

Tables

Table-1: Description of the main characteristics of the 8 standardized clinical cases.

| Case | Type of cancer | Age at diagnosis | Cyclophosphamide-equivalent cumulative dose (CED) | Radiation therapy | Orchidectomy |
|--|--|------------------|--|---|--------------|
| No risk of fertility alteration | | | | | |
| 1 | Nephroblastoma | 5 years | 0 | No | No |
| Low risk of fertility alteration | | | | | |
| 2 | B-cell acute lymphoblastic leukemia | 5 years | 3 g/m ² | No | No |
| Moderate risk of fertility alteration | | | | | |
| 3 | Localized para-meningeal rhabdomyosarcoma | 5 years | 13.2 g/m ² (Ifosfamide = 54 g/m ²) | No | No |
| 4 | Malignant testicular germ cell tumor | 15 years | No | No | Yes |
| High risk of fertility alteration | | | | | |
| 5 | Localized bladder/prostate rhabdomyosarcoma | 5 years | 13.2 g/m ² (Ifosfamide = 54 g/m ²) | Yes (bladder/prostate brachytherapy) | No |
| 6 | Localized costal Ewing sarcoma | 15 years | 25.1 g/m ² (Cyclophosphamide =10.5 g/m ² , Ifosfamide =54 g/m ²) | No | No |
| 7 | Cervico-mediastinal Hodgkin lymphoma treated with high dose chemotherapy | 5 years | 18 g/m ² (Cyclophosphamide =4 g/m ² , Ifosfamide =16 g/m ² , Carmustine 300 mg/m ² , Melphalan =140 mg/m ²) | Yes (cervico-mediastinal) | No |
| High risk of relapse and moderate risk of fertility alteration | | | | | |
| 8 | Localized osteosarcoma with pulmonary relapse | 15 years | 18.3 g/m ² (Ifosfamide = 75 g/m ²) | No | No |

Table-2: Characteristic of the national and European survey responders.

| | France | Europe |
|----------------------------|-------------------------------|-----------------------|
| | N (%) | N (%) |
| Age (years) | | |
| Mean (min-max) | 46.6 (30-62) | 51.9 (39-70) |
| Sex | | |
| Women | 22 (85) | 7 (78) |
| Men | 4 (15) | 2 (22) |
| Years of experience | | |
| < 5 years | 3 (12) | 0 (0) |
| Between 5 and 10 years | 4 (15) | 2 (22) |
| > 10 years | 19 (73) | 7 (78) |
| Work area | | |
| | Paris area, n=5 (19) | UK, n=4 (44) |
| | North East, n=7 (27) | Belgium, n=2 (22) |
| | North West, n=7 (27) | Switzerland, n=1 (11) |
| | South West, n=3 (12) | Italy, n=1 (11) |
| | South East, n=3 (12) | Greece, n=1 (11) |
| | Overseas territories, n=1 (4) | |

Table-3: Percentage of responders in France who would propose a secondary post-treatment fertility preservation based on different semen analysis scenarios

| Case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
|---|------------|------------|------------|------------|------------|
| No risk of fertility alteration | | | | | |
| 1- No alkylating agent, nor testis surgery or radiotherapy | 31% | 77% | 100% | 65% | 46% |
| Low risk of fertility alteration | | | | | |
| 2- Low dose of alkylating agents | 38% | 77% | 100% | 65% | 46% |
| Moderate risk of fertility alteration | | | | | |
| 3- Moderate dose of alkylating agents | 27% | 81% | 100% | 73% | 54% |
| 4- Unilateral orchidectomy | 54% | 85% | 100% | 69% | 46% |
| High risk of fertility alteration | | | | | |
| 5- Testis Radiation Therapy and moderate dose of alkylating agents | 38% | 81% | 100% | 73% | 54% |
| 6- High dose of alkylating agents | 42% | 81% | 100% | 73% | 50% |
| 7- High-dose of alkylating agents with high-dose chemotherapy followed by stem cell transplantation | 38% | 88% | 100% | 77% | 42% |
| High risk of relapse and moderate risk of fertility alteration | | | | | |
| 8- High risk of relapsing disease and moderate dose of alkylating agents | 54% | 85% | 100% | 77% | 46% |

N=26 responders. Scenario 1: Normal sperm parameters; scenario 2: moderate oligo-asthenoteratozoospermia (OAT); scenario 3: severe OAT; scenario 4: normal sperm count with alterations of motility and vitality; scenario 5: azoospermia. Proposed treatments were sperm cryopreservation (Scenarios 1 to 4) or testicular biopsy (Scenario 5).

Table-4: Multivariate analysis of fertility alteration factors and sperm parameters associated with sperm cryopreservation according to practices in France.

| | OR | 95%CI | <i>p</i> |
|-------------------------------------|-----------|--------------|-----------------|
| Age at diagnosis | | | |
| 5 years | Ref | | |
| 15 years | 1.1 | 1.0-1.2 | 0.01 |
| Dose of alkylating agents* | | | |
| No alkylating agent | Ref | | |
| Low | 1.0 | 0.9-1.1 | .065 |
| Moderate | 1.0 | 0.9-1.1 | 0.26 |
| High | 1.0 | 0.9-1.0 | 0.65 |
| High-dose chemotherapy | 1.1 | 1.0-1.2 | 0.07 |
| Testis radiation therapy | | | |
| No | Ref | | |
| Yes | 1.0 | 1.0-1.1 | 0.26 |
| Orchidectomy | | | |
| No | Ref | | |
| Yes | 1.0 | 0.9-1.1 | 0.65 |
| Sperm parameters | | | |
| <i>Sperm count</i> | | | |
| Normal count | Ref | | |
| Moderate OAT | 1.5 | 1.4-1.6 | <.0001 |
| Severe OAT | 1.8 | 1.7-1.9 | <.0001 |
| <i>Vitality and motility</i> | | | |
| No alteration | Ref | | |
| Alteration of vitality and motility | 1.4 | 1.3-1.5 | <.0001 |

* p-value of the overall fixed effect of the variable “Dose of alkylating agents”: p=0.30
OAT: oligo-astheno-teratozoospermia. OR: odds ratio. 95%CI: 95% confidence interval.

Table 5: Multivariate analysis of fertility alteration factors associated with testicular biopsy according to practices in France.

| | OR | 95%CI | <i>p</i> |
|-----------------------------------|-----------|--------------|-----------------|
| Age at diagnosis | | | |
| 5 years | Ref | | |
| 15 years | 1.0 | 0.8-1.2 | 1.00 |
| Dose of alkylating agents* | | | |
| No alkylating agent | Ref | | |
| Low | 1.00 | 0.9-1.2 | .1.00 |
| Moderate | 1.08 | 0.9-1.3 | 0.63 |
| High | 1.04 | 0.9-1.2 | 0.33 |
| High-dose chemotherapy | 0.96 | 0.8-1.1 | 0.63 |
| Testis radiation therapy | | | |
| No | Ref | | |
| Yes | 1.1 | 0.9-1.3 | 0.33 |
| Orchidectomy | | | |
| No | Ref | | |
| Yes | 1 | 0.9-1.2 | 1.00 |

* p-value of the overall fixed effect of the variable “Dose of alkylating agents”: p=0.65

Table 6 Percentage of responders in non-French European centres who would propose a secondary post-treatment fertility preservation based on different semen analysis scenarios

| Case | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
|---|------------|------------|------------|------------|------------|
| No risk of fertility alteration | | | | | |
| 1- No alkylating agent, nor testis surgery or radiotherapy | 22% | 67% | 56% | 44% | 56% |
| Low risk of fertility alteration | | | | | |
| 2- Low dose of alkylating agents | 33% | 67% | 56% | 44% | 33% |
| Moderate risk of fertility alteration | | | | | |
| 3- Moderate dose of alkylating agents | 22% | 67% | 56% | 33% | 56% |
| 4- Unilateral orchidectomy | 33% | 67% | 44% | 44% | 56% |
| High risk of fertility alteration | | | | | |
| 5- Testis Radiation Therapy and moderate dose of alkylating agents | 0% | 56% | 67% | 22% | 56% |
| 6- High dose of alkylating agents | 0% | 44% | 67% | 22% | 33% |
| 7- High-dose of alkylating agents with high-dose chemotherapy followed by stem cell transplantation | 0% | 56% | 56% | 22% | 44% |
| High risk of relapse and moderate risk of fertility alteration | | | | | |
| 8- High risk of relapsing disease and moderate dose of alkylating agents | 33% | 56% | 67% | 56% | 44% |

N=9 responders. Scenario 1: Normal sperm parameters; scenario 2: moderate oligo-asthenoteratozoospermia (OAT); scenario 3: severe OAT; scenario 4: normal sperm count with alterations of motility and vitality; scenario 5: azoospermia. Proposed treatments were sperm cryopreservation (Scenarios 1 to 4) or testicular biopsy (Scenario 5).