Hypofractionation radiotherapy in breast cancer

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Portsmouth
Radiotherapy in Breast ca: Dose-Time relationship

- Lionel Cohen—with personal observation and review of published data
- Breast cancer is more radiosensitive than skin cancer
- Fractionated regimen with treatment over 3 weeks is more effective
- No improvement in therapeutic ratio by prolonging the treatment time and increasing dose beyond skin tolerance
- Single dose of 1200r is curative

BJR:1952; Vol 25, No 300, 636-642
that the tumour dose could not be estimated. Neither the overall time nor the size of the tumour were available. There remained the 29 patients listed in Table II from which relevant data could be extracted.

Table II the minimum tumour doses calculated the number of fractions (usually daily) given together with the proportion of cases cured for each particular combination of treatment factors. In pre-operative irradiation this cure rate is given by the author and is usually based on biological examination of the surgical specimen. In post-operative irradiation one can estimate the clinical survival rate, and is subject to a constant percentage fluctuations of undetermined magnitude.)

The diverse set of data in Table II can be considered comparable by estimating, from the rates given, the actual median curative doses for each series of cases. Assuming, as we have shown true for our personally observed cases, that the dosage distribution is practically lognormal, if the standard deviation factor is about the magnitude \( f = 1.11 \), one can estimate that giving a 50 per cent. cure rate (M.L.D.) by computing the given dose by the appropriate probit formula. In this way we were able to calculate the 26 values...

Small white circles represent cured cases; black circles, failures.
Adjuvant breast Hypofractionation RT: Background

- EBCTCG-systematic overview confirms adjuvant radiotherapy after primary surgery reduced LRR and breast cancer death.
- For many decades schedules of adjuvant RT commonly used was 50Gy/25#/5weeks (+/- boost RT).
- At least 13 randomised studies testing adjuvant breast hypofractionated RT versus standard regimen were reported.
- 2.7Gy/# for 15 or 16# over 3 to 3.2 weeks hypofractionated regimen were confirmed safe & efficient and replaced standard schedule in many countries.
- Hypofractionated schedule is convenient and cost effective to both patient and health services.
NSABP-04 TRIAL

TWENTY-FIVE-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING RADICAL MASTECTOMY, TOTAL MASTECTOMY, AND TOTAL MASTECTOMY FOLLOWED BY IRRADIATION

Bernard Fisher, M.D., Jong-Hyeon Jeong, Ph.D., Stewart Anderson, Ph.D., John Bryant, Ph.D., Edwin R. Fisher, M.D., and Norman Wolmark, M.D.

Between July 1971 to September 1974
- 1765 women with operable breast cancer were randomized
- Radical mastectomy, Total mastectomy with or without regional irradiation
- Patients with clinically positive LN had ALND
- RT dose 50Gy/25# to chest wall & SCF and 10-20Gy boost for positive LN, 45Gy/25# to IMC
- No difference in DFS, RFS, OS and distant recurrence rate
- RT significantly reduced locoregional recurrence.
NSABP-04 TRIAL
NSABP-04 TRIAL

A. Distant-Disease-free Survival

- Radical mastectomy
- Total mastectomy + irradiation
- Total mastectomy

Women with negative nodes
Women with positive nodes

B. Overall Survival

Women with negative nodes
Women with positive nodes

Years of Follow-up
NSABP-06 TRIAL

FIVE-YEAR RESULTS OF A RANDOMIZED CLINICAL TRIAL COMPARING TOTAL MASTECTOMY AND SEGMENTAL MASTECTOMY WITH OR WITHOUT RADIATION IN THE TREATMENT OF BREAST CANCER

Bernard Fisher, M.D., Madeline Bauer, Ph.D., Richard Margolese, M.D., Roger Poisson, M.D.

NSABP-06 TRIAL: Results

- Started in 1976
- Total of 1843 patients randomized
- Stage I & II breast cancer, tumor <4cm
- Mastectomy, segmentectomy with or without breast irradiation.
- ALL patient had ALND and patient with positive nodes received chemotherapy
- Breast RT of 50Gy/25# over 5 wks; No boost and LN irradiation
- DFS, Distant DFS and OS in segmentectomy group is no worse than mastectomy
- Breast irradiation significantly reduced the local recurrence
NSABP-06 TRIAL

Percentage of patients remaining free of breast tumor after segmentectomy or segmentectomy plus irradiation
NSABP-06 TRIAL

DFS, Distant DFS and OS of patients treated by Total mastectomy or by segmentectomy plus irradiation
EFFECTS OF RADIOTHERAPY AND SURGERY IN EARLY BREAST CANCER

An Overview of the Randomized Trials

EARLY BREAST CANCER TRIALISTS’ COLLABORATIVE GROUP*

EBCTCG- A meta-analysis

- Mortality data from 36 randomized trials were analyzed
- Comparing surgery with or without RT in EBC
- Total of 29715 women
- Radiotherapy reduced the risk of local recurrence by 3 times c/w surgery alone
- RT prevents one death for every 4 local recurrence reduction at 10 years
- No difference in long term OS
EBCTCG- A meta-analysis

Ten-Year Survival among Approximately 3100 Women in Seven Randomized Trials Comparing Mastectomy with Breast-Conserving Surgery plus Radiotherapy.
Hypofractionation in Breast Ca RT

- Ontario Clinical Oncology Group Trial

Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node-Negative Breast Cancer


Ontario Clinical Oncology Group Trial

- 1234 patients, between April 1992 to September 1996
- 50Gy/25fx/35 days vs 42.5Gy/16 fx/22 days
- T1 –T2 tumors; all node negative
- Large breasted women excluded (separation > 25 cm)
- Non-inferiority with 80% power to rule out 5% increase in local recurrence
Ontario Clinical Oncology Group Trial-Results

Median follow-up: 12 years

Tam: 41%
Chemo: 11%

Whelan et al NEJM 362 (6), 2010
### Long-term Toxicity

<table>
<thead>
<tr>
<th>Site and Grade</th>
<th>5 Yr</th>
<th>10 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Regimen (N=424)</td>
<td>Hypofractionated Regimen (N=449)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82.3</td>
<td>86.1</td>
</tr>
<tr>
<td>1</td>
<td>14.4</td>
<td>10.7</td>
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<tr>
<td>2</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>Subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61.4</td>
<td>66.8</td>
</tr>
<tr>
<td>1</td>
<td>32.5</td>
<td>29.5</td>
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<tr>
<td>2</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>0.9</td>
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</table>

No difference in skin & subcutaneous toxicities
Long Term Cosmetic Results

<table>
<thead>
<tr>
<th>Rating</th>
<th>Baseline</th>
<th>5 Yr</th>
<th>10 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Regimen (N = 604)</td>
<td>Hypofractionated Regimen (N = 616)</td>
<td>Absolute Difference (95% CI)</td>
</tr>
<tr>
<td>percent of patients</td>
<td>46.3</td>
<td>34.3</td>
<td>36.4</td>
</tr>
<tr>
<td>percentage points</td>
<td>46.8</td>
<td>34.3</td>
<td>36.4</td>
</tr>
<tr>
<td>Excellent</td>
<td>46.3</td>
<td>34.3</td>
<td>36.4</td>
</tr>
<tr>
<td>Good</td>
<td>36.3</td>
<td>44.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Fair</td>
<td>15.1</td>
<td>17.3</td>
<td>19.0</td>
</tr>
<tr>
<td>Poor</td>
<td>2.3</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Excellent or good</td>
<td>82.6</td>
<td>79.2</td>
<td>77.9</td>
</tr>
</tbody>
</table>

*Absolute differences were calculated as the value in the group that received the standard regimen minus the value in the group that received the hypofractionated regimen. EORTC denotes European Organization for Research and Treatment of Cancer.

No difference in long-term cosmetic result
UK Start trials

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists’ Group†

UK Start B trial

- N=2215 patients, from 1999 to 2002
- Median follow-up: 9.9 years
- Standard Arm: 50Gy/25# over 5 weeks
- Experimental arm: 40.05Gy/15# over 3 weeks
- pT1-3 pN0-1 M0 EBC patients were included
- 23 centres in the UK participated

START A Trial: Experimental arm includes 39Gy/13# or 41.6Gy/13# over 5 weeks

Start B: Marked/Moderate Cosmetic Defect

% of patients with no moderate / marked effect

Time from randomisation (years)

HR .77 (.66-.89)

40 Gy

50 Gy
Start B: Disease free survival

- 40 Gy vs 50 Gy HR 0.79, 95% CI 0.65-0.97; p=0.022

Disease-free survival (%) over time from randomisation (years)
Fast forward trial

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt*, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group

Brunt et al; Lancet Oncology-April 2020
Fast forward trial

- From Nov 2011 to June 2014
- 97 (47 RT & 50 referring) hospitals in UK participated
- Total of 4096 patients enrolled
- pT1-3, pN0-1, M0, after BCS or mastectomy were eligible
- Patients randomised to:
  - 40Gy/15#/3wks (n=1361)
  - 27Gy/5#/1wk  (n=1367)
  - 26Gy/5#/1wk  (n=1368)
  - No SCF RT
- Median follow-up 71.5 months
Fast forward trial: Results

At 5yr IBTR: 1.7% in 40Gy, 1.6% in 27Gy, 1.2% in 26Gy arm
Fast forward trial: 26Gy/5# is better

<table>
<thead>
<tr>
<th></th>
<th>Number of moderate or marked events/total number of assessments over follow-up</th>
<th>Odds ratio for schedule (95% CI)</th>
<th>p value for comparison with 40 Gy</th>
<th>p value for comparison between 27 Gy and 26 Gy</th>
<th>Odds ratio for years of follow-up (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event in the breast or chest wall*</td>
<td>651/6121 (10.6%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>0.98 (0.96-1.00); 0.055</td>
</tr>
<tr>
<td>40 Gy</td>
<td>651/6121 (10.6%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>1004/6303 (15.9%)</td>
<td>1.55 (1.32-1.83)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>774/6327 (12.2%)</td>
<td>1.12 (0.94-1.34)</td>
<td>0.20</td>
<td>0.0001</td>
<td>...</td>
</tr>
<tr>
<td>Breast distortion†</td>
<td>222/5774 (4.0%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>0.99 (0.95-1.02); 0.38</td>
</tr>
<tr>
<td>40 Gy</td>
<td>222/5774 (4.0%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>363/5952 (6.1%)</td>
<td>1.51 (1.25-1.87)</td>
<td>0.0028</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>299/5945 (5.0%)</td>
<td>1.20 (0.91-1.60)</td>
<td>0.19</td>
<td>0.083</td>
<td>...</td>
</tr>
<tr>
<td>Breast shrinkage†</td>
<td>330/5728 (5.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>1.03 (1.00-1.06); 0.023</td>
</tr>
<tr>
<td>40 Gy</td>
<td>330/5728 (5.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>503/5944 (8.5%)</td>
<td>1.50 (1.20-1.88)</td>
<td>0.0004</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>369/5943 (6.2%)</td>
<td>1.05 (0.82-1.33)</td>
<td>0.71</td>
<td>0.0018</td>
<td>...</td>
</tr>
<tr>
<td>Breast induration (tumour bed)†</td>
<td>185/5713 (3.2%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>1.00 (0.96-1.04); 0.95</td>
</tr>
<tr>
<td>40 Gy</td>
<td>185/5713 (3.2%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>304/5948 (5.1%)</td>
<td>1.58 (1.29-2.05)</td>
<td>0.0013</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>236/5937 (4.0%)</td>
<td>1.19 (0.90-1.58)</td>
<td>0.22</td>
<td>0.047</td>
<td>...</td>
</tr>
<tr>
<td>Breast induration (outside tumour bed)†</td>
<td>45/5712 (0.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>0.96 (0.90-1.02); 0.17</td>
</tr>
<tr>
<td>40 Gy</td>
<td>45/5712 (0.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>137/5943 (2.3%)</td>
<td>2.79 (1.74-4.60)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>97/5930 (1.6%)</td>
<td>1.90 (1.53-2.34)</td>
<td>0.013</td>
<td>0.059</td>
<td>...</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>63/6087 (1.0%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>40 Gy</td>
<td>63/6087 (1.0%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>100/6272 (1.6%)</td>
<td>1.68 (1.07-2.65)</td>
<td>0.025</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>26 Gy</td>
<td>102/6300 (1.6%)</td>
<td>1.53 (0.96-2.43)</td>
<td>0.070</td>
<td>0.65</td>
<td>...</td>
</tr>
<tr>
<td>Breast or chest wall oedema</td>
<td>89/6097 (1.5%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>1.21 (1.14-1.29); &lt;0.0001</td>
</tr>
<tr>
<td>40 Gy</td>
<td>89/6097 (1.5%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>217/6287 (3.4%)</td>
<td>2.18 (1.57-3.03)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
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<tr>
<td>26 Gy</td>
<td>155/6318 (2.4%)</td>
<td>1.47 (1.03-2.09)</td>
<td>0.032</td>
<td>0.0097</td>
<td>...</td>
</tr>
<tr>
<td>Breast or chest wall discomfort</td>
<td>224/6086 (3.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>0.73 (0.69-0.78); &lt;0.0001</td>
</tr>
<tr>
<td>40 Gy</td>
<td>224/6086 (3.8%)</td>
<td>1 (ref)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>27 Gy</td>
<td>269/6285 (4.3%)</td>
<td>1.10 (0.86-1.40)</td>
<td>0.44</td>
<td>...</td>
<td>...</td>
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<tr>
<td>26 Gy</td>
<td>250/6309 (4.0%)</td>
<td>0.98 (0.76-1.26)</td>
<td>0.86</td>
<td>0.35</td>
<td>...</td>
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</tbody>
</table>
Fast forward trial: 26Gy/5# is better

<table>
<thead>
<tr>
<th>Protocol-specific items</th>
<th>Number of patients reporting moderate or marked event at baseline/total*</th>
<th>Number of moderate or marked events/total number of assessments over 3–60 months of follow-up</th>
<th>Odds ratio for schedule (95% CI)</th>
<th>p value for comparison with 40 Gy</th>
<th>p value for comparison between 27 Gy and 26 Gy</th>
<th>Odds ratio for years of follow-up (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast appearance</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.03 (1.01–1.05); 0.0010</td>
</tr>
<tr>
<td>Breast smaller</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.11 (1.09–1.13); &lt;0.0001</td>
</tr>
<tr>
<td>Breast harder or firmer</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.95 (0.93–0.97); &lt;0.0001</td>
</tr>
<tr>
<td>Skin appearance</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.96 (0.93–0.99); 0.0080</td>
</tr>
</tbody>
</table>
IORT-TARGIT A trial

Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial

Jayant S Vaidya et al.

BMJ 2020;370: 2836
TARGIT A trial-Results

- 2298 women, aged 45 years and older
- Between March 2000 to June 2012, international study
- IDC up to 3.5cm, cN0-N1, eligible for BCS
- Randomised to IORT or EBRT
- EBRT-daily fractionated course of 3-6 weeks
- IORT- by Intrabeam device, 50kV x-rays, tumor bed surface receives 20Gy/1#
- Patients with high risk pathology features received EBRT to whole breast
- Median FU 8.6yrs (max 18.9yrs)
TARGIT A trial - Results

Breast cancer death
No difference
Log rank p=0.54

Non-breast-cancer death
TARGIT-IORT lower
Log rank p=0.005
TARGIT A trial - Results

Local control
No difference

Breast preservation
No difference

Overall mortality
TARGIT-IORT improved overall survival compared to EBRT

Log rank p = 0.03
TARGIT A trial - Results

Mastectomy-free survival
0.96 (0.78 to 1.19), P=0.74

Distant disease-free survival
0.88 (0.69 to 1.12), P=0.30
CONCLUSION

For patients with early breast cancer who met our trial selection criteria, risk adapted immediate single dose TARGIT-IORT during lumpectomy was an effective alternative to EBRT, with comparable long term efficacy for cancer control and lower non-breast cancer mortality. TARGIT-IORT should be discussed with eligible patients when breast conserving surgery is planned.
Omission of adjuvant RT

- Safe omission of radiotherapy after breast-conserving surgery
- can be considered in women deemed to be at very low risk of local recurrence
- T1, N0, Grade 1 & 2
- ER + PR+ Her2 –
- >65 years
- willing to take adjuvant endocrine therapy for 5 years
- willing to have regular mammographic follow up to year 10.
Consider omitting radiotherapy for women who:

- have had breast-conserving surgery for invasive breast cancer with clear margins and
- have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) and
- are willing to take adjuvant endocrine therapy for a minimum of 5 years.
The National Comprehensive Cancer Network clinical guidelines allow for the use of lumpectomy plus tamoxifen/AI without breast irradiation in
- women greater than or equal to 70 years of age
- clinically node negative
- ER positive
- T1 breast cancer
- pathological negative margin required
- category I data
PRIME II Trial

- RT + hormonal therapy vs hormonal therapy alone
- Age greater than 65
- Tumour < 3.0 cm, N0
- HR positive
- Margins >1 mm
- Grade 3 or LVI permitted (not both)
- N=1326 patients

Kunkler I, Lancet Oncol. 2015 Mar;16(3):266-73
## PRIME II: 5-year Results

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>NO RT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBTR (%)</td>
<td>1.3</td>
<td>4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>.3</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>OS (%)</td>
<td>94.2</td>
<td>93.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
Omission of adjuvant RT - Other trials

- **CALGB 9343**
  - 650 pts, >70yrs, Tam or Tam+RT, median FU 12.6yrs
  - No difference in MFS, DMFS & OS
  - LRR free survival 90% & 98%

- **Princess Margaret Hospital trial**
  - 769pts, >50yrs, Tam or Tam +RT, T1 & T2 disease
  - No difference in OS
  - At 8 yrs, LRR 17.6% vs 3.5%

Hughes KS et al JCO 2013, 45: 2615
Fyles, A. et al. NEJM 2004;351:963-970
Thank you