Ett multimarkörtest för återfallsrisk efter bröstbevarande kirurgi för duktal bröstcancer in situ (DCIS)

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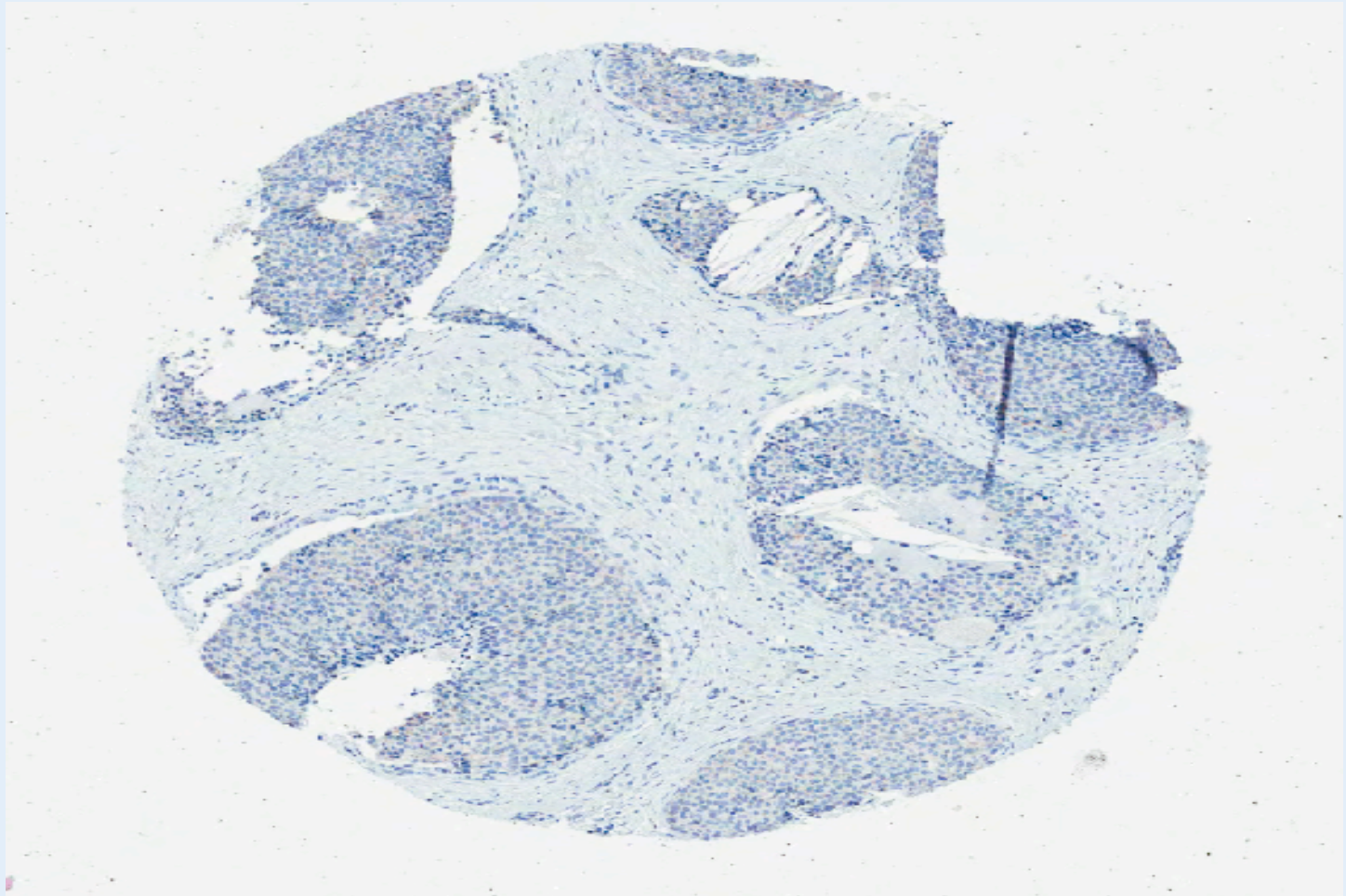

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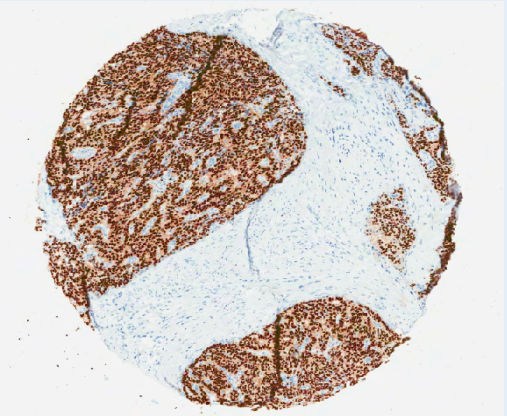
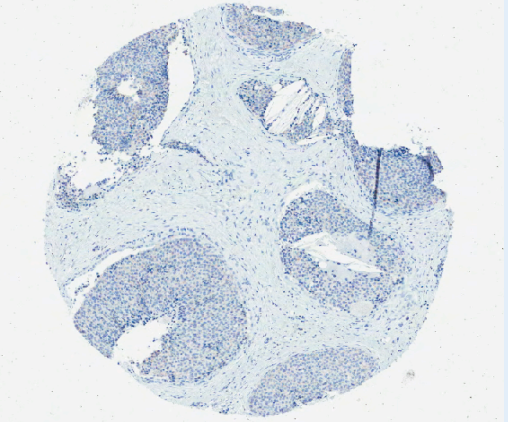
Bakgrund





DCIS – god prognos för överlevnad

Lokala återfall – 32% efter 20 år

Radioterapi minskar lokala återfall med 50%

Relativ riskminskning gäller alla undergrupper

Lågrisk SweDCIS – RT(-) 20% lokala återfall

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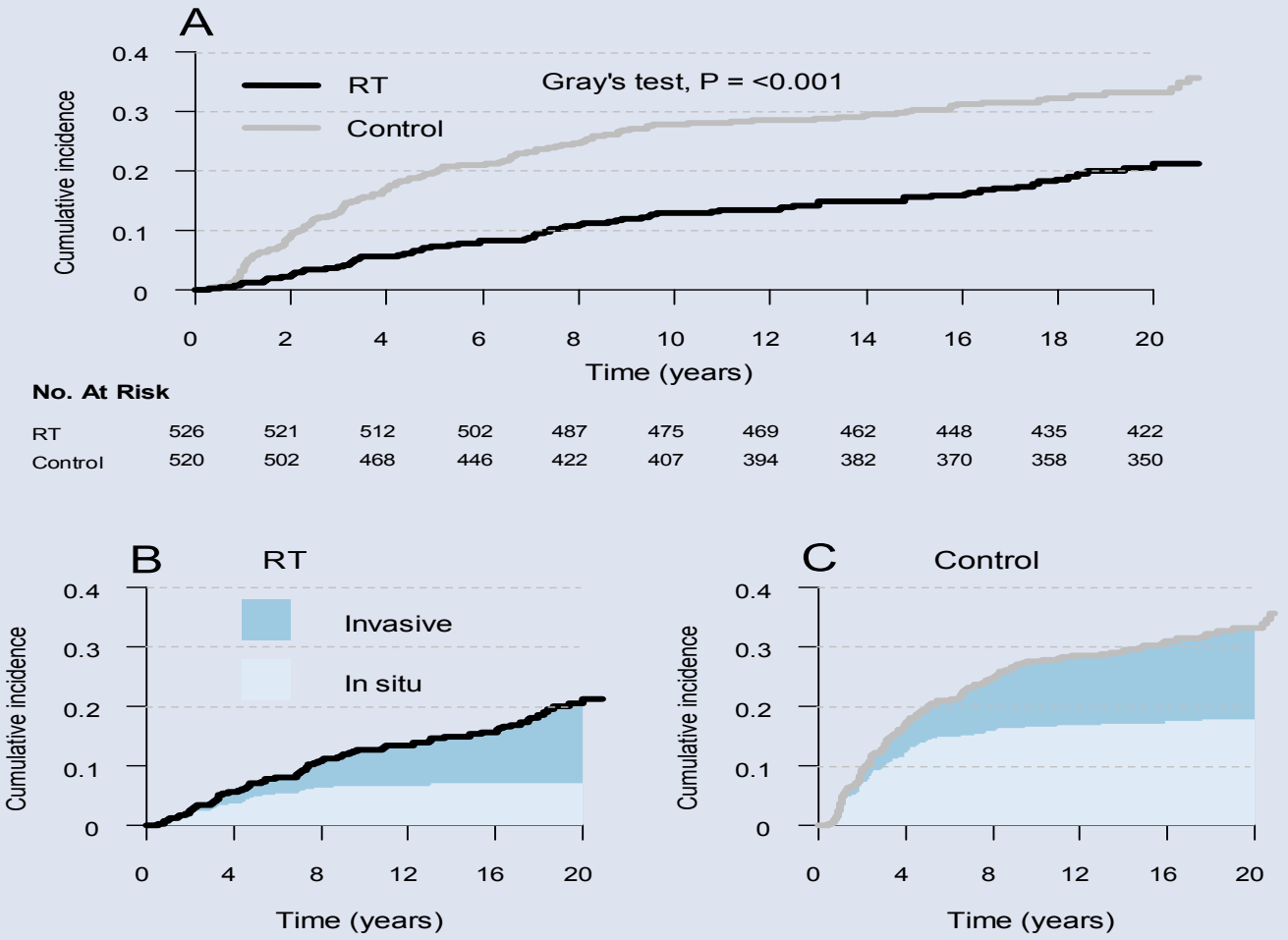

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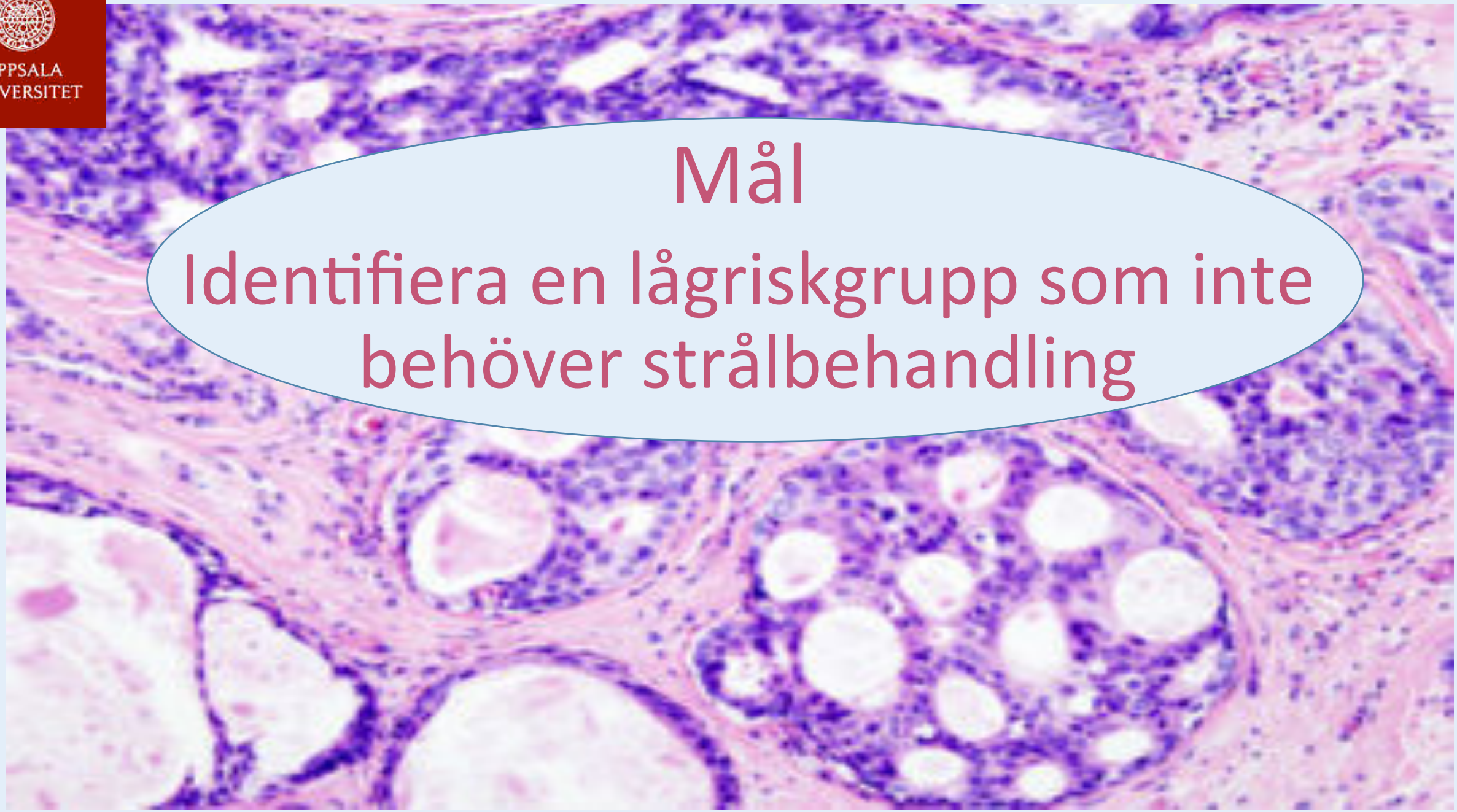


Mål

Identifiera en lågriskgrupp som inte behöver strålbehandling

Patienter och Metod

Två kohorter

- Uppsala/Västerås 1986-2004, n=354,

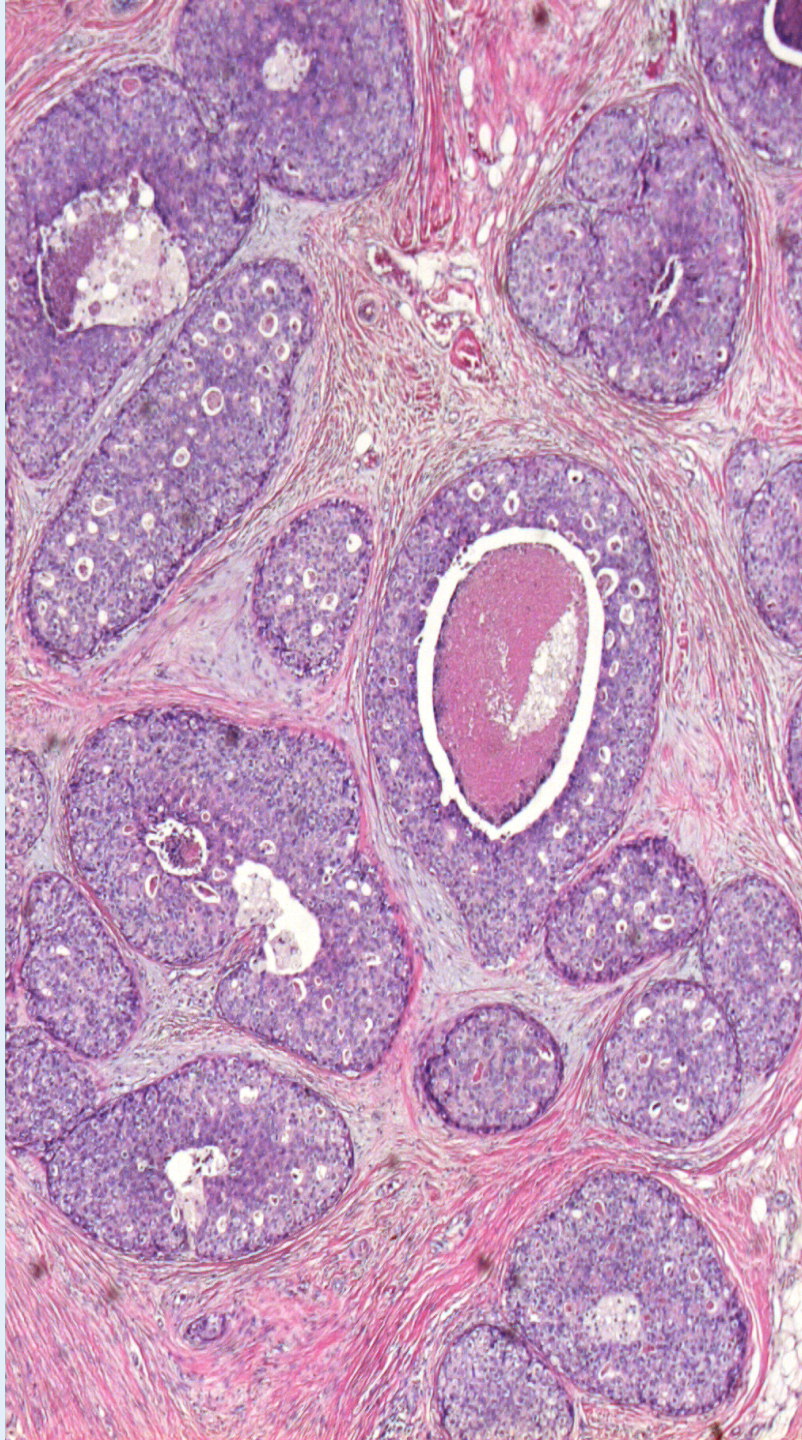
DCIS, bröstbevarande kirurgi +/- RT, follow-up 12,2 år

- University of Massachusetts 1997-2006, n=296,

DCIS, bröstbevarande kirurgi +/- RT, follow-up 7,2 år

Endpoints

- Invasiva lokala återfall
- Alla lokala återfall (invasiva + DCIS)



Patienter och Metod

Tumörmarkörer

HER2, PgR, Ki-67, COX2, p16/INK4A, FOXA1, SIAH2

Kliniska faktorer

Ålder, storlek, marginal, palpabel

Statistisk modell

"Multipel n-fold cross validation" med en pre-definierad statistisk analysplan för att förutse förväntat utfall i praktiken

Återfallsrisk efter 10 år

Invasiva återfall resp. Alla återfall

	BCS utan strålning			BCS med strålning		
	95% CI	Prevalens	n	95% CI	Prevalens	n
Invasiva "Lågrisk"	4% ±3%	70%	184	5% ±4%	71%	242
Invasiva "Högrisk"	30% ±11%	30%	80	6% ±6%	29%	97
Alla "Lågrisk"	8% ±6%	36%	95	7% ±6%	45%	153
Alla "Högrisk"	32% ±8%	64%	169	15% ±6%	55%	186

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Slutsats

- Med multimarkörtestet kan vi identifiera en lågriskgrupp DCIS som inte har någon nytta av strålbehandling
- Testet bygger på immunhistokemi och kliniska parametrar
- Resultaten kommer valideras i flera kohorter, bl. a. SweDCIS

Frågor?

Tack!

Patienter och Metod

- The COX enzymes play a central role in the biosynthetic pathway of prostanoids. COX-2 gene is upregulated during inflammation, hypoxia and in many cancers.

The COX genes encode for enzymes that catalyse the conversion from arachidonic acid to prostaglandins. The increased expression of COX-2 in tumourigenesis is secondary to multiple activations and as a response to growth factors and oncogenes, including those in the EGFR/HER2/RAS/MAP kinase pathway. Conversely, COX-2 is rarely expressed in normal tissue.

- The tumor suppressor gene p16 (also called MTS1, CDKN2 and INK4A) is a cyclin-dependent kinase (CDK) inhibitor and a negative cell cycle regulator. The inactivation of p16 appears to be a common event in many cancers. Several other functions of p16, including induction of apoptosis and senescence, have been correlated to p16's anti-tumor/anti-proliferation effects. p16 is able to induce apoptosis of tumor cells: Adenoviral-mediated expression of p16 (Adp16) inhibits ovarian cancer cell growth and causes apoptosis.
- Forkhead box A1 (FOXA1), is a tumor and stromal markers that recently have been proposed as predictors of local recurrence in invasive breast cancer. FOXA1 expression appears to be relevant in the sub-classification of luminal/ER positive tumors into two sub-groups with different biological behavior and prognosis corresponding to the luminal A and luminal B classes, identified by gene expression profiling studies. FOXA1 is expressed in close association with ERα, encoding for transcription factors with a plausible involvement in the ERα-mediated action in breast cancer. FOXA1 has been thought to be a significant predictor of a good outcome in breast cancer.
- SIAH2 was one of the genes significantly related with response and progression-free survival. SIAH2 is an ubiquitin E3 ligase which ubiquitinates proteins for proteasomal-dependent degradation and has target proteins in the RAS and estrogen signaling pathway, DNA damage response, cell growth and differentiation, angiogenesis and hypoxia. Studies in breast cancer showed SIAH2 mainly in ER-positive tumors. In addition, estrogens upregulated SIAH2 on both mRNA and protein level by a rapid transcriptional response mediated by the ER. A positive relationship between SIAH2 mRNA and ER protein levels. SIAH2 protein levels were predominantly upregulated in ER-negative breast cancer. They also observed increased SIAH2 protein expression during the transition of carcinoma in situ to invasive cancer and concluded that high SIAH2 protein expression is associated with an unfavorable survival. Increased SIAH2 mRNA levels with a favorable disease outcome in patients with ER-positive primary breast cancer. A positive association between SIAH2 mRNA and disease-free survival (DFS). As yet, it is unknown why SIAH2 protein and mRNA levels have opposed prognostic value in these heterogeneous tumor specimens.