Intermediate Endpoints in Cancer Treatment Studies

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Uses of Intermediate Endpoints

- Screening and Optimization of Promising Treatments in Phase II Trials
- Reducing Number of Patients and Time Needed in Phase III Trials

Screening and Optimizing Promising Treatments

- Addresses proliferation of molecular targets and clinical evaluation bottleneck
- Intermediate endpoint may be true endpoint, not surrogate
  - Ras expression, tumor shrinkage
- Relevance of endpoint may be uncertain

Screening and Optimizing Promising Treatments

- Intermediate endpoints needed for prevention, development of cytostatic agents, study of vaccines in patients without visable tumor

- Great opportunity to identify biologically relevant intermediate endpoints
  - micro-arrays, diagnostic imaging, pcr, immunodiagnostics

Surrogate Endpoints in Phase III Trials

- No adequate definition
- Not needed for most metastatic cancer trials
  - CR's, PR's used to avoid randomized trials
- Useful for primary cancer trials with long survivals and competing causes of death

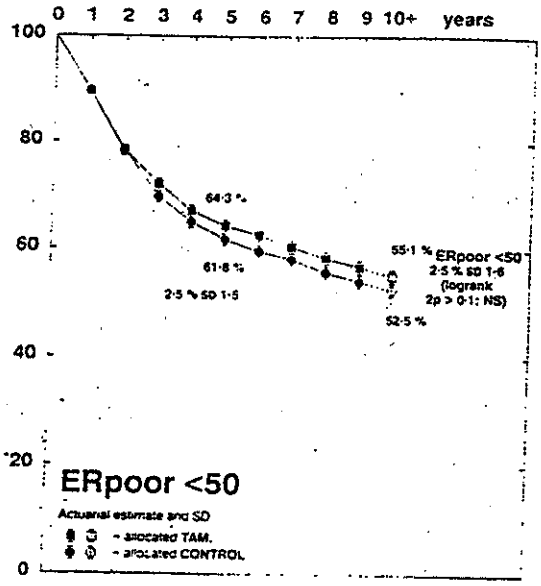
Surrogate Endpoints in Phase III Trials

- Sensitive quantitative markers of amount of sub-clinical disease could dramatically increase efficiency of therapeutics development
- Useful for early rejection of therapy even if intermediate endpoint is not validated surrogate

Surrogate Endpoints in Phase III Trials

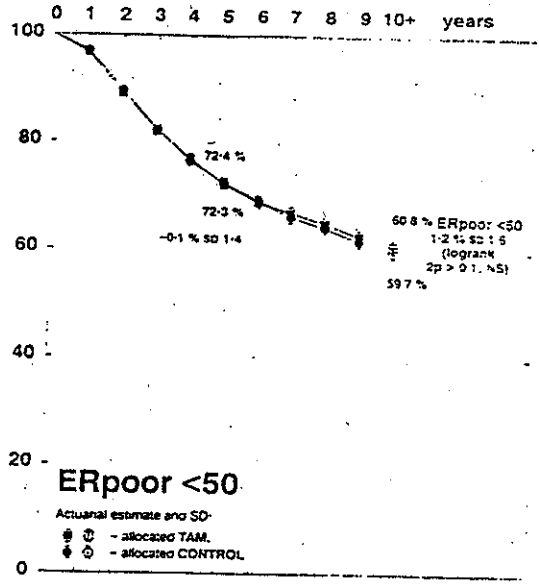
- Disease-free survival has been used as primary endpoint in many primary breast cancer trials, relying on meta-analysis to address survival

Tamoxifen vs. Not
RECURRENCE OR DEATH



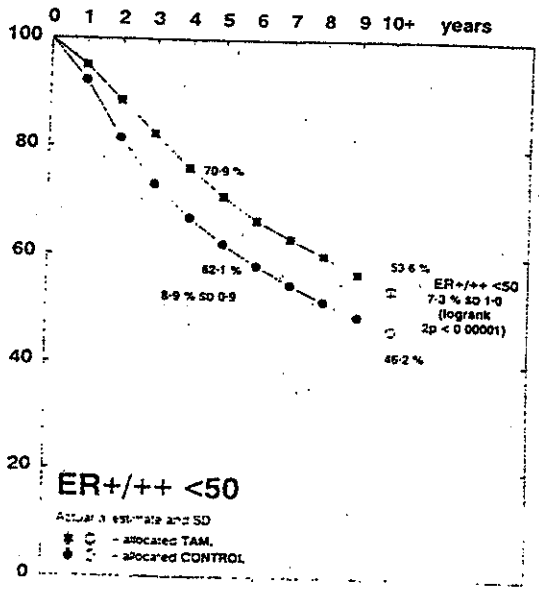
Annual rates	Years 0 – 4	Years 5 – 9	Years 10+
Tam.	9·37 % ± 0·33	3·10 % ± 0·27	3·18 % ± 0·51
Control	9·95 % ± 0·34	3·08 % ± 0·27	3·29 % ± 0·55
Events / person–years:			
Tam.	793 / 8460	132 / 4264	39 / 1228
Control	853 / 8577	129 / 4191	36 / 1094

Tamoxifen vs. Not
MORTALITY



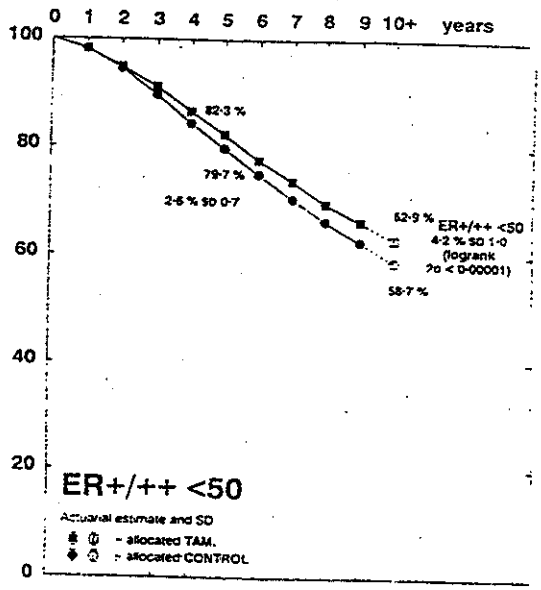
Annual rates	Years 0 – 4	Years 5 – 9	Years 10+
Tam.	6·47 % ± 0·26	3·65 % ± 0·28	2·93 % ± 0·45
Control	6·32 % ± 0·26	3·71 % ± 0·28	3·94 % ± 0·55
Events / person–years:			
Tam.	607 / 9381	175 / 4776	41 / 1398
Control	608 / 9614	180 / 4849	52 / 1319

Tamoxifen vs. Not
RECURRENCE OR DEATH



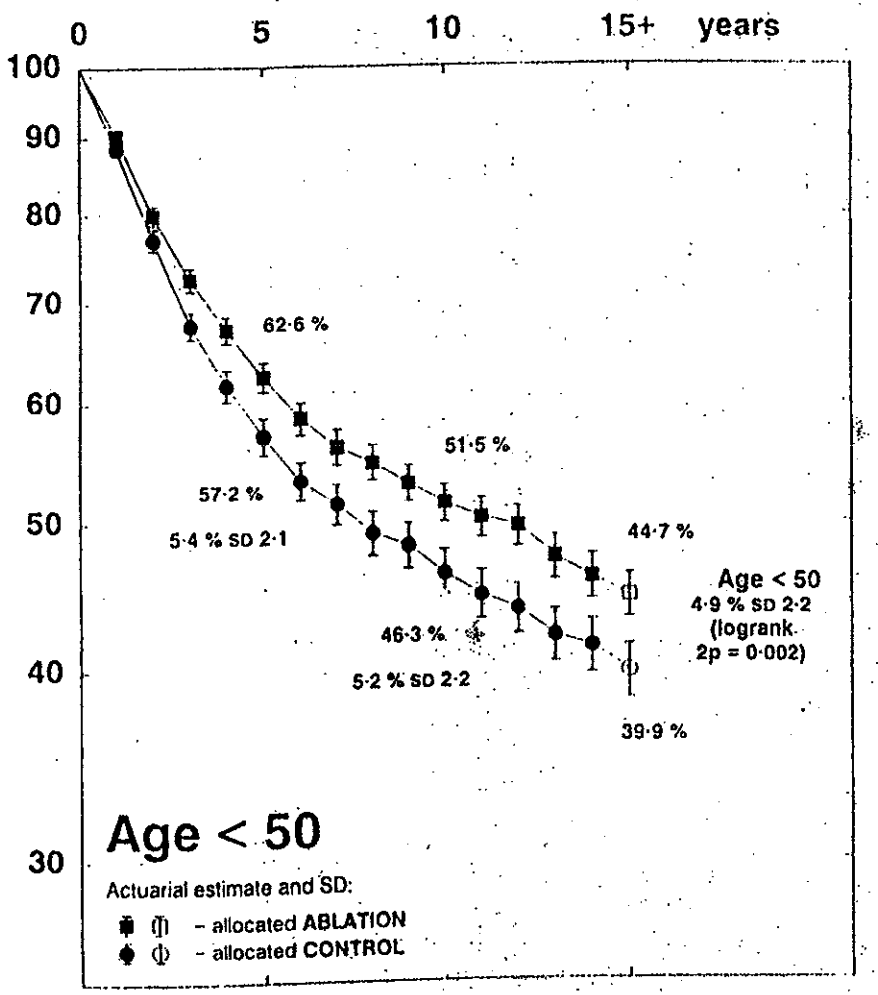
Annual rates	Years 0 – 4	Years 5 – 9	Years 10+
Tam	6·89 % ± 0·16	5·68 % ± 0·21	5·16 % ± 0·49
Control	9·50 % ± 0·20	5·98 % ± 0·23	4·97 % ± 0·46
Events person–years			
Tam.	1747 25353	741 13036	156 2533
Control	2251 23534	664 11099	116 2333

Tamoxifen vs. Not
MORTALITY



Annual rates	Years 0 – 4	Years 5 – 9	Years 10+
Tam	3·81 % ± 0·12	5·42 % ± 0·19	5·83 % ± 0·42
Control	4·41 % ± 0·13	6·07 % ± 0·20	6·16 % ± 0·45
Events · person–years:			
Tam	1047 / 27461	837 15457	192 / 3296
Control	1185 / 26851	878 13471	188 / 3053

Ovarian Ablation vs. N t
RECURRENCE OR DEATH



nual rates	Years 0 – 4	Years 5 – 9	Years 10 – 14	Years 15+
lation	9·88 % ± 0·43	3·97 % ± 0·37	2·62 % ± 0·36	3·07 % ± 0·36
ontrol	11·56 % ± 0·52	4·52 % ± 0·46	2·91 % ± 0·46	4·02 % ± 0·51
lation	523 / 5295	116 / 2922	53 / 2024	74 / 2414
ontrol	504 / 4359	98 / 2169	40 / 1375	61 / 1518

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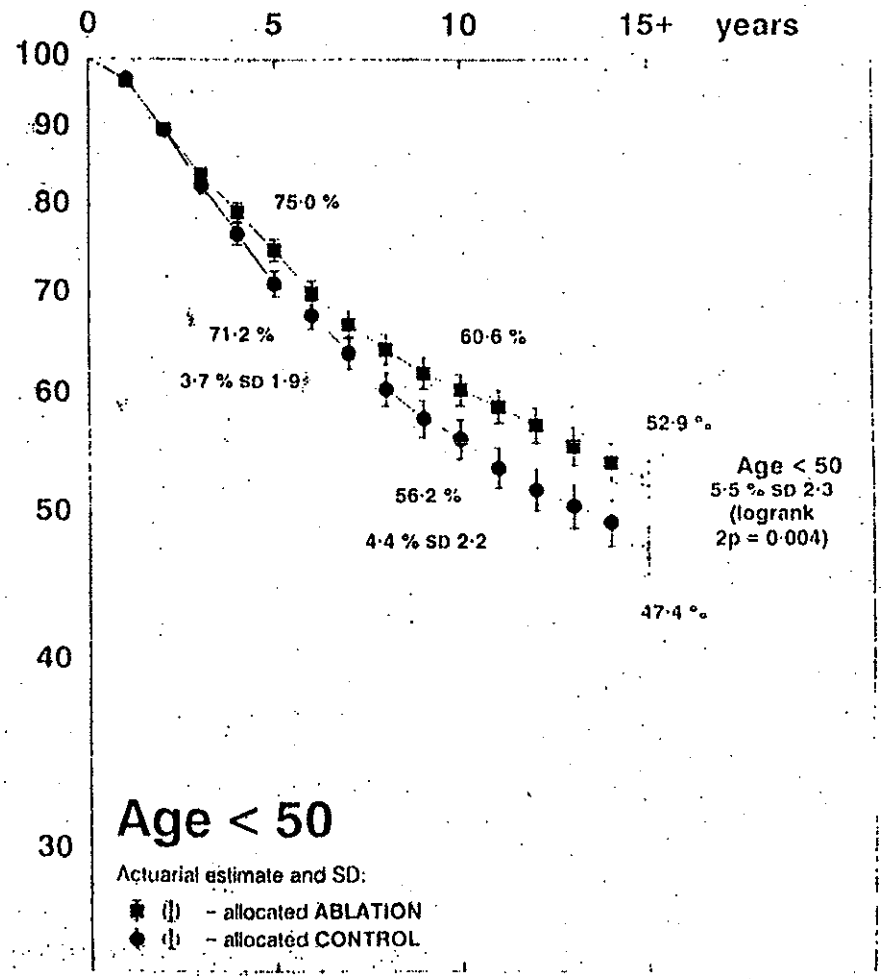
O· arian Ablation vs. Not
MORTALITY



Annual rates	Years 0 – 4	Years 5 – 9	Years 10 – 14	Years 15+
Ablation	5·86 % ± 0·31	4·42 % ± 0·36	2·90 % ± 0·36	2·80 % ± 0·33
Control	6·43 % ± 0·36	4·91 % ± 0·43	3·17 % ± 0·44	4·31 % ± 0·51
Ablation	347 / 5918	150 / 3397	65 / 2240	73 / 2609
Control	323 / 5024	131 / 2670	51 / 1611	72 / 1672

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Tumor Shrinkage in Advanced Ovarian Cancer