Basics and limitations of **adjuvant online** – an internet based decision tool

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Comprehensive Cancer Center Ulm
Referees make roughly 200 decisions per soccer game
Adjuvant OnLine

Who knows AOL?

Who uses AOL?
- frequently
- sometimes
- never

Who knows background information of AOL?
Adjuvant OnLine – Why?

Treatment decisions in the adjuvant therapy of early breast cancer

- small tumors, negative lymph nodes
- older patients > 70 years
- tumors ER/PgR + and N0-3+
Adjuvant OnLine – Why?

Treatment decisions in the adjuvant therapy of early breast cancer

- Individual risk of relapse – without therapy
  → Prognosis

- Individual risk of relapse - with therapy
  → benefit of treatment

- Toxicities of treatment

- Comorbidities and life expectancy
Adjuvant OnLine

- Webbased tool to estimate the (absolute) net benefit of adjuvant treatment for an individual patient

- By estimating a patient`s risk of a negative outcome (death, relapse) and then multiplying that by the proportion of negative events that a given adjuvant therapy is known to prevent.

More informed decision about adjuvant therapy for health care physicians and patients
pT1c pN0 G2 M0 ER+ Relapse: 23.6%
pT1c pN1-3 G2 M0 ER+ Relapse: 34.9%
pT1c pN1-3 G2 M0 ER+ BCSM: 16.0%
Adjuvant OnLine - Background

- AOL estimates prognosis based on
  - Tumor size
  - Number of involved lymph nodes
  - Grading
  - ER status
Adjuvant OnLine - Background

- **Source:** SEER data bank
  (Surveillance Epidemiology and End Results)

  - big population-based databank
    (comprises 10% of all breast cancer cases in the US)

- **Limitations:**
  - Only overall mortality is documented
  - Relapse rate is **not** documented
  - Cause of death **not** reliably reported
  - Adjuvant treatment is **not** known
  - Grading, ER and PgR are frequently **not** available
Assessment of treatment effect is mainly based on:

- EBCCTG Overview Metaanlyse

**Limitations**
- many old trials included
  (frequently not according to current quality standards)
- ER und PgR is only documented as positive or negative
- only few patients above 70 years included
- HER2 Status is not considered
**STEPP 5-year DFS by Composite Risk**

- **Node** neg
  - **T** 1.5cm
  - Her2 neg
  - PVI neg
  - ER 90%
  - PgR 80%
  - Ki-67 7%

- **Node** 3+
  - **T** 1.9cm
  - Her2 neg
  - PVI neg
  - ER 95%
  - PgR 75%
  - Ki-67 11%

- **Node** neg
  - **T** 2.1cm
  - Her2 pos
  - PVI neg
  - ER 75%
  - PgR 0%
  - Ki-67 35%

- **Node** 12+
  - **T** 2.5cm
  - Her2 neg
  - PVI pos
  - ER 80%
  - PgR 75%
  - Ki-67 20%

*Increasing Composite Risk*
Node-positive: *Tam vs Tam → CMF/AC*

- Benefit of additional CHT is low in pts with high ER-expression
SWOG S 8814

MACA postmenopausal
N +
Rez +
n = 1477

45% > 65 Jahre

RANDOMIZE

Tam (n=361)

6 x CAF + Tam (n=550)

6 x CAF → Tam (n=566)

Albain et al. Lancet 2011
INT 0100 (S8814)
Disease-Free Survival

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

0 5 10 15
Years from Registration

10-year Estimate

CAF T 60 %
CAFT 53 %
T alone 48 %

Log rank p = 0.002
DFS: INT 0100 (S8814)
No benefit by CAF when HER2 - , N+1-3

![Graph showing disease-free survival with log rank p = 0.71. The graph compares Tamoxifen + CAF (n = 283, 87 failures) with Tamoxifen alone (n = 102, 34 failures).]
DFS: INT 0100 (S8814)
no benefit with CAF when ER highly expressed

Disease-Free Survival

Log rank p = 0.98

- Tamoxifen + CAF (n = 262, 104 failures)
- Tamoxifen alone (n = 82, 34 failures)

Years Since Registration
IBCSG 11-93: Prämenop., N-pos
n=174; 1993-1998 (97% with 1-3 N+)

Thürlimann et al, BCRT 2009;113,137-144.
IBCSG 11-93: AOL underestimates endocrine therapy only (OFS+Tam)

- **OFS+AC+Tam**: $\lambda = 0.029$
- **OFS+Tam**: $\lambda = 0.044$

**Trial 11-93 Exponential Hazards**

- **OFS+AC+Tam**: $\lambda = 0.029$
- **OFS+Tam**: $\lambda = 0.027$

**RFS (%)**

- 76% 10-yr RFS
- 64% 10-yr RFS

**P=0.03**
Is AOL equally valid in different regions of the world?
**Aim:**
Validation of AOL in breast cancer pts of Netherlands

**Enrollment:**
from 1987-1998. Pts had at least part of their treatment at the Netherlands Cancer Institute

**Inclusion criteria:**
- Invasive breast cancer
- T1-3 tumors
- Information about axillary lymph nodes available
- no distant metastases
- Surgery including axillary staging and radiotherapy according to national guidelines

**Endpoints:**
- overall survival
- breast cancer specific survival
Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! program: a hospital-based retrospective cohort study

Steffie Mook, Marjanka K Schmidt, Emiel J Rutgers, Anthonie O van de Velde, Otto Visser, Sterre M Rutgers, Nicola Armstrong, Laura J van ’t Veer, Peter M Ravdin

Summary

Background Adjuvant! is a web-based program that calculates individualised 10-year survival probabilities and predicted benefit of adjuvant systemic therapy. The Adjuvant! model has not been validated in any large European series. The aim of our study was to validate Adjuvant! in Dutch patients, investigating both its calibration and discriminatory accuracy.

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<thead>
<tr>
<th></th>
<th>Observed</th>
<th>AOL</th>
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<tbody>
<tr>
<td>10-years OS (%)</td>
<td>69,0</td>
<td>69,1</td>
</tr>
<tr>
<td>10-years BCSS (%)</td>
<td>78,6</td>
<td>77,8</td>
</tr>
</tbody>
</table>

**Differences in:**

women < 40 years (OS 4,2% BCSS 4,7% overememestimated by AOL)

Women > 69 years (OS 3,9% overestimated)

N 1-3 LK (BCSS 3,1% underestimated)

T1c und T2 (BCSS 2,4% overestimated, 3,2 % underestimated)

**UK-trial:**

OS und BCSS were overestimated by AOL up to 10%!
Assessment of importance of therapeutic benefits by patients.

Improvement of survival by 1 year with 6 months chemotherapy:

\[ 5 \rightarrow 6 \text{ Jahre:} \quad 77\% \]
\[ 15 \rightarrow 16 \text{ Jahre:} \quad 61\% \]

Improvement of probability of survival by 2 % after 5 years with 6 months chemotherapy:

\[ 85 \rightarrow 87\% \quad 54\% \]
\[ 65 \rightarrow 67\% \quad 53\% \]
Adjuvant OnLine - CAVEATS

- The Calculation of risk and treatment effect is based on insufficient data
- The effect of endocrine treatment is underestimated
- The validity of AOL in different regions with different culture of treatment is questionable
Adjuvant OnLine - CAVEATS

If pts decide to have chemotherapy because of small anticipated differences in overall survival even small inaccuracies of a tool calculating risk of relapse and treatment benefit may lead to wrong decisions
Literatur:

S Mook et al. Calibration and discriminatory accuracy of prognosis calculation for breast cancer with the online Adjuvant! Program: a hospital based retrospective cohort study
Lancet Oncology 2009; 10: 1070-1076

J Huober, B Thürlimann
Adjuvant! When the new world meets the old world
Lancet Oncology 2009; 10: 1028-1029

Campbell HE et al. An investigation into the performance of the Adjuvant! Online prognostic programme in early breast cancer for a cohort of patients in the United Kingdom
B J Cancer 2009; 101:1074-1084

P Ravdin et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.
J Clin Oncol 2001; 19: 980-991
INT 0100 (S8814) Overall Survival

Overall Survival

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%

Years from Registration

- 0
- 5
- 10
- 15

Log rank p = 0.05

10-year Estimate

- CAF + T: 68%
- CAFT: 62%
- T alone: 60%
STEPP Analyse: Korrelation CHT-Benefit und quantitative ER Expression

Nodal -negativ: Tam vs Tam→ CMF

IBSCG, JNCI 2002
Dilemma der adjuvanten Therapie

Breast cancer mortality
8575 women
RR 0.79 (95% CI 0.72–0.85)
Log-rank 2p<0.00001
10-year gain 6.5% (SE 1.2)

Überbehandlung

No CTX
35.8%

RR 0.86 (95% CI 0.79–0.93)
Log-rank 2p=0.0005
8-year gain 2.8% (SE 0.9)

Unterbehandlung oder falsche Behandlung

21.0%

15.9%

29.3%

Anthracycline

23.9%

21.1%

16.7%

Taxane+anthracycline

EBCTCG Lancet 2012;379: 432-444
Prognose MACA in Abhängigkeit von Nodalstatus und Tumorgröße

<table>
<thead>
<tr>
<th></th>
<th>5-Jahres Überleben (n = 24 740)</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>T1 N0</td>
<td>96 %</td>
</tr>
<tr>
<td>T1 N1-3</td>
<td>87 %</td>
</tr>
<tr>
<td>T1 N ≥ 4</td>
<td>66 %</td>
</tr>
<tr>
<td>T2 N0</td>
<td>89 %</td>
</tr>
<tr>
<td>T2 N1-3</td>
<td>80 %</td>
</tr>
<tr>
<td>T2 N ≥ 4</td>
<td>59 %</td>
</tr>
<tr>
<td>T3 N0</td>
<td>82 %</td>
</tr>
<tr>
<td>T3 N1-3</td>
<td>73 %</td>
</tr>
<tr>
<td>T3 N ≥ 4</td>
<td>45 %</td>
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</tbody>
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Carter et al. 1989
Prognose MACA in Abhängigkeit vom Nodalstatus

**5-Jahres Überleben** \((n = 505)\)

<table>
<thead>
<tr>
<th>Nodalstatus</th>
<th>DFS</th>
<th>OAS</th>
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<tbody>
<tr>
<td>N0</td>
<td>85 %</td>
<td>83 %</td>
</tr>
<tr>
<td>N1-3</td>
<td>60 %</td>
<td>73 %</td>
</tr>
<tr>
<td>N (\geq 4)</td>
<td>30 %</td>
<td>46 %</td>
</tr>
<tr>
<td>N 4-6</td>
<td>42 %</td>
<td>54 %</td>
</tr>
<tr>
<td>N 7-12</td>
<td>28 %</td>
<td>50 %</td>
</tr>
<tr>
<td>N (\geq 13)</td>
<td>16 %</td>
<td>28 %</td>
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