Rare Tumors in Children
The Italian Experience
TREP Project

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Pediatric Surgery Department
University-Hospital of Padua, Italy
TUMORS IN CHILDREN: A RARITY

Annual incidence 1 in 7000 children younger than 15 years

12000 new cases a year in the United States
1800 new cases a year in Italy
Ever since the Seventies
Cooperative groups
Clinical protocols
Basic research
have enabled a progressive increase in our understanding of pediatric tumors and a consequent improvement in the outcome of treatment
However..

this has not happened for the less common histotypes, on which there is still little knowledge and a shortage of clinical and biological research.
RARE TUMORS:
A RARITY IN THE RARITY

“ORPHAN DISEASES”
WHAT DOES “RARE” MEAN?
Rare tumors in the adult population:
Incidence < 2 cases/100,000/year

In children, although cancer is the main cause of disease-related mortality, all pediatric tumors could be virtually defined as “rare” in the sense generally attributed to the term “rare disease” in Europe:
PREVALENCE < 50/100,000
RARE TUMORS IN CHILDHOOD

Incidence < 2 cases/1,000,000 children

Tumors not included in treatment protocols
TREP: Histotypes

Thyroid carcinoma
Neuroendocrine tumors (carcinoid)
Skin tumors
Non-germ cell gonadal tumors
Nasopharyngeal carcinoma
Renal cell carcinoma
Adrenocortical tumors
Pancreatic exocrine tumors

Pheochromocytoma/Paraganglioma
Pleuro-Pulmonary blastoma
Salivary gland tumors
Epithelial GI tumors
Thymus tumors
Breast cancer
Others (mesothelioma, uracus c)
Others border line malignancy
RARE AT ANY AGE
COMMON IN ADULTS
RARE IN CHILDREN
TREP: Background

Italian multicentric retrospective study on rare tumors

Recruitment of data from 1982 to 1998

259 Patients (age < 16 years)
AIEOP
Associazione Italiana di Emato-Oncologia Pediatrica

SICP
Associazione Italiana di Chirurgia Pediatrica

TREP
TREP: Network

Coordinators
Scientific Committee
Pathologists Panel
Statistical & Data Management Panel
TREP: Objectives

Recruitment of children with rare tumors in Italy
Diagnosis centralization and database creation
Guidelines formulation
Histology review and biological studies development
Collaboration with other Specialists
Website
International collaboration
TREP: Forms

Patient registration
personal data, tumor histology and site

Diagnostic work-up
symptoms, tumor characteristics, lab, imaging

Treatment
surgery, chemotherapy, radiotherapy

Pathology

Follow-up

Events
The participating Centers were expected to:

- Confirm the intention to participate
- Name a clinician responsible for communication with data office
- Obtain parents written consent for data processing
- Provide diagnostic material for central pathology review and biological studies
Guidelines

The guidelines for each histotype created on the basis of the international literature and personal experience

Before being applied, the guidelines had to be approved by the steering and scientific committees of AIEOP and SICP

For each histotype, one or two “expert physicians” (from different Italian centers)
The term “guidelines” was defined in 1992 by the Institute of Medicine of the National American Academy of Sciences

Recommendations that assist physicians and patients in deciding the appropriate approach to specific clinical conditions

Decisional support
All the scientific knowledge are examined and evaluated critically
864 Patients
749 Eligible (age 0-18 years)
442 F, 307 M

378 (50.5%) Pediatric Oncology Centers
203 (27.1%) Pediatric Surgery Centers
120 (16%) National Cancer Database
48 (6.4%) “Other” Centers
TREP: Centralization

Clinical Trials and Biostatistics Unit
Istituto Oncologico Veneto
Padova, Italy
115 Non Eligible

Existing protocols
Diagnosis before 2000
Benign Tumors
Patients > 18 years
<table>
<thead>
<tr>
<th>TREP: Registered histotypes</th>
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<tbody>
<tr>
<td><strong>Thyroid carcinoma</strong></td>
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<tr>
<td><strong>Neuroendocrine tumors (carcinoid)</strong></td>
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<tr>
<td><strong>Skin tumors</strong></td>
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<td><strong>Non-germ cell gonadal tumors</strong></td>
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<td><strong>Nasopharyngeal carcinoma</strong></td>
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<td><strong>Renal cell carcinoma</strong></td>
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<td><strong>Adrenocortical tumors</strong></td>
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<td><strong>Thymus tumors</strong></td>
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<tr>
<td><strong>Breast cancer</strong></td>
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<tr>
<td><strong>Others (mesothelioma, uracus c.)</strong></td>
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<td><strong>Others borderline malignancy</strong></td>
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</table>
TREP: Histotypes in adolescents/total

- Thyroid carcinoma 76/152
- Neuroendocrine tumors 31/122
- Skin tumors 18/84
- Non-germ cell gonadal tumors 9/76
- Nasopharyngeal carcinoma 24/51
- Renal cell carcinoma 10/47
- Adrenocortical tumors 5/47
- Pancreatic exocrine tumors 19/42
- Pheochromocytoma/Paraganglioma 10/39
- Pleuro-Pulmonary blastoma 2/26
- Salivary gland tumors 6/18
- Epithelial GI tumors 6/10
- Thymus tumors 4/10
- Breast cancer 2/7
- Others (mesothelioma, uracus c.) 8/14
- Others border line malignancy 0/4
### TREP: Recruitment

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
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<td>2000</td>
<td>42</td>
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<td>2010</td>
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<td>2011</td>
<td>50</td>
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<tr>
<td>2012</td>
<td>50</td>
</tr>
<tr>
<td>2013</td>
<td>8</td>
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- Estimated incidence of 1400 malignancies in patients 0-18 y
- Relative frequency of rare tumors 8-10% (100-140 cases per year)

**TREP: 50 cases a year**
TREP

Diagnostic/Therapeutic forms  716/749
Hystologic review  403 (53.8%)
TREP: Guidelines

From 2000 to 2001
Nasopharyngeal carcinoma
Adrenocortical tumors
Pleuro-pulmonary blastoma
Carcinoid of the appendix
Pancreatic tumors
Gonadal non-germ cell tumors

From 2002 to 2003
Pheochromocytoma
Thyroid carcinoma
Melanoma
Renal cell carcinoma

2008
Medullary thyroide carcinoma
Salivary glands tumors
Thymus tumors
Preliminary analyses have shown that the guidelines have been widely accepted and used, improving the quality of patients’ diagnostic work-up.

Too early to think in terms of improving survival rates.
University of Padua –
Palazzo del Bo’
Anatomical theatre
1594
University of Padua
Palazzo del Bo’
GALILEO’S DESK
1592 – 1610
TREP: Adrenocortical tumors

ST I   Complete resection and tumor volume $< 200 \, \text{cm}^3$ and negative markers after surgery
       
       No further therapy

ST II  Micro residue or N1 or tumor volume $>200 \, \text{cm}^3$ or positive markers after surgery
       
       Adjuvant Mitotane

ST III Macro residue or biopsy

ST IV Metastases
       
       Mitotane + EDP
Pediatric adrenocortical tumors: morphological diagnostic criteria and immunohistochemical expression of matrix metalloproteinase type 2 and human leucocyte-associated antigen (HLA) class II antigens. Results from the Italian Pediatric Rare Tumor (TREP) Study project

Gaetano Magro PhD a, *, Giovanni Esposito MD b, Giovanni Cecchetto MD c, Patrizia Dall'Igna MD c, Raffaella Marcato MD b, Claudio Gambini MD d, Renata Boldrini MD e, Paola Collini MD f, Vittoria D'Onofrio MD g, Nunzio Salfi MD h, Emanuele d'Amore MD i, Andrea Ferrari MD j, Gianni Bisogno MD k, Rita Alaggio MD l
TREP: Pheochromocytoma

- Doxorubicine, Etoposide, Cysplatin
  - in unresectable tumors
  - in residual disease after surgery

- Genetic testing also in non-syndromic cases
  - frequency of heterozygous germ line disease-causing mutations in NF1, RET, VHL, SDHB, SDHC and SDHD genes is higher than predicted
TREP: Pancreatoblastoma

Close relationship between genetic events causing PB and hepatoblastoma

LOH chromosome 11p

(genetic background of Beckwith-Wiedemann syndrome)

Patway APC/β-catenine anomalies
<table>
<thead>
<tr>
<th>ST I</th>
<th>PLADO 4 cycles</th>
</tr>
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<tbody>
<tr>
<td>ST II</td>
<td>PLADO 6 cycles</td>
</tr>
<tr>
<td>ST III</td>
<td>Biopsy + PLADO 4 cycles + S + PLADO 2 cycles</td>
</tr>
<tr>
<td>ST IV</td>
<td>Biopsy or complete resection on primitive tumor + PLADO 4 cycles + S on primitive tumor and metastases + PLADO 2 cycles</td>
</tr>
</tbody>
</table>
TREP: Renal cell carcinoma

• ST I / S
• S + IL2 in cases of local invasiveness and metastases
• Biological study of VHL
TREP: Pleuro-pulmonary blastoma

Gr I  Complete resection, favorable histology (type 1), no pleural involvement

No therapy

Gr I  Complete resection, unfavorable histology (type 2,3), or pleural involvement

VAIA x 6

Gr II  Micro residue

VAIA x 6

Gr III Macro residue or biopsy

VAIA x 3 – delayed S – VAIA x 6
TREP: Non germ cell gonadal tumors

Stromal ovarian tumors
Testicular tumors

(POG/CCG staging system)

St I     S
St II    PEB x 3
St III   PEB x 4 + delayed S
St IV    PEB x 4 + delayed S
Controversy in literature on total or partial thyroidectomy

Surgeons’ personal decision

Our preliminary data demonstrate a clear advantage of conservative approach
TREP: Thyroid carcinoma

One lobe involvement, no LN

Hemithyroidectomy + TSH suppressive therapy

Bilateral or multifocal tumors, bilateral LN, mets

Total thyroidectomy + TSH suppressive therapy or radioactive iodine ablation according to residual disease at scintigraphy and thyroglobulin value

One lobe involvement with monolateral LN, minimal multifocal tumor, capsule involvement

Two options: hemithyroidectomy or total thyroidectomy according to physician’s decision
TREP: Carcinoid of the appendix (NET)

After appendectomy

Evaluation of serum serotonin and chromogranin, and urinary 5-HIAA

Thorax XR, Abdominal US, CTscan/MRI if tumor > 2 cm

Octreotide Scintiscan ??

Treatment after appendectomy

No, if tumor ≤ 2 cm (with or without invasion of serosa or periappendiceal fat invasion)

Caecum resection, if residual on resection margins

No hemicolecotomia if tumor > 2 cm
TREP: Where we are

Best knowledge
Accessible database
Diagnostic/therapeutic guidelines
Website
from: TREP

to: EXPeRT

European Cooperative Study for Pediatric Rare Tumors
First European Meeting on Rare Tumors
Padova - June 26, 2008

- Italy (G. Bisogno, G. Cecchetto, GL De Salvo, A. Ferrari)
- UK (B. Brennan)
- Poland (J. Godzinsky, A. Balcerska)
- Germany (I. Brecht, D. Schneider)
- France (D. Orbach, Y. Reguerre)
First European Meeting on Rare Tumors
Padova - June 26, 2008

• Discussed the feasibility of an European collaboration
• Some tumors considered to have a low priority (carcinoid, salivary glands tu., gastrointestinal ca) for different reasons (good prognosis, extensive experience in adults)
Second European Meeting on rare Tumors
Paris - March 3, 2009

• 3 Histotypes confronted
  – Pancreatic tumors
  – Gonadal non-germ cell tumors
  – Pleuropulmonary blastoma

• European Group structure
Third European Meeting on rare Tumors
Dortmund, Germany 2010

SIOP 2011

• First collaborative abstract on pancreatoblastoma

• Official group of SIOP

• Name proposal: EXPERT (European Cooperative Study for Pediatric Rare Tumors)
Fourth European Meeting
Breslavia, Polonia – March 23, 2012

• How to collaborate with other countries
• Group statute
• Melanoma
• Thymus tumors
• GIST
Fifth European Meeting
Erlagen, April 11-12, 2013
Fifth European Meeting
Erlagen, April 11-12, 2013

• Data presentation of melanoma, ACT, nasopharyngeal ca
• Guidelines discussion for colon ca, salivary gland tumors, pleuropulmonary blastoma, pancreatoblastoma, mesothelioma, myoepithelial ca
• Consultation network
• eXper networking (ENCCA, SIOP, ITTC)
TREP: Where we are going…

Creation of a Tissue Bank

INVOLVEMENT OF MORE CENTERS FOR ADULTS
TREP: Where we are going...

INTERNATIONAL COOPERATION
Rare Tumors Committee
Committee Chair: Carlos Rodriguez-Galindo
Coordinators:
Gianni Bisogno, Padova
Giovanni Cecchetto, Padova
Andrea Ferrari, Milano

Scientific Committee:
Gianni Bisogno, Padova
Michela Casanova, Milano
Giovanni Cecchetto, Padova
Patrizia Dall’Igna, Padova
Andrea Ferrari, Milano
Paolo Indolfi, Napoli
Alessandro Inserra, Roma
Antonino Rizzo, Bari

Pathologists Panel:
Rita Alaggio, Padova
Renata Boldrini, Roma
Paola Collini, Milano
Claudio Gambini, Genova
Nunzio Salfi, Bologna
Guido Pettinato, Napoli

Statistician and Data Manager:
Gianluca De Salvo, Padova
Elisa Mancini, Padova

the TREPPers
TREP: However…..

Why and how an International Research project should be set up?
The need to make treatment recommendations available to Pediatric Oncologists and Surgeons encountering a child with rare tumor

To select those rare tumors with biological-clinical issues (pheochromocytoma, adrenocortical tumors)
TREP: How?

Key Ingredients:
- Network of Pediatric Oncologists and Surgeons
- Accepted common treatment guidelines
- Effective data collection system
- Central pathology review
- Dedicated financial resources
Coordinators:
Gianni Bisogno, Padova
Giovanni Cecchetto, Padova
Andrea Ferrari, Milano

Scientific Committee:
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Gianluca De Salvo, Padova
Elisa Mancini, Padova
We hope you will join us
Strategy Committee for Rare Tumors Study and Research

GERM CELL TUMORS
RETINOBLASTOMA
HEPATIC TUMORS
TREP
The Italian Study on Pediatric Rare Tumors (TREP Project): Preliminary results

P Dall’Igna*, R Alaggio, E Basso, G Bernini, R Boldrini, M Casanova, R Cozza, P D’Angelo,
GL De Salvo, A Di Cataldo, A Ferrari, P Indolfi, R Lo Piccolo, E Mancini, M Massimino,
G Perilongo, P Pierani, A Rizzo, A Schiavetti, C Spinelli, P Tamaro, G Cecchetto

for the Italian Study on Pediatric Rare Tumors (TRE

*Pediatric Surgery Division, Dept. of Pediatrics,
University of Padua, Italy

Vancouver - SIOP 2005
Prognostic Factors: HISTOLOGY

Vena cava invasion, necrosis and increased mitotic activity (> 15 mitotic figures/ 20 high power fields) independently suggest malignant clinical behavior in children

<table>
<thead>
<tr>
<th>Wieneke class</th>
<th>Stage</th>
<th>MMP2</th>
<th>HLA-DR Tumor Cells</th>
<th>HLA-DR Stromal Cells</th>
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<tbody>
<tr>
<td>Benign 12</td>
<td>I 11</td>
<td>6* (75%)</td>
<td>3 (25%)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>II 2</td>
<td></td>
<td></td>
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<tr>
<td>Malignat 5</td>
<td>II 2</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
<td>5</td>
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<tr>
<td></td>
<td>III 3</td>
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<td></td>
<td>IV 2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Uncertain 1</td>
<td>I 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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*analysis done in 8 cases
<table>
<thead>
<tr>
<th>Wieneke class</th>
<th>Stage</th>
<th>p53 Mutation</th>
<th>P53 IHC</th>
<th>EGFR FISH</th>
<th>EGFR IHC</th>
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</thead>
<tbody>
<tr>
<td>Benign 12</td>
<td>I 11</td>
<td>3</td>
<td>3</td>
<td>3* (33%) polisomy</td>
<td>5</td>
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<tr>
<td></td>
<td>II 2</td>
<td></td>
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<tr>
<td>Malignant 5</td>
<td>II 2</td>
<td>1</td>
<td>4</td>
<td>2 (40%) polisomy 1</td>
<td>3</td>
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<tr>
<td></td>
<td>III 3</td>
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<td>IV 2</td>
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<tr>
<td>Uncertain 1</td>
<td>I 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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</table>

*analysis done in 9 cases
“Biological” Prognostic Factors

- MMP2: no prognostic role
- HLA-DR prevalent expression in tumor cells found in “malignant” ACT e’ sbagliato : benigni
- p53 mutations in 3 benign tumors (all patients < 24 months, 1 LiFraumeni disease)
- EGFR polisomies more frequent in malignant or uncertain ACT (50% vs 33%)
Conclusive observations

Endocrine manifestations need to be correctly evaluated

Surgery mainstay of treatment (no rupture, biopsy of LN and suspected areas, nephrectomy if kidney involved, laparoscopic procedures)

CT recommended in metastatic cases and inoperable tumors

Efficacy of o,p’DDD and other drugs to be confirmed
Conclusive observations

• Wiencke scoring system highly predictive of clinical behavior

• HLA-DR potential marker of aggressive behavior

• EGFR potential therapeutic target
Clinical-pathologic criteria for distinguishing benign from malignant tumors equivocal

Prognostic Factors
Clinical Prognostic Factors:

AGE

< 4 y
BETTER PROGNOSIS

> 12 y
WORSE PROGNOSIS

SEX

NO SIGNIFICANCE

NON SPECIFIC CUSHING’S SYMPTOMS
WORSE OUTCOME

ST I and ST II
SIGNIFICANT BETTER OUTCOME
Wieneke-Thompson Score
For ADR in childhood

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Count</th>
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<tbody>
<tr>
<td>&gt; 400 gr</td>
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<tr>
<td>&gt; 10.5 cm</td>
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<tr>
<td>Extension periadrenal tissue</td>
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<td>Vena Cava invasion</td>
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<td>Capsular invasion</td>
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<td>Necrosis</td>
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<td>&gt; 15 mitosis per 20 HPF</td>
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<td>Atypical mitotic figures</td>
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</table>

18 Patients evaluated (TREP)

0-2 Parameters: Benign
12 cases 12 NED

3 Parameters: Indetermined
1 case 1 NED

> 3 Parameters: Malignant
5 cases 3 DOD, 2 AWD
“Biological” Prognostic Factors:

In adult patients:

• Metalloproteinase 2: poor prognostic marker

  Volante, Mod Pathol 2006; 1-7

In pediatric patients:

• HLA-DR: good prognostic marker

  West, Cancer Res 2007; 600-608
“Biological” Markers and therapeutic targets

• p53
• EGFR
• c-kit
First European Meeting on Rare Tumors
Padova - June 26, 2008

- Italy: TREP 2000
- UK: 1998
- Poland: Polish PRTS 2005
- Germany: German Rare Tumor Working Party 2008
- France: Young Group but still working hard