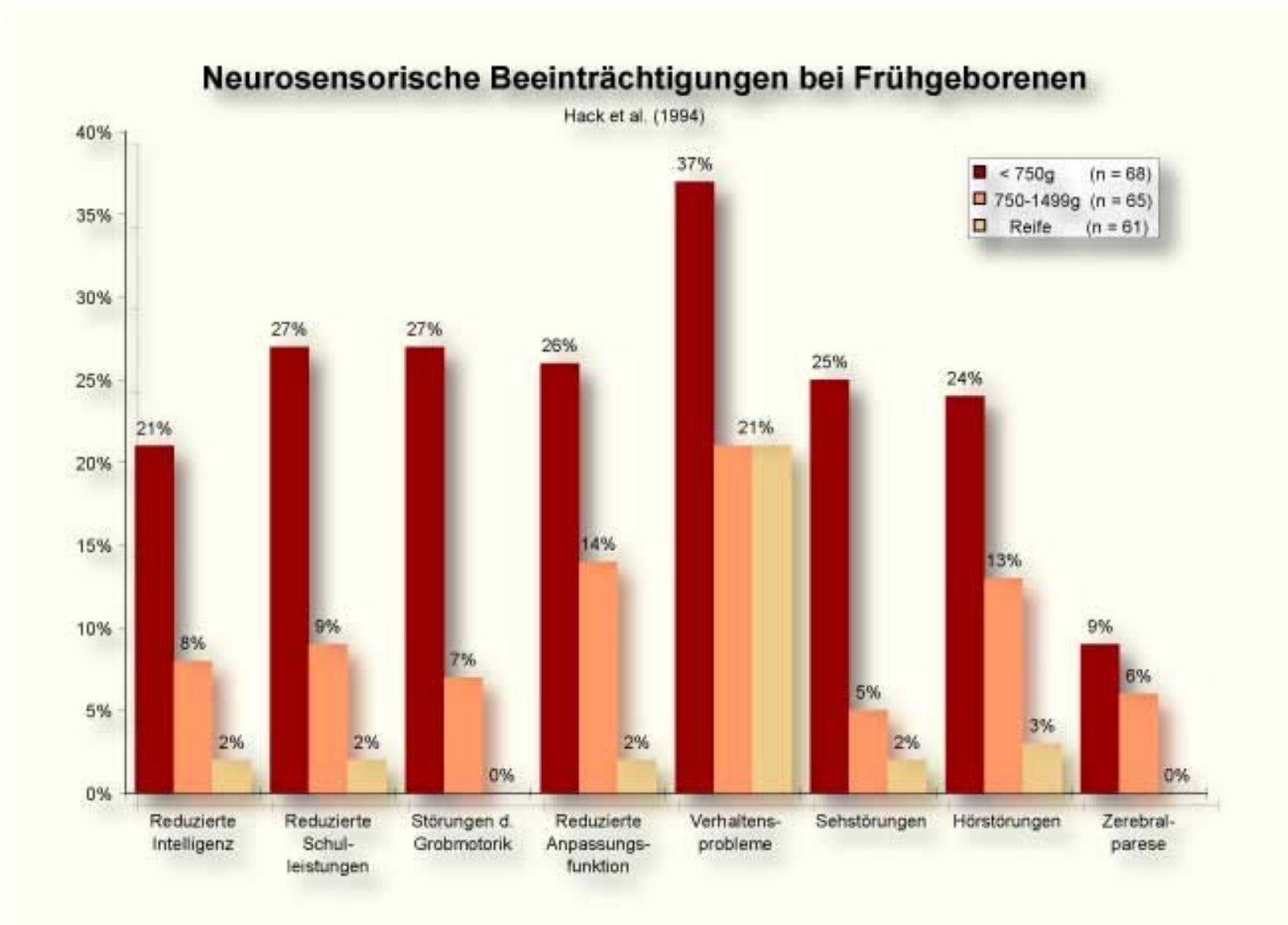
Abbildung 1.4.8: Entwicklung der Säuglingssterblichkeit im europäischen Vergleich. Quelle: HFA-Database, WHO Januar 2006





Aufgeschlüsselt nach Geburtsgewicht (errechnet laut Angaben des Statistischen Bundesamtes)


Neurosensorische Beeinträchtigungen bei Frühgeborenen
Hack et al. (1994)
< 750g (n = 68)
750-1499g (n = 65)
Reife (n = 61)
40%
35%
30%
25%
20%
15%
10%
5%
0%
21%
8%
2%
27%
9%
2%
27%
7%
0%
26%
14%
2%
37%
21%
25%
5%
2%
24%
13%
3%
9%
6%
0%
Reduzierte Intelligenz
Reduzierte Schul-leistungen
Störungen d. Grobmotorik
Reduzierte Anpassungs-funktion
Verhaltens-probleme
Sehstörungen
Hörstörungen
Zerebral-parese

Guidelines Breast
Version 2010.1.1D

Brustkrebs in der Schwangerschaft*

	Oxford / AGO LOE	GR	
➢ Diagnostik und Biopsie, wie außerhalb der Schwangerschaft (keine MRT Indikation)	4	C	++
➢ Staging: Ultraschall, Rö-Thorax, wenn indiziert	5	D	+/-
➢ OP, wie bei Nicht-Schwangeren	4	C	++
➢ Sentinel-Node Biopsie (nur Technetium)	4	C	+
➢ SNB im 1. Trimester	5	D	+/-
➢ Sensitivität und Spezifität sind unklar (während Stillzeit); Stillen sollte für 24 Stunden vermieden werden	4	C	++
➢ Farbstoffblau (keine Studiendaten in der Schwangerschaft)	4	C	--

* Teilnahme an Register-Studie empfohlen

FORSCHEN
LEHREN
HEILEN

Guidelines Breast
Version 2010.1.1D

Brustkrebs in der Schwangerschaft*

	Oxford / AGO LOE	GR	
➢ **Bestrahlung während der Schwangerschaft**	4	C	-
➢ **(Neo-)adjuvante Chemotherapie nur nach erstem Trimester (Indikation wie bei Nicht-Schwangeren)**			++
➢ **AC, FA (FEC)**	3b	C	++
➢ **MTX (e.g. CMF)**	4	D	- -
➢ **Taxane**	4	D	+/-
➢ **Endokrine Therapie**	4	D	- -
➢ **Trastuzumab**	4	D	- -

*** Teilnahme an Register-Studie empfohlen**

Brustkrebs in der Schwangerschaft*

	Oxford / AGO LOE / GR		
➢ Entbindung erst bei ausreichender kindlicher Reife; eine frühere Entbindung verbessert den mütterlichen Erkrankungsverlauf nicht	4	C	++
➢ Entbindungsmodus wie bei gesunder Schwangerer; Entbindung ≤ 3 Wochen nach Chemotherapie sollte vermieden werden	4	C	++
➢ Sollte eine Systemtherapie nach der Entbindung fortgeführt werden müssen, kann Stillen evtl. kontraindiziert sein (cave: Toxizität !)			++

* Teilnahme an Register-Studie empfohlen

„Die Interdisziplinäre
Kunst des ... Heilens“

„... in the face of general enthusiasm for terminating the pregnancy we believe the evidence is that the cancer should be terminated.“

B.F. Byrd, 1962