Evaluation of ovarian tissue cryopreservation and transplantation based on Edinburgh Selection Criteria

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O maneki itadaki arigatōgozaimasu
Improved Five Year Survival (1966-2000)

Figure 3.1: Survival of childhood cancer patients diagnosed 1966-2000, by period of diagnosis

% still alive

Years since diagnosis

1996-2000
1991-1995
1986-1990
1981-1985
1976-1980
1971-1975
1966-1970
Panel 1: Intrinsic and extrinsic factors for fertility preservation strategies in children and young adults

Intrinsic factors
- Health status of patient
- Psychosocial factors
- Consent (patient or parent)
- Assessment of pubertal status
- Assessment of ovarian reserve (female patients)

Extrinsic factors
- Risk of predicted treatment (high, medium, low, or uncertain risk)
- Time available
- Expertise and technical options available

Anderson RA...Wallace WH. Lancet Diabetes Endocrinol. 2015
<table>
<thead>
<tr>
<th>Risk of infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk (&lt;20%)</strong></td>
</tr>
<tr>
<td>• Acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>• Soft-tissue sarcoma: stage 1</td>
</tr>
<tr>
<td>• Retinoblastoma</td>
</tr>
<tr>
<td>• Wilms Tumour</td>
</tr>
<tr>
<td>• Germ cell tumours (no radiotherapy)</td>
</tr>
<tr>
<td>• <strong>Hodgkin lymphoma</strong></td>
</tr>
<tr>
<td><strong>Medium risk (20-80%)</strong></td>
</tr>
<tr>
<td>• Acute myeloblastic leukaemia</td>
</tr>
<tr>
<td>• Hepatoblastoma</td>
</tr>
<tr>
<td>• Osteosarcoma</td>
</tr>
<tr>
<td>• Ewing's sarcoma: non metastatic</td>
</tr>
<tr>
<td>• Soft tissue sarcoma</td>
</tr>
<tr>
<td>• Neuroblastoma</td>
</tr>
<tr>
<td>• Non- Hodgkins lymphoma</td>
</tr>
<tr>
<td>• <strong>Hodgkin lymphoma (Alkylating agents)</strong></td>
</tr>
<tr>
<td><strong>High risk (&gt;80%)</strong></td>
</tr>
<tr>
<td>• Total body irradiation</td>
</tr>
<tr>
<td>• Localised radiotherapy (pelvic/testis)</td>
</tr>
<tr>
<td>• Chemotherapy for BMT</td>
</tr>
<tr>
<td>• <strong>Hodgkin lymphoma (Pelvic RT)</strong></td>
</tr>
<tr>
<td>• Soft tissue sarcoma: stage IV (metastatic)</td>
</tr>
<tr>
<td>• Ewing's sarcoma: metastatic</td>
</tr>
</tbody>
</table>

Wallace WH et al, Lancet Oncology, 2005
Anderson RA...Wallace WH. Lancet Diabetes Endocrinol. 2015
### Key features of the 3 options for fertility preservation for women

<table>
<thead>
<tr>
<th>Technique</th>
<th>Main advantages</th>
<th>Main disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo cryopreservation</td>
<td>Established technique</td>
<td>May incur delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sperm required: partner or donor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fixed potential for future fertility</td>
</tr>
<tr>
<td>Oocyte cryopreservation</td>
<td>Does not require sperm</td>
<td>May incur delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not appropriate for pre-pubertal child</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited numbers of eggs can be stored in time available</td>
</tr>
<tr>
<td>Ovarian tissue cryopreservation</td>
<td>Minimal delay</td>
<td>Requires surgical procedure</td>
</tr>
<tr>
<td></td>
<td>No lower age limit</td>
<td>Malignant contamination in some conditions</td>
</tr>
<tr>
<td></td>
<td>Allows for spontaneous and repeated conception</td>
<td>precludes reimplantation</td>
</tr>
<tr>
<td></td>
<td>Greater allowance for future developments</td>
<td>In vitro follicle growth unlikely to be available for several years.</td>
</tr>
</tbody>
</table>
Ovarian tissue cryopreservation: World-wide experience

At least 60 pregnancies worldwide after othotopic reimplantation of frozen-thawed ovarian cortex
Success rate is unclear as the denominator is unknown
No pregnancies reported following the reimplantation of ovarian tissue harvested pre-pubertally
Young children are potentially ideal candidates

Ovarian Reserve?
The Wallace-Kelsey Model
(Five parameter asymmetric double-Gaussian cumulative curve)


\[ \log_{10}(y) = \frac{a}{4} \left[ 1 + \text{Erf}\left( \frac{x+b+c}{d\sqrt{2}} \right) \right] \left[ 1 - \text{Erf}\left( \frac{x+b-c}{e\sqrt{2}} \right) \right] \]

\[ n = 325 \]

\[ r^2 = 0.81 \]
Ovarian reserve: Conception to Menopause

Current model of follicular depletion

Wallace and Kelsey 2010 PLoS One 5; e8772
AMH reflects the number of small growing follicles.

Inhibin B, estradiol

Anderson RA 2012 Clin Endocrinol 77, 652
Anti Mullerian Hormone (AMH) is an important product of the adult ovary, produced by the granulosa cells of small growing follicles.

AMH has little variation across and between menstrual cycles.

AMH is the best currently available marker of the number of small-growing follicles in the ovary.

But there was no validated reference model for AMH available.

A validated model of serum anti-Mullerian hormone (AMH) from conception to menopause

Kelsey et al. PLoS ONE 2011
AMH in childhood cancer

22 girls age 0.3-15yr
17 prepubertal

Brougham et al 2012 JCE&M
AMH in 3 girls with cancer

Age 1.2; neuroblastoma

Age 2.4; rhabdomyosarcoma

Age 14.6: Hodgkin’s lymphoma

Brougham et al 2012 JCE&M
Summary

AMH is detectable before puberty

AMH falls rapidly during cancer treatment in both pre-pubertal and pubertal girls

AMH levels recover in those patients at low/medium risk of gonadotoxicity

AMH fails to recover in those at high risk. This could be indicative of future reproductive impairment

Brougham et al 2012 JCE&M
AMH profiles in the oncology patient

[Graph showing AMH concentration over time with phases labeled: Onset of disease, Cancer Diagnosis, Treatment, Recovery Period, Age-related Decline. The graph highlights changes in AMH concentration with time.]
Pretreatment anti-Müllerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer.

Anderson and Cameron 2011 JCE&M

Anderson et al 2013 Eur J Cancer

sensitivity 98.2%
specificity 80.0%
for correct classification of amenorrhoea

n=75
Fertility preservation for girls and young women with cancer: population-based validation of criteria for ovarian tissue cryopreservation

W Hamish B Wallace, Alice Grove Smith, Thomas W Kelsey, Angela E Edgar, Richard A Anderson

Edinburgh experience in children (< 18 yrs) 1996-2012
Panel 2: The Edinburgh Selection Criteria for gonadal tissue cryopreservation

These criteria were established with ethics committee review and approval because they refer to experimental procedures, and should be regarded as a starting point for future discussion, research, and refinement.

Female patients

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
- A realistic chance of 5-year survival
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology
- Not pregnant and no existing children

Male patients

- Age 0–16 years
- A high risk of infertility (>80%)
- Unable to produce a semen sample by masturbation
- No clinically significant pre-existing testicular disease (eg, cryptorchidism)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology

Anderson RA…Wallace WH. Lancet Diabetes Endocrinol. 2015
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age at cryopreservation (years)</th>
<th>Method of ovarian tissue collection</th>
<th>Complications from procedure</th>
<th>Duration since cryopreservation (years)</th>
<th>Age at last assessment (years)</th>
<th>Current Ovarian Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hodgkin's Lymphoma</td>
<td>14.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.8</td>
<td>30.2</td>
<td>Not POI</td>
</tr>
<tr>
<td>2</td>
<td>Ewing's Sarcoma (pubic bone)</td>
<td>14.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>16.6</td>
<td>25.6</td>
<td>POI (+1 child)</td>
</tr>
<tr>
<td>3</td>
<td>Sacral Ependymoma</td>
<td>11.3</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.8</td>
<td>24.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>4</td>
<td>Hodgkin's Lymphoma</td>
<td>13.7</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>15.6</td>
<td>28.9</td>
<td>Not POI</td>
</tr>
<tr>
<td>5</td>
<td>Hodgkin's Lymphoma</td>
<td>11.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>14.7</td>
<td>On COCP</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Chronic Granulocytic Leukaemia</td>
<td>9.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>12.2</td>
<td>21.7</td>
<td>Not POI</td>
</tr>
<tr>
<td>7</td>
<td>Rhabdomyosarcoma</td>
<td>5.3</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>8.2</td>
<td>13.1</td>
<td>POI</td>
</tr>
<tr>
<td>8</td>
<td>Ewing's Sarcoma (pelvic)</td>
<td>9.8</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>6.7</td>
<td>15.6</td>
<td>POI</td>
</tr>
<tr>
<td>9</td>
<td>Uterine Cervix Rhabdomyosarcoma</td>
<td>16.4</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>5.1</td>
<td>17.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>10</td>
<td>Hodgkin's Lymphoma</td>
<td>14.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.2</td>
<td>17.2</td>
<td>POI</td>
</tr>
<tr>
<td>11</td>
<td>Abdominal Embryonal Rhabdomyosarcoma</td>
<td>7.9</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.9</td>
<td>15.2</td>
<td>POI</td>
</tr>
<tr>
<td>12</td>
<td>Ewing's Sarcoma</td>
<td>12.1</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>3.3</td>
<td>14.3</td>
<td>POI</td>
</tr>
<tr>
<td>13</td>
<td>Hodgkin's Lymphoma</td>
<td>12.7</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.9</td>
<td>16.9</td>
<td>Not POI</td>
</tr>
<tr>
<td>14</td>
<td>Metastatic Medulloblastoma</td>
<td>8.1</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>2.9</td>
<td>Not assessed</td>
<td></td>
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<tr>
<td>15</td>
<td>Hodgkin's Lymphoma</td>
<td>15.2</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.9</td>
<td>16.9</td>
<td>Not POI</td>
</tr>
<tr>
<td>16</td>
<td>Alveolar Rhabdomyosarcoma</td>
<td>10.5</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.4</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Embryonal Rhabdomyosarcoma</td>
<td>3.0</td>
<td>Oophorectomy</td>
<td>None</td>
<td>1.4</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Ewing's Sarcoma</td>
<td>12.0</td>
<td>Laparoscopic Cortical Strip</td>
<td>None</td>
<td>1.4</td>
<td>13.5</td>
<td>Not POI</td>
</tr>
<tr>
<td>19</td>
<td>Undifferentiated Sarcoma</td>
<td>12.3</td>
<td>Laparoscopic Cortical Strip†</td>
<td>None</td>
<td>1.0</td>
<td>13.4</td>
<td>Not POI</td>
</tr>
<tr>
<td>20</td>
<td>Wilms's Tumour</td>
<td>1.2</td>
<td>Oophorectomy</td>
<td>None</td>
<td>0.6</td>
<td>Not assessed</td>
<td></td>
</tr>
</tbody>
</table>
15 year, population-based analysis of criteria for ovarian cryopreservation

Female cancer patients age <18 at diagnosis 01/01/1996 - 30/6/2012  
\[ n = 410 \]

Offered cryopreservation  
\[ n = 34 \]
- Tissue cryopreserved  
\[ n = 20 \]
- Procedure declined  
\[ n = 13 \]
- Procedure unsuccessful  
\[ n = 1 \]
- Deceased  
\[ n = 1 \]

Not offered cryopreservation  
\[ n = 376 \]
- Deceased  
\[ n = 81 \]
- <12 years old  
\[ n = 91 \]
- On COCP  
\[ n = 17 \]
- Insufficient information on follow-up  
\[ n = 42 \]

Do the ‘Offered’ group have a higher prevalence of POI?

Wallace WH et al. 2014 Lancet Oncology
Cumulative incidence of POI

15-year probability 35% [95% CI 10–53] vs 1% [0–2] p<0.0001

Hazard ratio 56.8 [95% CI 6.2–521.6] at 10 years

Wallace WH et al., 2014 Lancet Oncology
Conclusion

Ovarian cryopreservation was offered to 9% of our patients, and performed in 5%
The procedure was safe and without complications
No patients have asked for re-implantation of their tissue – to date
All patients who have thus far developed premature ovarian insufficiency were identified except one patient
The Edinburgh Selection Criteria have proved to be helpful in selecting those patients at highest risk of POI

Wallace WH et al., 2014 Lancet Oncology
Challenges

Provide fertility counseling to all young patients with cancer

Cryopreserve ovarian and pre-pubertal testicular tissue from the right (high risk) patients

Define the success rate of the procedures

Develop IVG/M as a safe alternative to re-implantation through basic research
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どうもありがとうとうございます
Domo arigatou gozaimasu