MOLECULAR PROFILING & MANAGEMENT OF EPENDYMOMA

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INTRODUCTION

• Ependymoma → third most common CNS tumor in children

• About half of all cases arise in children younger than 5 yrs

• Sites:
  - Intracranial
    - Supratentorial
    - Infratentorial
  - Spinal canal Tumors

• In children approximately 2/3\(^{rd}\) arises in the ependymal lining of 4th ventricle

• Posterior fossa tumours typically present with symptoms & signs of ↑ed intracranial pressure
IMAGING

• MRI: imaging modality of choice
• The entire neuraxis needs to be imaged to rule out leptomeningeal spread
• Large, relatively well circumscribed tumor with displacement rather than invasion of adjacent structures
• Extension through the foramen magnum into the upper cervical region not uncommon

-Courtesy: Perez & Brady’s Principles & Practice of Radiation Oncology 6E(2013)
HISTOLOGICAL SUBTYPES OF EPENDYMOMA

• Myxopapillary ependymoma/subependymoma (WHO grade I)
• Ependymoma (WHO grade II)
• Anaplastic ependymoma (WHO grade III)
• Changes in 2016 WHO classification system:

<table>
<thead>
<tr>
<th>Ependymal tumours</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subependymoma</td>
<td>9383/1</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>9394/1</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>9391/3</td>
</tr>
<tr>
<td>Papillary ependymoma</td>
<td>9393/3</td>
</tr>
<tr>
<td>Clear cell ependymoma</td>
<td>9391/3</td>
</tr>
<tr>
<td>Tanycytic ependymoma</td>
<td>9391/3</td>
</tr>
<tr>
<td>Ependymoma, ( RELA ) fusion–positive</td>
<td>9396/3*</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>9392/3</td>
</tr>
</tbody>
</table>

MYXOPAPILLARY EPENDYMOMA

• Myxopapillary ependymomas commonly located in the conus filum terminale region of the spinal cord
• Usual presenting symptom: back pain
• Despite LG histology, leptomeningeal spread is not uncommon
• Surgical resection ➔ mainstay of treatment
  ➢ complete resection usually possible for tumour in the filum
  ➢ complete resection difficult & may be associated with significant neurological sequel for tumour in the conus
• If tumour not resected en bloc/ macroscopic residual tumor ➔ Post-op RT ↑es local control in this high risk situation
• RT dose: 50.4Gy/28#/5.5 weeks
• RT volume: GTV+1.5 cm/1 vertebrae craniocaudal margin+ IM+ SM
• Patients with leptomeningeal seeding at diagnosis/relapse: curative intent CSI ➔ boost to the primary site
EPENDYMOMA

• Surgical resection → mainstay of treatment
• The completeness of surgical resection → most powerful prognostic factor
• Currently, complete resection achieved in 70% -90% of supratentorial & spinal ependymomas
• Complete resection-less frequently possible in patients with infratentorial ependymomas
• “Second-look” surgery may be considered, if feasible, either after the realignment of structures that takes place following resection of an initially bulky tumor in an often unstable young child or after chemotherapy
ROLE OF RADIOTHERAPY IN EPENDYMOMA

• Postoperative radiotherapy ➔ standard of care for all children (>12 months) with ependymoma

• Omission of RT may be considered acceptable in:
  - complete resection in patients with ependymoma of the spinal cord (DFS approaches 100%)
  - selected patients with supratentorial ependymoma in non-eloquent areas, which can be resected with a wider margin

• In the past, CSI recommended for treatment of infratentorial (HG) ependymoma

• However local conformal RT is the present standard of care
RADIOTHERAPY TARGET VOLUME

- GTV: tumour bed + residuum + any extension caudal to the foramen magnum
- CTV: GTV+0.5-1 cm margin
- PTV: CTV+ IM+SM (usually 3 mm)

-Courtesy: Perez & Brady’s Principles & Practice of Radiation Oncology 6E(2013)
Evidence for a dose–response in ependymoma, with improved tumor control with doses >45 to 50 and even 54 Gy

The current standard for children with intracranial ependymoma older than 18 months is a dose of at least 54 Gy/30#/6wks

Higher dose desirable in patients with macroscopic residual disease-59.4Gy/33#/6.5wks (CTV beyond the foramen magnum may be reduced at 54Gy)

Hyperfractionated radiotherapy up to a total dose of 60-70Gy feasible but without clear evidence of benefit, particularly in the context of improved surgery and modern radiotherapy
ROLE OF CHEMOTHERAPY IN EPENDYMOMA

- The role of chemotherapy in ependymoma remains to be defined.

- Indications:
  - Infants with ependymoma to delay/avoid cranial RT
  - Post-operative residual disease to facilitate complete resection during second-look surgery

- Active agents: Vincristine, Etoposide, Cyclophosphamide, Cisplatin/Carboplatin

- Outcome: Use of post-op chemotherapy alone to delay/avoid cranial RT associated with inferior PFS compared with surgery followed by post-op RT approach
PATTERNS OF FAILURE & SALVAGE TREATMENT

• Failure:
  - Local
  - Leptomeningeal
  - Local & leptomeningeal

• Salvage treatment:
  - Resurgery
  - Reirradiation: local/CSI for local/leptomeningeal failure
  - Chemotherapy
RECENT UPDATES

• Molecular classification of ependymoma

• Current SIOP studies

• Current ACNS studies

• Current consensus on the clinical management of ependymoma in the era of molecular pathology
MOLECULAR CLASSIFICATION OF EPENDYMOMA

Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups

Kristian W. Pajtler,1,2,37 Hendrik Witt,1,3,4,37 Martin Sill,5,37 David T.W. Jones,1 Volker Hovestadt,6 Fabian Kratochwil,1 Khalida Wani,7 Ruth Tatevosian,8 Chandanamali Punchiherwa,8 Pascal Johann,1 Jüri Reimand,9 Hans-Jörg Warnatz,10 Marina Ryzhova,11 Steve Mack,12 Vijay Ramaswamy,12,13 David Capper,14,15 Leonille Schweizer,14,15 Laura Sieber,1 Andrea Wittmann,1 Zhiqiu Huang,6 Peter van Sluis,16 Richard Volckmann,16 Jan Koster,16 Rogier Versteeg,16 Daniel Fults,17 Helen Toledano,18 Smadar Avidad,19 Lindsey M. Hoffman,20 Andrew M. Donson,20 Nicholas Foreman,20 Ekkehard Hewer,21 Karel Zitterbart,22,23 Mark Gilbert,24 Terri S. Armstrong,24,25 Nalin Gupta,26 Jeffrey C. Allen,27 Matthias A. Karajannis,28 David Zagzag,29 Martin Hasselblatt,30 Andreas E. Kulozik,3 Olaf Witt,3,31 V. Peter Collins,32 Katja von Hoff,33 Stefan Rutkowski,33 Torsten Pietsch,34 Gary Bader,8 Marie-Laure Yaszpo,10 Andreas von Deimling,14,15 Peter Lichter,4,6 Michael D. Taylor,12 Richard Gilbertson,35 David W. Ellison,9 Kenneth Aldape,36 Andrey Korshunov,14,15,38 Marcel Kool,1,38,* and Stefan M. Pfister1,3,4,38,*

-Cancer Cell 2015;27, 728–743.
**Graphical Abstract**

Molecular Subgrouping of Ependymal Tumors is Superior to Histopathological Grading for Risk Stratification

- **ST-SE**
  - Subependymoma
  - Balanced Genome
  - I
  - People
  - Green

- **ST-EPN-YAP1**
  - (Anaplastic) Ependymoma
  - YAP1-fusion
  - II / III
  - People
  - Green

- **ST-EPN-RELA**
  - (Anaplastic) Ependymoma
  - Chromothripsis; RELA-fusion
  - II / III
  - People
  - Green
  - Red

- **PF-SE**
  - Subependymoma
  - Balanced Genome
  - I
  - People
  - Green

- **PF-EPN-A**
  - (Anaplastic) Ependymoma
  - Balanced Genome
  - II / III
  - People
  - Green

- **PF-EPN-B**
  - (Anaplastic) Ependymoma
  - Chromosomal Instability
  - II / III
  - People
  - Green

- **SP-SE**
  - Subependymoma
  - 6q deletion
  - I
  - People
  - Green

- **SP-MPE**
  - Myxopapillary Ependymoma
  - Chromosomal Instability
  - I
  - People
  - Green

- **SP-EPN**
  - (Anaplastic) Ependymoma
  - NF2 mutation
  - II / III
  - People
  - Green

**WHO grade**

**Age Group**

**Outcome**

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**In Brief**

Pajtler et al. classify 500 ependymal tumors using DNA methylation profiling into nine molecular subgroups. This molecular classification outperforms the current histopathological grading in the risk stratification of patients.
<table>
<thead>
<tr>
<th>Anatomic Compartment</th>
<th>SPINE (SP-)</th>
<th>Posterior Fossa (PF-)</th>
<th>Supratentorial (ST-)</th>
</tr>
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<tbody>
<tr>
<td>Molecular Subgroup</td>
<td>SE</td>
<td>MPE</td>
<td>EPN</td>
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<tr>
<td></td>
<td>SE</td>
<td>EPN-A</td>
<td>EPN-B</td>
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<tr>
<td></td>
<td>SE</td>
<td>EPN-YAP1</td>
<td>EPN-RELA</td>
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<td>Histopathology</td>
<td>sub-ependymoma (WHO I)</td>
<td>myxopapillary ependymoma (WHO I)</td>
<td>(anaplastic) ependymoma (WHO II/III)</td>
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<td>sub-ependymoma (WHO I)</td>
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<td>YAP1-fusion</td>
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<td>RELA-fusion</td>
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<td>Tumor Location</td>
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<tr>
<td>Age Distribution</td>
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<td>(years)</td>
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<td>Gender Distribution</td>
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<tr>
<td>Patient Survival</td>
<td>120</td>
<td>120</td>
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<td>(OS; months)</td>
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</table>
Figure 5. Molecular Subgroups of Ependymal Tumors Correlate with Distinct Clinical Outcome

(A–D) Kaplan-Meier curves for overall (A) and (C) and progression-free (B and D) survival for infratentorial (A and B) and ST (C and D) molecular ependymal tumor subgroups defined by methylation profiling. The p values were computed by log rank tests between subgroups. Numbers of patients at risk are indicated. See also Figure S5.
SIOP EPENDYMOMA STUDY II

FIRST STEP
Staging Phase

MRI

Surgery

Study entry
Post-Operative MRI + CSF

Central review of imaging and pathology:
Confirm diagnosis and evaluate need of second look surgery

SECOND STEP
Interventional or observational Phase

Patients > 12 months
with no measurable residue
Randomized phase III trial to
evaluate the efficacy of post
radiation maintenance
chemotherapy
(VEC CDDP for 16 weeks)
Stratum 1

Patients > 12 months
with measurable
inoperable residue
Randomized frontline
phase II chemotherapy
study and exploration of
the efficacy of a boost of
radiotherapy
Stratum 2

Patients < 12 months
and patients not eligible to
receive RT
Randomized phase II
chemotherapy study:
Alternated myelosuppressive
and non myelosuppressive
chemotherapy +/- HDACi
(Valproate)
Stratum 3

Patients not included in
one of the interventional
studies
Observational study
REGISTRY
**STRATUM 1**
Patients with **no** measurable residual disease (R0-1-2), WHO Grade II-III ependymoma  
**No metastasis**  
Age ≥ 12 months and < 22 years  
Adequate bone marrow, renal and liver function.

Randomisation

Conformal RT  
59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)  
Daily fraction 1.8 Gy, 5 fractions/week

Observation

Maintenance CT (***)  
**WEEK 1 => WEEK 6 => WEEK 11 => WEEK 16**  
D1: Vincristine (VCR) 1.5 mg/m²  
D1-D3: Etoposide (VP16) 100 mg/m²  
D1: Cyclophosphamide 3000 mg/m²  
**WEEK 4 => WEEK 9 => WEEK 14**  
D1: Cisplatin (CDDP) 80 mg/m²  
D1: Vincristine (VCR) 1.5 mg/m²

(*) multiple surgeries (more than 2) or poor neurological status.  
(***) dose adaptation for children less than 10 kg
**STRATUM 2**

Patients with measurable inoperable residual disease (R3-R4), WHO Grade II-III ependymoma
No metastasis
Age ≥ 12 months and < 22 years
Adequate bone marrow, renal and liver function

---

**Randomisation**

**VEC-HD-MTX (**)**
**WEEK 1 => WEEK 4 => WEEK 7**
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3: Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide 3000 mg/m²

**VEG-MTX**

**VEG**

**WEEK 1 => WEEK 4 => WEEK 7**
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3: Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide 3000 mg/m²

---

**MRI with central review 2nd look surgery**

---

**No residual disease**

---

**Residual disease**

---

**Conformal RT**
59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)
Daily fraction of 1.8 Gy, 5 fractions/week

---

**Boost of RT of 8 Gy to residue**
(Daily fraction of 4 Gy: 2 fractions)

---

**Maintenance CT (if no prior progression under VEC) (**)**
**WEEK 1 => WEEK 6 => WEEK 11 => WEEK 16**
D1: Vincristine (VCR) 1.5 mg/m²
D1-D3: Etoposide (VP16) 100 mg/m²
D1: Cyclophosphamide 3000 mg/m²

---

**WEEK 4 => WEEK 9 => WEEK 14**
D1: Cisplatin (CDDP) 80 mg/m²
D1: Vincristine (VCR) 1.5 mg/m²

(*) multiple surgeries (more than 2) or poor neurological status.
(**) dose adaptation for children less than 10 kg
**STRATUM 3**
Children < 12 months or those not eligible to receive radiotherapy
Adequate bone marrow, renal and liver function and ammonia

Randomisation

**STANDARD CHEMOTHERAPY**

**STANDARD CHEMOTHERAPY**
+ HDACI = valproate

**Maintenance HDACI**
Treatment for one year period
If no progression during frontline chemotherapy

<table>
<thead>
<tr>
<th>CYCLE No.</th>
<th>CHEMO +/- HDACI (**)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vincristine - Carboplatin</td>
<td>D1</td>
</tr>
<tr>
<td>Vincristine - Methotrexate</td>
<td>D15</td>
</tr>
<tr>
<td>Vincristine - Cyclophosphamide</td>
<td>D29</td>
</tr>
<tr>
<td>Cisplatin 2-day Continuous infusion</td>
<td>D43</td>
</tr>
<tr>
<td>+/- Valproate (**)</td>
<td>44</td>
</tr>
</tbody>
</table>

Initial dose: 30 mg/kg/day for two weeks in 2 divided doses (BID 15mg/Kg)
Increasing weekly up to 40-50-60 mg/kg/day in 2 divided doses until serum target level of 100-150 µg/ml achieved.

<table>
<thead>
<tr>
<th>Dosing schedule (***)</th>
<th>Dose over 1 year Or &gt; 10 kg</th>
<th>Dose for infants 6 to 12 months Or ≤ 10Kg</th>
<th>Dose for infants less than 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine (Maximum dose: 2mg)</td>
<td>1.5 mg/m² x 1</td>
<td>1.125 mg/m² x 1</td>
<td>0.75 mg/m² x 1</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>550 mg/m² x 1</td>
<td>412.5 mg/m² x 1</td>
<td>275 mg/m² x 1</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8000 mg/m² x 1</td>
<td>6000 mg/m² x 1</td>
<td>4000 mg/m² x 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1500 mg/m² x 1</td>
<td>1125 mg/m² x 1</td>
<td>750 mg/m² x 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>40 mg/m² x 2</td>
<td>30 mg/m² x 2</td>
<td>20 mg/m² x 2</td>
</tr>
<tr>
<td>Valproate * (BID)</td>
<td>30 mg/kg/day*</td>
<td>30 mg/kg/day*</td>
<td>30 mg/kg/day*</td>
</tr>
</tbody>
</table>

* Initial dosing then according to monitoring
** If residual disease please consider for further surgery at each reassessment point.
*** For patients in stratum III:
  - Those aged 12 months and over receive the full surface area based dose of chemotherapy.
  - Those ages 6-11 months receive 75% of the surface-area-based dose if chemotherapy
  - Those under 6 month receive 50% of the surface-area-based dose of chemotherapy
COG ACNS-0831 STUDY

• Phase III trial in young children with newly diagnosed ependymoma

• **No residual disease; no disseminated disease**-research questions:
  ➢ whether adding chemotherapy after RT results in improved survival over RT alone
  ➢ whether children with supratentorial nonanaplastic ependymoma who receive a complete resection or who achieve a complete remission after being treated with chemotherapy can be successfully treated without RT

• **Residual disease; no disseminated disease**-research question:
  ➢ whether adding chemotherapy before and after RT results in improved survival compared with previous studies of children who did not receive additional chemotherapy after RT
The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants

Kristian W. Pajtler1,2,3 · Stephen C. Mack4,5 · Vijay Ramaswamy6,7 · Christian A. Smith6 · Hendrik Witt1,2,3 · Amy Smith8 · Jordan R. Hansford9 · Katja von Hoff10 · Karen D. Wright11 · Eugene Hwang12 · Didier Frappaz13 · Yonehiro Kanemura14 · Maura Massimino15 · Cécile Faure-Conter13 · Piergiorgio Modena16 · Uri Tabori7 · Katherine E. Warren17 · Eric C. Holland18 · Koichi Ichimura19 · Felice Giangaspero20 · David Castel21,22 · Andreas von Deimling23,24 · Marcel Kool1,3 · Peter B. Dirks6 · Richard G. Grundy25 · Nicholas K. Foreman26 · Amar Gajjar11 · Andrey Korshunov23,24 · Jonathan Finlay27 · Richard J. Gilbertson28 · David W. Ellison29 · Kenneth D. Aldape30 · Thomas E. Merchant31 · Eric Bouffet7 · Stefan M. Pfister1,2,3 · Michael D. Taylor6

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**General Consensus Statements**

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

**Subgroup Consensus Statements**

<table>
<thead>
<tr>
<th>Molecular subgroup</th>
<th>Tumor Location</th>
<th>Genetics</th>
<th>Age Distribution (yrs)</th>
<th>Gender Distribution</th>
<th>Survival (OS, months)</th>
<th>Subgroup-specific consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-EPN-RELA</td>
<td>Brain</td>
<td>Aberrant 11q</td>
<td>▽ ▼ ▲ ▽</td>
<td>▲ &gt; ▼</td>
<td>▲ ▽ ▼ ▾</td>
<td>There is not enough evidence to recommend distinct treatment approaches. Outcome should be further validated in prospective and retrospective studies.</td>
</tr>
<tr>
<td>ST-EPN-YAP1</td>
<td>Brain</td>
<td>Aberrant 11q</td>
<td>▽ ▼ ▲ ▽</td>
<td>▽ ▽ ▽ ▽</td>
<td>▽ ▽ ▽ ▽</td>
<td>It should be rapidly determined whether the YAP1 subgroup is associated with favorable clinical outcome.</td>
</tr>
<tr>
<td>PF-EPN-A</td>
<td>Brain</td>
<td>Balanced</td>
<td>▼ ▽ ▼ ▽</td>
<td>▼ ▽ ▽ ▽</td>
<td>▽ ▽ ▽ ▽</td>
<td>Outside of clinical trials, in patients &gt; 12 months of age, maximal safe resection and focal radiotherapy is the standard of care.</td>
</tr>
<tr>
<td>PF-EPN-B</td>
<td>Brain</td>
<td>Chromosomal Instability</td>
<td>▽ ▽ ▽ ▽</td>
<td>▽ ▽ ▽ ▽</td>
<td>▽ ▽ ▽ ▽</td>
<td>An observation only clinical trial will be implemented to determine the opportunity of de-escalating therapy.</td>
</tr>
</tbody>
</table>

**Fig. 1** General and molecular subgroup specific consensus statements on the clinical management of intracranial ependymoma
CONCLUSIONS

• Surgery-mainstay of management, complete resection should be attempted whenever feasible

• Post-operative RT improves local control & PFS

• For localised disease-local conformal RT

• For leptomeningeal dissemination- CSI → boost

• The role of chemotherapy evolving

• The future holds promise for risk adapted therapy as per the molecular classification of ependymoma