Professor Maurice Tubiana
The French way of life
Dr. Odile Schweisguth
Pediatric Radiation Oncology
<table>
<thead>
<tr>
<th>Stanford Visitors from France</th>
</tr>
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<tbody>
<tr>
<td>A Massiot 1958</td>
</tr>
<tr>
<td>C Rouquette 1967</td>
</tr>
<tr>
<td>Michel Schlienger 1963</td>
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<tr>
<td>Guy Juillard 1958</td>
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<tr>
<td>Jean-Pierre Wolff 1968</td>
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<tr>
<td>Alain Laugier 1968</td>
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<tr>
<td>Le Fur 1969</td>
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<tr>
<td>Bernard Pierquin 1969</td>
</tr>
<tr>
<td>M Raynal 1969</td>
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<tr>
<td>Henri Pourquier 1964</td>
</tr>
<tr>
<td>C Vrousos 1972</td>
</tr>
<tr>
<td>S Schraub 1972</td>
</tr>
<tr>
<td>P Conbes 1972</td>
</tr>
<tr>
<td>JP Le Bourgeois 1973</td>
</tr>
<tr>
<td>Alain Daban 1977</td>
</tr>
<tr>
<td>Jean-Marc Cosset 1979</td>
</tr>
<tr>
<td>Maurice Tubiana 1979</td>
</tr>
<tr>
<td>Regis Soleilhac 1980</td>
</tr>
<tr>
<td>Philippe Pouletty 1982</td>
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<tr>
<td>Jean Kadouche 1982</td>
</tr>
<tr>
<td>Olivier LeFloch 1983</td>
</tr>
<tr>
<td>Robert Flamant 1983</td>
</tr>
<tr>
<td>Francoise Flamant 1983</td>
</tr>
<tr>
<td>Michele Mangold 1988</td>
</tr>
<tr>
<td>A Kervazo 1990</td>
</tr>
<tr>
<td>Bruno Cutuli 1993</td>
</tr>
<tr>
<td>Catherine Schumacher 1993</td>
</tr>
<tr>
<td>Nathalie Pinto 1995</td>
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<tr>
<td>Francoise Mornex 1995</td>
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<td>Eric Lartigau 2014</td>
</tr>
</tbody>
</table>
Lessons Learned

Radiation Therapy
- Large fields
- High doses

Chemotherapy with radiotherapy
- EORTC trials
- Reduction of toxicity

- International cooperation on clinical trials
- Quality Assurance
- Medical education
“A historical glimpse of Hodgkin’s disease and The IGR- Stanford Connection”
Pediatric Hodgkin's Lymphoma
Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care
April 1970

21 mos old
PS III$_S$B NSHD
Radiotherapy - TLI - 1970
Lessons

1) Be Innovative
- Novel approach - 1500 rads TLI + MOPP
- Success - Cure of HD, No growth /development abnormalities
Treatment - Combined Modality Therapy

Chemotherapy:
- 6 cycles MOPP alternating with radiotherapy

Volumes:
- Involved fields
- Extended ST/TLI fields

<table>
<thead>
<tr>
<th>Age</th>
<th>Radiation Dose</th>
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</thead>
<tbody>
<tr>
<td>≤ 5 yrs.</td>
<td>1500 rads</td>
</tr>
<tr>
<td>6 – 10 yrs.</td>
<td>2000 rads</td>
</tr>
<tr>
<td>11 – 14 yrs.</td>
<td>2500 rads + Boost</td>
</tr>
</tbody>
</table>
Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care

- MOPP x 6 + 15 - 25.5 Gy IFRT
  - for children < 15 years
  - surgical staging
  - all stages included
  - age dependent RT
  - 10 Gy boost to bulky sites

Low Dose Radiation + MOPP

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>1</td>
<td>19</td>
</tr>
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<td>III</td>
<td>17</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>3</td>
<td>6</td>
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<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>44</td>
<td>11</td>
</tr>
</tbody>
</table>

- MOPP x 6 + 15 - 25.5 Gy IFRT
  - post splenectomy bacteremia and meningitis
  - infertility
  - leukemia


• ABVD/MOPP x 6 + 15 - 25.5 Gy IF RT
  - for children < 16 years
  - clinical staging
  - all stages (except IA LPHD)
  - 15 Gy IF RT
  - 10 Gy boost for PR or bulky disease

Low Dose Radiation + MOPP/ABVD
Second cancers
Stanford data 1968 - 84 (n = 1510)

All Cancers (17.6%)
Solid Tumors (13.2%)
Leukemia (3.3%)
Lymphoma (1.6%)

Tucker et al. NEJM 318:76, 1988
New cancers in Pediatric HL patients

- Sarcoma: 22%
- Melanoma: 7%
- Other: 8%
- NHL: 5%
- Lung: 7%
- Thyroid: 5%
- Breast: 27%
- Salivary: 5%
- Leukemia: 14%
- Breast: 27%
- Salivary: 5%
- Leukemia: 14%
- Lung: 7%
- Thyroid: 5%
- Other: 8%
- NHL: 5%
- Melanoma: 7%
- Sarcoma: 22%

59 cancers in 56 pts

Wolden et al. JCO 16, 1998
Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care
Excess cancers per 1000 patients followed 20 years

Wolden et al. JCO 16:536, 1998
# Secondary Cancers in Pediatric HL Survivors

## Cumulative Incidence

<table>
<thead>
<tr>
<th></th>
<th>20 year</th>
<th>30 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford</td>
<td>17%</td>
<td>29.4%</td>
</tr>
<tr>
<td>LESG</td>
<td>9.3%</td>
<td>23.7%</td>
</tr>
<tr>
<td>CCSS</td>
<td>7.6%</td>
<td>-</td>
</tr>
<tr>
<td>Nordic</td>
<td>6.9%</td>
<td>18%</td>
</tr>
<tr>
<td>Roswell Park</td>
<td>12.7%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

*O’Brien et al. J Clin Oncol 28, 2010*  
*Bhatia et al. J Clin Oncol 21, 2003*  
*Neglia et al. J Natl Cancer Inst 93, 2001*  
*Sankila et al. J Clin Oncol 14, 1996*  
*Green et al. J Clin Oncol 18, 2000*
Breast Cancer in Young Women with Hodgkin's Lymphoma

Cumulative Incidence

![Graph showing cumulative incidence of breast cancer for different treatment scenarios: Mantle 35 Gy, IFRT 35 Gy, and IFRT 20 Gy.](image)
Relative risk of breast cancer by age

Hancock et al, JNCI 85:1, 1993
Wolden et al. JCO16:536, 1998
Risk of Congestive Heart Failure
Multivariate Analysis

Relative Risk*:
- P < 0.05
- * Adjusted for race, BMI, income, education, smoking, treatment era

Sex: M,F
Age at Diagnosis:
- ≤ 4
- 5 - 9
- 10 - 14
- 15 - 20

Cardiac RT dose (Gy):
- 0
- 1 - 5
- 6 - 15
- ≥ 35

Anthracycline (mg/m²):
- < 250
- ≥ 250

Mulrooney BMJ 2009
Risk of Valvular Disease Multivariate Analysis

Relative Risk*

Sex
M
F

Age at Diagnosis (yrs)
10 - 14
5 - 9
≤ 4
15 - 20
15 - 35
15 - 35

Cardiac RT dose (Gy)
1 - 5
6 - 15

Anthracycline (mg / m²)
< 250
≥ 250

P <0.05 * Adjusted for race, BMI, income, education, smoking, treatment era

Mulrooney BMJ 2009
Is there curative treatment for children that is free of toxicity?

- Risk adapted non-toxic chemotherapy with low dose, small volume XRT to optimize the therapeutic ratio
- Cure without toxicity
1990
Stanford, Dana Farber, St Jude
Risk adapted, response driven therapy
Early Stage, Favorable
Stanford, Dana Farber, St. Jude

• VAMP x 4 + 15-25.5 Gy IF RT
  - Velban, Adria, Mtx, Prednisone
  - for children < 18 yrs.
  - CS I-II A/B, non-bulky
  - RT after VAMP x 2
  - RT dose dependent on response
  • 15 Gy CR
  • 25.5 Gy PR
Early Stage, Favorable Stanford, Dana Farber, St. Jude

- Stage I-II A, non-bulky, < 3 sites involved
- VAMP x 4
  - Vinblastine, doxorubicin, methotrexate, prednisone
- 110 children
- Response based IFRT
  - Assessed after cycle 2
  - CR: 15 Gy (7%)
  - PR: 25.5 Gy (92%)
- Results
  - Median follow-up: 9.6 years
  - 10 year EFS 89%
  - 10 year OS 96%

Donaldson et al. JCO, 2007
Advanced Stage Pediatric Hodgkin’s Disease

**HOD 90 – VEPA x 6 + LD IFRT**

- **HOD 90**
  - 5 yr OS 82%, EFS 68%

- but the outcome was disappointing
- we needed improved therapy

**HOD 94 – VAMP/COP x 6 + LD IFRT**

- **HOD 94**
  - 5 yr OS 93 %, EFS 76%
Current Pediatric Hodgkin Lymphoma Protocols

Low Risk

Intermediate Risk

High Risk
**Pediatric Hodgkin’s Lymphoma**

*Low risk - IA / IIA, Non-Bulky, < 3 nodal regions*

- **Cycle 1**: VAMP
- **Cycle 2**: VAMP
- **Cycle 3**: VAMP
- **Cycle 4**: VAMP

**Assess Response**

- Response = CR
  - **STOP**
- Response < CR
  - RT 25.5 Gy
Pediatric Hodgkin’s Lymphoma

Low risk - IA / IIA, Non-Bulky, < 3 nodal regions

5 yr OS & EFS

5 yr EFS

OS - 100%
EFS - 88%

median FU – 5.6 yrs

CR - No IFRT
PR - IFRT

p = 0.98

Metzger, M et al. JAMA, 307, 2012
Intermediate and Unfavorable Hodgkin’s Disease: Stanford V + IF XRT

Assess Response

If Response = CR:
- XRT 15 Gy

If Response < CR:
- XRT 25.5 Gy

8 wks
- Vinblastine, Doxorubicin, Nitrogen Mustard, Vincristine, Bleomycin, Prednisone

4 wks
- Vinblastine, Doxorubicin, Nitrogen Mustard
- Vinblastine, Bleomycin, Doxorubicin, Etoposide
## Intermediate / High Risk Pediatric HL

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Therapy</th>
<th>EFS (3 yrs)</th>
<th>OS (3 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOD 99</td>
<td>Stanford V + LD IFRT</td>
<td>79%</td>
<td>98%</td>
</tr>
<tr>
<td>POG 8725</td>
<td>MOPP/ABVD x 8 + TNI MOPP/ABVD x 8</td>
<td>81% 83%</td>
<td>98% 87%</td>
</tr>
<tr>
<td>POG 9425</td>
<td>ABVE-PCx3 (+ABVE-PC x2) + RT</td>
<td>88% (2)</td>
<td></td>
</tr>
<tr>
<td>CCG 5942</td>
<td>Ara-C/VP - 16 + COPP/ABV + CHOP + RT Ara-C/VP - 16 + COPP/ABV + CHOP</td>
<td>90% 81%</td>
<td>100% 94%</td>
</tr>
<tr>
<td>CCG-59704</td>
<td>BEACOPP x4 + ABVD x2 + IFRT BEACOPP x4 + COPP/ABV x 4</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td>GPOH - HD 2002</td>
<td>(boys) OEPA / COPDAC + IFRT (girls) OEPA / COPDAC + IFRT</td>
<td>91% 88%</td>
<td>98%</td>
</tr>
</tbody>
</table>
Lessons from the Children

• Need large clinical trials to find answers – i.e., multiple institutions or country-wide trials

• Need many years of FU to prove efficacy, especially when the goal is to maintain high cure rates and also to reduce toxicity
Pediatric Hodgkin Lymphoma
SEER 5 -Yr Relative Survival

Success
toxicity
Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care