Hypersensitivity of intracranial germinomas for low-dose radiation
relationship between diagnostic radiation dose and volumetric changes before chemoradiotherapy

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Background

Spontaneous regressions in intracranial germinomas have been reported in some cases, but the natural history of them has not been well known. To answer a part of that question, we retrospectively measured the tumor volume before and after chemo-radiotherapy and analyzed volumetric changes and the correlation with other clinical parameters.

Spontaneous regression in case of germinoma

MRI on admission

MRI before chemoradiotherapy
## Summary of germinoma cases showing regression in past literatures

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</thead>
<tbody>
<tr>
<td><strong>Age /sex</strong></td>
<td>21/M</td>
<td>39/M</td>
<td>17/M</td>
<td>13/M</td>
<td>43/M</td>
<td>15/M</td>
<td>19M</td>
</tr>
<tr>
<td><strong>lesion</strong></td>
<td>NH</td>
<td>P,V</td>
<td>P</td>
<td>NH, P</td>
<td>NH, P,V</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td><strong>Size (mm)</strong></td>
<td>&gt;20 mm</td>
<td>&gt;20 mm</td>
<td>30mm</td>
<td>13mm</td>
<td>32mm</td>
<td>60mm</td>
<td>20mm</td>
</tr>
<tr>
<td><strong>steroid</strong></td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
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<tr>
<td><strong>Diagnostic radiation</strong></td>
<td>CT:1</td>
<td>Xray:1</td>
<td>CT: 7</td>
<td>CT:1</td>
<td>CT:1</td>
<td>CT:2</td>
<td>CT:3</td>
</tr>
<tr>
<td><strong>Period until treatment</strong></td>
<td>6 days</td>
<td>15 days</td>
<td>56 days</td>
<td>13 days</td>
<td>12 days</td>
<td>9 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>

**Abbreviation.** NH: neurohypophyseal, P: pineal, V: intraventricular, AOG: angiography
Spontaneous regression (SR) of neoplasm

**Definition of SR:**
‘when the malignant tumor mass partially or completely disappears without any treatment, or as a result of therapy considered inadequate to influence systemic neoplastic disease.’

Possible mechanism of SR:
1. **immunological mechanism:** IgM, GD2 ganglioside, TIL, CTL, IL-2
2. **oncogene and growth hormone:** H,K-ras, eRBB2
3. **hormonal mechanism:** estrogen (receptor)
4. **intratumoral cell differentiation:** retinoid, NGF, cyclic nucleotide
5. **effect of stress:** blood flow, solid stree, extracellular matrix, tissue reforming
6. **inflammation**
7. **low-dose radiation:** hyperradiosensitivity

Bodey B. Expert Opin. Biol Ther. 2002
Cole WH. Ann NY Acad Sci. 1974
Spontaneous Regression of Testicular Germ Cell Tumors
An Analysis of 42 Cases

SR of testicular GCT is well-recognized phenomenon.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Only in Metastasis</th>
<th>In Metastasis and Testis</th>
<th>Only in Testis</th>
<th>Totals</th>
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<td>14</td>
<td>3</td>
<td>3</td>
<td>20</td>
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<tr>
<td>Mixed w/seminoma</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6</td>
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<tr>
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<td>3</td>
<td>0</td>
<td>4</td>
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<tr>
<td>“Pure” EC</td>
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<td>0</td>
<td>1</td>
<td>3</td>
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<tr>
<td>“Pure” YST</td>
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<td>0</td>
<td>0</td>
<td>2</td>
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<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>5*</td>
</tr>
<tr>
<td>Total(s)</td>
<td>21</td>
<td>10</td>
<td>6</td>
<td>42</td>
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</table>

Question 1:
Is spontaneous regression of intracranial germ cell tumor rare?

Question 2:
What is its mechanism?
Does low dose radiation by diagnostic purpose influence in shrinking of intracranial germ cell tumor before chemoradiotherapy?
Patients and methods

Patients:
✓ Cases with plural MRI before the 1st CMT: 12 cases
✓ Age: 8-26 years old.
✓ Operation: Endoscopic or open biopsies were performed in all.
✓ Histological finding: germinoma in all cases
✓ Location: 8 pineal, 3 neurohypophyseal, 2 basal ganglia, 3 bifocal.
✓ 15 lesions were analyzed by volumetric assessment based on MRI.

Methods:
✓ Shrinking rate, response rate was calculated.
✓ Diagnostic radiation dose was calculated in each case.
✓ Immunohistochemistry: PLAP, c-KIT, OCT4 for large tumor cell.
✓ Immunohistochemistry: CD3, CD20, CD68 for lymphcytic cell.
✓ lymphocyte/tumor cell ratio (L/T ratio) was calculated in each case.
✓ TUNEL positive cell was counted, apoptotic ratio was calculated.
✓ Relationship between shrinking rate and prognosis was analyzed.
Volumetric measurement, shrinking rate and response rate of intracranial germinoma

Volumetric analysis:
tumor volume (TV) = d x ΣS

\( d = \text{depth of slices}, \quad S = \text{traced area of enhancement} \)

Shrinking rate (%)
\[
\text{Shrinking rate (\%) } = \frac{(\text{initial TV}) \text{ cm}^3 - (\text{TV before 1st chemotherapy}) \text{ cm}^3}{(\text{initial TV}) \text{ cm}^3} \times 100
\]

Response rate (%)
\[
\text{Response rate (\%) } = \frac{(\text{initial TV}) \text{ cm}^3 - (\text{TV after 1st chemotherapy}) \text{ cm}^3}{(\text{initial TV}) \text{ cm}^3} \times 100
\]
**volumetric data, diagnostic radiation dose**
and **histopathological data in intracranial germinomas**

<table>
<thead>
<tr>
<th>lesion No</th>
<th>origin</th>
<th>age</th>
<th>gender</th>
<th>diagnostic radiation Dose (mGy)</th>
<th>initial volume</th>
<th>volume before chemotherapy (cm³)</th>
<th>volume after 1st chemotherapy (cm³)</th>
<th>shrinking rate</th>
<th>Response rate</th>
<th>Lymphocyte/Tumor cells</th>
<th>TUNEL (+) %</th>
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<tr>
<td>1</td>
<td>PR</td>
<td>22</td>
<td>M</td>
<td>101.948</td>
<td>1.611</td>
<td>1.416</td>
<td>0.649</td>
<td>0.121</td>
<td>0.542</td>
<td>1.636</td>
<td>19.3</td>
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<td>M</td>
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<td>0.316</td>
<td>0.17</td>
<td>0.763</td>
<td>0.462</td>
<td>1.362</td>
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<td>3</td>
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<td>M</td>
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<td>5.683</td>
<td>4.074</td>
<td>0.2</td>
<td>0.283</td>
<td>0.951</td>
<td>1.994</td>
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<tr>
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<td>52.174</td>
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<td>0.532</td>
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<td>0.953</td>
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<tr>
<td>5</td>
<td>PR(Bi)</td>
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<td>M</td>
<td>652.685</td>
<td>1.743</td>
<td>0.255</td>
<td>0.124</td>
<td>0.854</td>
<td>0.514</td>
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<td>0.323</td>
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<td>0.248</td>
<td>0.312</td>
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<td>150.271</td>
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<tr>
<td>8</td>
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<td>M</td>
<td>250.073</td>
<td>9.965</td>
<td>5.284</td>
<td>1.076</td>
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<td>0.796</td>
<td>1.225</td>
<td>31.4</td>
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<tr>
<td>9</td>
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<td>24</td>
<td>M</td>
<td>250.073</td>
<td>6.84</td>
<td>1.722</td>
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<td>0.748</td>
<td>0.820</td>
<td>1.507</td>
<td>34.9</td>
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<tr>
<td>10</td>
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<td>20</td>
<td>F</td>
<td>102.659</td>
<td>4.461</td>
<td>3.883</td>
<td>0.074</td>
<td>0.130</td>
<td>0.981</td>
<td>0.768</td>
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<tr>
<td>11</td>
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<td>12</td>
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<td>150.0031</td>
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<td>8.901</td>
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<td>0.914</td>
<td>0.282</td>
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<tr>
<td>13</td>
<td>BG</td>
<td>11</td>
<td>F</td>
<td>150.507</td>
<td>4.795</td>
<td>3.958</td>
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<td>0.077</td>
<td>0.878</td>
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<td>14</td>
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<td>2.02</td>
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<td>0.554</td>
<td>0.311</td>
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<tr>
<td>15</td>
<td>BG</td>
<td>24</td>
<td>M</td>
<td>202.346</td>
<td>72.356</td>
<td>28.11</td>
<td>18.45</td>
<td>0.612</td>
<td>0.344</td>
<td>2.554</td>
<td>68.7</td>
</tr>
</tbody>
</table>

**PR:** pineal region, **NH:** neurohypophyseal resion, **BG:** basal ganglia, **Bi:** bifocal type
Case presentation
Case 1: 19y.o., M  
CC: headache, nausea

Tumor markers in serum: AFP 2.3ng/ml, HCG < 0.4ng/ml

Head MRI at introduction

Before chemotherapy

Day 0
Head CT
Head MRI

Day 1
Head CT

Day 3
Head CT

Day 3
ETB, ETV

On admission

Head CT on Day 1

Head CT on Day 3
Histopathological finding: HE staining
<table>
<thead>
<tr>
<th>TUNEL staining and IHC for lymphocyte</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>TUNEL</th>
<th>CD3</th>
<th>CD20</th>
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</table>

Table:**

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*Images showing TUNEL staining and IHC for lymphocytes.*
shrinking rate of intracranial germinomas

On admission vs. before chemoradiotherapy

Shrinking = group A
Non-shrinking = group B

Lesions: lesion1, lesion2, lesion3, lesion4, lesion5, lesion6, lesion7, lesion8, lesion9, lesion10, lesion11, lesion12, lesion13, lesion14, lesion15
**Relationship between diagnostic radiation dose and shrinking rate**

Shrinking rate (%)

Modified shrinking rate (%/day)

![Graph showing the relationship between diagnostic radiation dose and shrinking rate.](image)

- $R^2 = 0.349$, $P = 0.02$
- $R^2 = 0.42$, $P = 0.009$
Relationship between initial volume and shrinking rate

P<0.05
Histological parameter and shrinking rate

Apoptotic ratio and shrinking rate

\[ R^2 = 0.04 \]
\[ P = 0.63 \]

L/T ratio and shrinking rate

\[ R^2 = 0.019 \]
\[ P = 0.45 \]

T cell ratio and shrinking rate

\[ R^2 = 0.031 \]
\[ P = 0.53 \]

B cell ratio and shrinking rate

\[ R^2 = 0.086 \]
\[ P = 0.33 \]
Summary of results

Clinical outcome:
✓ Initial tumor volume: 0.962 to 72.356 cm³ (mean: 8.55).
✓ Diagnostic radiation dose: 52.2 to 910.1 mGy.
✓ Shrinking rate: -57.8 to 85.4% (mean: 24.0).
✓ In only 7 regions, shrinking rate was within 30%.
✓ Prognosis: 1 recurrence in Group A, no recurrence in group B, No death was seen during follow up (9-81months).

Statistical analysis:
✓ Significant relationship between diagnostic radiation dose and shrinking rate.
✓ Shrinking rate had no correlation with age, sex and response rate.
✓ Shrinking rate was negatively influenced by initial volume.
✓ Shrinking rate had no correlation with histological parameter (L/T ratio, apoptotic ratio).
High sensitivity of rat fetal germ cells to low dose irradiation

Dose-effect of $\gamma$-irradiation for testis weight

For condition of seminiferous tubules

Normal germ cells have hyper-radiosensitivity to low dose radiation

Radioresponsiveness at low doses: hyper-radiosensitivity and increased radioresistance in mammalian cells

HRS: hyper-radiosensitivity
IRR: increased radioresistance
LQ: linear quadratic model
Evidence for HRS in vitro by cell origin:
53 cell lines from 16 different cell types (14 mammalian, 2 hamster)

HRS is identified in many cell lines in vitro. 
HRS+ cell (tumor) ≠ good prognosis

Skov KA et al. Mutation Res. 1999
Time line of studies informing the current understanding of the mechanism of low dose radiation hypersensitivity

Conclusion

✓ This study shows that the volume of intracranial germinomas are changing dynamically in many cases for a short time before chemoradiotherapy.

✓ Low dose radiation by diagnostic purpose (diagnostic radiation dose) may influences tumor regression.

✓ The mechanism should be studied furthermore.