A systematic review of the gonadotoxicity of Osteoscarcoma and Ewing´s sarcoma chemotherapies in postpubertal females and males

Running title: Gonadotoxictity of bone cancer treatments

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Abstract

Data on gonadotoxicity of chemotherapies are essential to better counsel young females and males about the risk of infertility and to better indicate fertility preservation measures before cancer therapies. However, such data have not recently be reviewed for bone cancer.

Therefore a systematic literature search was conducted considering papers published since 2000. Only relapse-free women and men were included. Gonadotoxic therapy induced suspected infertility was defined as very low Anti mullerian hormone, high gonadotropin concentration, amenorrhea, oligomenorrhea, azoospermia or oligozoospermia. The quality of the individual studies was assessed using the Newcastle-Ottawa Scale.

In total 11 out of 831 studies were included in the review. Suspected infertility was found in 10/190 (5.1%, range 0-66%) of female osteosarcoma patients (6 studies), in 24/46 (52.2%, range 46-100%) of male osteosarcoma patients (3 studies), in 18/138 (13.0%, range 3-18%) of female Ewing's sarcoma patients (3 studies) and in 34/38 (89.5%) of male Ewing´s sarcoma patients (1 study). A risk calculation in relation to specific chemotherapies was not possible. Risk for suspected infertility tended to by higher in Ewing's sarcoma in which all patients received chemotherapies with alkylants. Two of the 11 included studies received a high NOS quality score, while the remaining nine studies received a low quality score, mainly due to the lack of a comparator group.

Published data are too limited for precise estimation of the gonadotoxicity. However, data indicate clinically relevant risk for infertility, supporting counselling patients before chemotherapy about fertility preservation measures.

Key words

FertiTOX, FertiPROTEKT, osteosarcoma, Ewing´s sarcoma, fertility, Anti mullerian hormone, amenorrhoea, sperm count, gonadotoxicity, chemotherapy, radiotherapy

Introduction

Since the first three milestones in fertility preservation had been reached, such as the first birth after transplantation of cryopreserved ovarian tissue [1], the introduction of

stimulation protocols which allow oocyte collection within 2 weeks [2] and vitrification of oocytes [3], fertility preservation measures have been introduced in most countries. Fertility preservation has now been accepted and defined as an important element to be considered before cancer treatments in females and males [4-9].

One of the most important criteria that has to be met to recommend fertility preserving measures is the actual risk of infertility due to the gonadotoxicity of the applied cancer therapy. However, data on the gonadotoxicity of therapies of different forms of cancer and the numerous cancer treatment protocols are mostly very limited. Accordingly, indications for or against fertility preserving measures are not well defined, which on the one hand carries the risk of overtreatment of patients with fertility-preservation measures, imposing unnecessary medical risks and burdens to patients as well as unnecessarily postponing cancer therapies. On the other hand it carries the risk of undertreatment with fertility-preserving measures, which in the case of infertility after surviving cancer, can substantially impair the quality of life [10].

Osteosarcoma and Ewing´s sarcoma are two types of cancer with a high incidence in adolescents and young adults with still limited survival rates. In osteosarcoma survival rates have not substantially increased since the introduction of chemotherapies in the 80th. Currently the 5-years survival rate of osteosarcoma is 76% for localized cancer, 64% for regional and 24% for distant spread of cancer [11].

In Ewing's sarcoma new treatment protocols gradually increased survival rates but overall survival rates are still relatively low with 82% for localized cancer, 71% for regional and 39% for distant spread of cancer [11].

Due to the strong chemotherapies fertility is still a major issue in bone cancer disease [8]. European guidelines state that the rate of treatment-induced amenorrhoea in survivors of osteosarcoma and Ewing´s sarcoma treated with anthracycline- and cyclophosphamide-based chemotherapy regimens with or without radiotherapy ranges between 3% and 25% [12,13] and that predisposing factors for a higher risk of permanent amenorrhea are older age, use of high-dose chemotherapy and radiotherapy [12]. However, this statement is based on only one large Italian registry analysis [12], including patients treated between 1983 and 2006 and another systematic review on osteosarcoma [13], including only three studies with a total of 29 survivors

treated. A recent and systematic review to specifically review the gonadotoxicity of bone cancer is still missing.

We therefore set up a series of systematic reviews (www.fertitox.com) [14,15] to close the gap of data regarding gonadotoxicity of cancer therapies to better counsel young adults about treatment related risk of infertility and the necessity to undergo fertility preservation measures.

As published data are only available for osteosarcoma and Ewing´s sarcoma, the most common bone sarcomas, but not on chondrosarcoma and fibrosarcoma, this systematic review analyses only these two cancer types. To evaluate the impact of the chemotherapies on fertility, only relapse-free cases were included. Prepubertal individuals were excluded as fertility could hardly be analysed if chemotherapy was applied at very young age.

Materials and Methods

Protocol registration

The study protocol was registered at the international Prospective Register of Systematic Reviews, PROSPERO (Registry number 331654). The Preferred Reporting Items for Systematic reviews and Meta Analysis (PRISMA) [16] were used.

Information Sources and Search Methods

To identify all potentially relevant documents on the topic, complex literature searches were designed and executed for the following information sources: MEDLINE, Embase, and Cochrane Library.

An initial search strategy was developed in MEDLINE by a medical information specialist and tested against a list of core references to see if they were included in the search result. After refinement and consultation, complex search strategies were set up for each information source based on database-specific controlled vocabulary (thesaurus terms / subject headings) and textwords. Synonyms, acronyms and similar terms were included in the textword search. The only limit that was applied to all searched databases was the year of publication from 2000 to the present.

All searches were run on August 11th 2022.

The search concepts included were 1. four types of sarcoma (chondrosarcoma, fibrosarcoma, osteosarcoma and Ewing´s sarcoma), 2. two types of cancer therapies

(chemotherapy, radiotherapy), and 3. gonadotoxic effects, respectively influences on fertility parameters. Synonyms, acronyms and similar terms were used for all concepts in the textword search, as well as the respective thesaurus terms.

Studies concerning exclusively animals were excluded from the searches in MEDLINE and Embase by using a double-negative search strategy based on the "humans only" filters by Ovid.

The detailed final search strategies are presented as a Supplement file (S1).

In addition to electronic database searching, reference lists and bibliographies from relevant publications were checked for relevant studies.

Study Selection Process

All identified citations were imported into EndNote and duplicates were removed. The screening of titles and abstracts was performed by SG, IB and SW and tested against the inclusion criteria (Table 1) with the support of the software Covidence (www.covidence.org). Cancer treatments were evaluated regarding their clinically relevant gonadotoxicity. Clinically relevant gonadotoxicity was defined as suspected infertility, defined by the criteria shown in Table 2.

Table 1

Inclusion and exclusion criteria

Inclusion criteria

- Any original papers with information on tumor type, tumor therapy and fertility results (fertility parameters as shown in Table 2),
- Papers in which fertility data were analysed and described separately for the different cancer types and for females and males

Exclusion criteria

- Patients with prepubertal status or > 40 years of age at time of potentially gonadotoxic therapy,
- Patients with cancer relapse and palliative treatment,
- Patients with stem cell transplantation,
- Females with radiotherapy of the pelvis,

- Papers with < 40% subject participation in the evaluation of reproductive markers.

Table 2

Definition of suspected infertility

Females:

- Menstrual cycle disorders (amenorrhea, oligomenorrhea),
- Gonadotropins (Follicle stimulating hormone, FSH; Luteinizing hormone, LH) above the normal range,
- Anti mullerian hormone (AMH) below the detection limit,
- Premature ovarian insufficiency (POI).

Males:

- Significant reduction in sperm quality (azoospermia, oligozoospermia)

Quality assessment

The quality of the individual studies was assessed using the Newcastle-Ottawa Scale (NOS) [17]. The assessment system is based on a "star system", according to which each study is assessed according to three aspects: the selection of the study groups, the comparability of the groups and the coverage of the exposure or outcome of interest. Rating: good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

All included studies were reviewed by SG, IB and SW to independently assess risk of bias. Disagreements were resolved by consensus. With the exception of the study by Bishop et al. 2020 [18] and Mörse et al. 2016 [19] in which the methodological quality was rated good, corresponding to a low risk of bias, the methodological quality of the remaining nine studies [12,20-27] was rated low, mainly due to the lack of a comparison group (Table 3).

Results

Study characteristics

In total 11 out of 831 studies were included in the review (Table 4, Figure 1). All studies were registry analyses or observational studies. The reported outcome parameters regarding fertility were mainly the menstrual status (amenorrhoea or oligomenorrhea), as wells as AMH and FSH concentration indicating POI and ejaculate quality (azoospermia or oligozoospermia) not allowing or substantially reducing the chance of spontaneous conception. Number of participants with osteosarcoma or Ewing´s sarcoma per study varied in females from 1 to 154 and in males from 3 to 38 included patients. In some studies, certain parameters such as age at diagnosis/therapy and length of follow up were calculated for the total number of patients evaluated in the study rather than for the subpopulation of osteosarcoma and Ewing´s sarcoma patients separately (see comments in Table 4). Accordingly these information might be slightly different for the subset of patients included in the analysis.

Data analysis in osteosarcoma patients

Suspected infertility was found in 10/190 (5.3%, range 0-66%) of female osteosarcoma patients (6 studies) [12,19,20,22,23,27] and in 24/46 (52.2%, range 46-100%) of male osteosarcoma patients (3 studies) [18,24,26]. Around 40% of osteosarcoma females and around 90% of males received chemotherapies with alkylants (Table 3). Rate of suspected infertility varied considerably. Overall rates of suspected infertility seemed to be higher in males than in females. However, it needs to be noted that not all men accepted semen analysis, potentially leading to some bias in the selection of patients.

Data analysis in Ewing´s sarcoma patients

Suspected infertility was found in 18/138 (13.0%, range 3-18%) of female Ewing´s sarcoma patients (3 studies) [12,21,25] and in 34/38 (89.5%) of Ewing´s Sarcoma male patients (1 study) [18] (Table 3). All Ewing's sarcoma received chemotherapies with alkylants. Rate of suspected infertility also varied considerably in Ewing´s sarcoma patients. As in osteosarcoma rates of suspected infertility seemed to be higher in males than in females. However, as in the osteosarcoma group not all men accepted semen analysis and furthermore, only one male study was included in the analysis.

Discussion

The purpose of the systematic review was to summarize data on the gonadotoxicity of osteosarcoma and Ewing´s sarcoma chemotherapies to better counsel females and males about the risk of infertility and the need to perform fertility preservation measures before cancer therapy.

Our study showed that in osteosarcoma the risk for suspected infertility is around 5.3% in females and 52.2% in males. In Ewing´s sarcoma it is around 13.0% in females and 89.5% in males.

The strength of our study is that it is based on clinically relevant infertility parameters such as very low AMH or high gonadotropin concentrations, amenorrhea, oligomenorrhea, azoospermia or oligozoospermia, indicating reduced chances of spontaneous conception, which we summarized under the term “suspected infertility”. Another strength is that only postpubertal patients and with unknown pubertal status without pelvic radiation (in females) and patients without bone marrow transplantation were included in our analysis which allowed us to evaluate specifically the gonadotoxicity of chemotherapies.

However, both strengths could also be defined as weaknesses. The chosen fertility markers indicate some disruption of the hypothalamic-pituitary-gonadal axis and thus suspected infertility but not definite infertility. Furthermore, due to the exclusion of prepubertal patients and those with pelvic radiation and bone marrow transplantation, our study does not cover the whole spectrum of cancer therapies in this specific patient population. Another weakness is that in the majority of studies (9/11) it is not known if the selected markers were affected due to the gonadotoxic therapies or if fertility was already reduced before chemotherapy.

However, due to the limited data available and the heterogeneity of the fertility-related outcome parameters described in the included studies, we decided to summarize the mentioned markers under the term "suspected infertility" and to evaluate the papers accordingly. Hence, the introduction of the term "suspected infertility" can be seen as the best possible option to draw at least some conclusions regarding the gonadotoxicity of the chemotherapies used in osteosarcoma and Ewing´s sarcoma patients.

The very limited und heterogenous data might also be a reason why almost no other systematic reviews have been published so far addressing the gonadotoxicity of bone cancer therapies. Only one systematic review has been published in 2017 [13]. It included only three studies with a total of 29 survivors treated. Another systematic review was published in 2020 [28], but this review only included three studies with pregnancy and child birth as outcome parameters.

Our study demonstrates variability of data regarding the risk of infertility after chemotherapy. However, in spite of the variability the available data indicate a clinically relevant infertility risk. The risk in Ewing´s sarcoma seems to be higher than in osteosarcoma, probably due to a higher proportion of patients receiving chemotherapies with alkylants. In line with this the rate of suspected infertility was higher in male than in female osteosarcoma patients as males received more frequently alkylants. Alkylants, especially in combination with cisplatin, seems to be highly gonadotoxic as shown in males [20,24,29]. However, due to the high variability of our data, with a broad range of suspected infertility of 0-66% in female and 46-100% in male osteosarcoma patients, and of 3-18% in female and 90% in male Ewing´s sarcoma patients, respectively, our findings need to be taken with great care.

The same applies to our finding that the risk of infertility seems to be higher in males than in females. In males we can expect a substantial bias in the data as only a limited number of males performed a semen analysis. It can be assumed that the proportion of included males who had not fathered a child when the study was performed is higher than those had not.

We tried to reduce this bias by excluding papers with < 40% of subject participation in the evaluation of reproductive markers. However, 40% of participation is a very low cut off level which still might have caused substantial bias. But choosing a higher level would have led to exclusion of most, if not of all studies in males.

Our study did not allow us to review systematically the impact of factors such as intensified chemotherapies or age on fertility. These factors were only analyzed sporadically in very few studies.

Yonemoto et al., 2009, found out that the intensity of chemotherapies has an impact on fertility [30]. They analysed the fertility rate, defined as offspring of 29 married male patients who had received chemotherapy for osteosarcoma and compared these

275 couples with 52 siblings of the male patients. In males being treated with intensified
276 chemotherapy but not with moderate-dose chemotherapy the fertility rate was
277 significantly lower.
278 Longhi et al. [12], revealed that female age also has an impact on fertility. In
279 osteosarcoma and Ewing´s sarcoma patients older age was a predisposing factor for
280 infertility.
281 Several guidelines [4-9] recommend that female and male cancer patients should be
282 counselled about the risk of infertility and the options for fertility preservation
283 measures. Based on the available studies patients can only be informed that
284 chemotherapies used 1964 to 2012 do impose a clinical risk of infertility. However, it
285 is not possible to provide accurate and age-related data.
286 This raises the question if the limited data on the fertility risk still applies to more
287 recent chemotherapy protocols. Overall chemotherapy protocols have not
288 substantially changed in the last decades. In Ewing's sarcoma ifosfamide was
289 introduced in the early 1980s because of its milder myelotoxicity [31] and therefore
290 possibly lower gonadotoxicity, but the milder meyolotoxicity allowed the introduction
291 of high-dose chemotherapies which would have neutralized such a putative lower
292 gonadotoxic risk.
293 In postpubertal males the deficit of data is clinically not that relevant as
294 cryopreservation of sperm is easy, not very expensive and can be performed within
295 one day. In contrast, in prepubertal men and in females this deficit is a major
296 challenge. Freezing of testicular tissue in prepubertal boys is experimental [8,32] and is
297 only performed by few clinics and therefore requires extensive logistics. Freezing of
298 oocytes requires at least 2 weeks and freezing of ovarian tissue ½ to 1 week of lead
299 time [33,34]. These techniques are invasive and expensive and possibly require
300 postponement of the chemotherapy which might be a risk for the patients. This risk
301 need to be weighed against the potential success rate of the fertility preservation
302 techniques. In males the chance to father a baby using cryopreserved sperm is around
303 50% [35] but the chance is unknown for cryopreserved prepubertal testicular tissue. In
304 females < 35 years of age the live birth rate is around 40% for oocytes vitrified before
305 cancer therapies [36] and around 30-40% for cryopreserved ovarian tissue [37,38].

Therefore, to improve infertility risk counselling and sharpen indications for fertility-preserving interventions, large studies are needed to acquire more recent, age-related and sex-specific fertility data of high quality after osteosarcoma, Ewing´s sarcoma, cancer therapies. The collection of such data requires multicenter and multinational approaches to get a sufficient amount of data and to reflect the different treatment modalities applied around the world. Approaches such as the FertiTOX project, involving around 70 centers in three countries to collect data from 5000 females and 5000 males over a four-year period (www.fertitox.com) [14] are a model for such a study. These data should be made available to any physician worldwide and need to be easily accsessible so that physicians have the required information quickly when they need to counsel patients under time pressure before starting chemotherapies.

In conclusion, published data reveal a high variability of data regarding the risk of infertility in young female and male patients treated by chemotherapy for osteosarcoma and Ewing´s sarcoma. As some studies indicate a high and therefore clinically relevant infertility risk, female and male patients should be counselled about this risk and also about fertility preservation measures. This seems to be especially relevant if chemotherapy regimes containing alkylants. However, further prospective and large scale studies are urgently needed to better calculate the fertility risk and to sharpen the indications for or against fertility preservation measures.

Legends

Table 3

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Table 4

Characteristics of the included studies

Figure 1

PRISMA flow diagram

Supplement S1

Database Search Strategies

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Conflict of interest

The authors have stated that there are no conflicts of interest in connection with this article.

Author's roles

M. von Wolff, S. Weidlinger and J. Pape designed the systematic review. T. Karrer set up the templates for literature search. Literature was searched by S. Graber, I. Bratschi and S. Weidlinger. Data analysis was performed by S. Weidlinger and M. von Wolff. Oncological advice was given by A. Kollár. The manuscript was written by S. Weidlinger and M. von Wolff. All authors revised the final manuscript.

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References

1. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;364(9443):1405-10, doi:10.1016/S0140-6736(04)17222-X
2. von Wolff M, Thaler CJ, Frambach T, et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril 2009;92(4):1360-1365, doi:10.1016/j.fertnstert.2008.08.011
3. Cobo A, Meseguer M, Remohi J, et al. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod 2010;25(9):2239-46, doi:10.1093/humrep/deq146

4. Dittrich R, Kliesch S, Schuring A, et al. Fertility Preservation for Patients with Malignant Disease. Guideline of the DGGG, DGU and DGRM (S2k-Level, AWMF Registry No. 015/082, November 2017) - Recommendations and Statements for Girls and Women. Geburtshilfe Frauenheilkd 2018;78(6):567-584, doi:10.1055/a-0611-5549
5. Harada M, Kimura F, Takai Y, et al. Japan Society of Clinical Oncology Clinical Practice Guidelines 2017 for fertility preservation in childhood, adolescent, and young adult cancer patients: part 1. Int J Clin Oncol 2022;27(2):265-280, doi:10.1007/s10147-021-02081-w
6. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31(19):2500-10, doi:10.1200/JCO.2013.49.2678
7. Practice Committee of the American Society for Reproductive Medicine. Electronic address aao. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019;112(6):1022-1033, doi:10.1016/j.fertnstert.2019.09.013
8. Preservation EGGoFF, Anderson RA, Amant F, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open 2020;2020(4):hoaa052, doi:10.1093/hropen/hoaa052
9. Suzuki N. Clinical Practice Guidelines for Fertility Preservation in Pediatric, Adolescent, and Young Adults with Cancer. Int J Clin Oncol 2019;24(1):20-27, doi:10.1007/s10147-018-1269-4
10. Ussher JM, Perz J. Infertility-related distress following cancer for women and men: A mixed method study. Psychooncology 2019;28(3):607-614, doi:10.1002/pon.4990
11. American Cancer Society. Available from: https://www.cancer.org [Last Accessed; 01.06.2023].
12. Longhi A, Ferrari S, Tamburini A, et al. Late effects of chemotherapy and radiotherapy in osteosarcoma and Ewing sarcoma patients: the Italian Sarcoma Group Experience (1983-2006). Cancer 2012;118(20):5050-9, doi:10.1002/cncr.27493
13. Overbeek A, van den Berg MH, van Leeuwen FE, et al. Chemotherapy-related late adverse effects on ovarian function in female survivors of

childhood and young adult cancer: A systematic review. Cancer Treat Rev 2017;53(10-24, doi:10.1016/j.ctrv.2016.11.006

14. von Wolff M, Germeyer A, Böttcher B, et al. FertiTOX – a retrospective systematic data analysis and a prospective cohort study to implement an internet platform on gonadotoxicity of cancer therapies to improve counselling of patients regarding fertility and fertility preservation by the network FertiPROTEKT. Submitted.
15. FertiTOX. Available from: www.fertitox.com [Last Accessed; 01.06.2023].
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(n71, doi:10.1136/bmj.n71
17. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. . Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Last Accessed; 18.04.2023].
18. Bishop MW, Ness KK, Li C, et al. Cumulative Burden of Chronic Health Conditions in Adult Survivors of Osteosarcoma and Ewing Sarcoma: A Report from the St. Jude Lifetime Cohort Study. Cancer Epidemiol Biomarkers Prev 2020;29(8):1627-1638, doi:10.1158/1055-9965.EPI-20-0076
19. Morse H, Elfving M, Turkiewicz A, et al. Severe gonadotoxic insult manifests early in young girls treated for Ewing sarcoma. Medicine (Baltimore) 2016;95(33):e4512, doi:10.1097/MD.0000000000004512
20. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000;18(24):4016-27, doi:10.1200/JCO.2000.18.24.4016
21. Bacci G, Forni C, Longhi A, et al. Long-term outcome for patients with non-metastatic Ewing's sarcoma treated with adjuvant and neoadjuvant chemotherapies. 402 patients treated at Rizzoli between 1972 and 1992. Eur J Cancer 2004;40(1):73-83, doi:10.1016/j.ejca.2003.08.022

22. Durrieu G, Rigal M, Bugat R, et al. Fertility and outcomes of pregnancy after chemotherapy in a sample of childbearing aged women. Fundam Clin Pharmacol 2004;18(5):573-9, doi:10.1111/j.1472-8206.2004.00267.x
23. Gupta AA, Lee Chong A, Deveault C, et al. Anti-Mullerian Hormone in Female Adolescent Cancer Patients Before, During, and After Completion of Therapy: A Pilot Feasibility Study. J Pediatr Adolesc Gynecol 2016;29(6):599-603, doi:10.1016/j.jpag.2016.04.009
24. Kenney LB, Duffey-Lind E, Ebb D, et al. Impaired testicular function after an ifosfamide-containing regimen for pediatric osteosarcoma: a case series and review of the literature. J Pediatr Hematol Oncol 2014;36(3):237-40, doi:10.1097/MPH.0b013e3182a27c39
25. Raciborska A, Bilska K, Filipp E, et al. Ovarian function in female survivors after multimodal Ewing sarcoma therapy. Pediatr Blood Cancer 2015;62(2):341-345, doi:10.1002/pbc.25304
26. Rendtorff R, Beyer M, Muller A, et al. Low inhibin B levels alone are not a reliable marker of dysfunctional spermatogenesis in childhood cancer survivors. Andrologia 2012;44 Suppl 1(219-25, doi:10.1111/j.1439-0272.2011.01167.x
27. Wikstrom AM, Hovi L, Dunkel L, et al. Restoration of ovarian function after chemotherapy for osteosarcoma. Arch Dis Child 2003;88(5):428-31, doi:10.1136/adc.88.5.428
28. Busnelli A, Vitagliano A, Mensi L, et al. Fertility in female cancer survivors: a systematic review and meta-analysis. Reprod Biomed Online 2020;41(1):96-112, doi:10.1016/j.rbmo.2020.02.008
29. Longhi A, Macchiagodena M, Vitali G, et al. Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. J Pediatr Hematol Oncol 2003;25(4):292-6, doi:10.1097/00043426-200304000-00005
30. Yonemoto T, Ishii T, Takeuchi Y, et al. Recently intensified chemotherapy for high-grade osteosarcoma may affect fertility in long-term male survivors. Anticancer Res 2009;29(2):763-7
31. Ruymann FB, Vietti T, Gehan E, et al. Cyclophosphamide dose escalation in combination with vincristine and actinomycin-D (VAC) in gross residual sarcoma. A pilot study without hematopoietic growth factor support

evaluating toxicity and response. J Pediatr Hematol Oncol 1995;17(4):331-7, doi:10.1097/00043426-199511000-00009

32. Picton HM, Wyns C, Anderson RA, et al. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. Hum Reprod 2015;30(11):2463-75, doi:10.1093/humrep/dev190

33. von Wolff M, Germeyer A, Liebenthron J, et al. Practical recommendations for fertility preservation in women by the FertiPROTEKT network. Part II: fertility preservation techniques. Arch Gynecol Obstet 2018;297(1):257-267, doi:10.1007/s00404-017-4595-2

34. von Wolff M, Nawroth F. Fertility Preservation in Oncological and Non-Oncological Diseases. Springer: 2020.

35. Ferrari S, Paffoni A, Filippi F, et al. Sperm cryopreservation and reproductive outcome in male cancer patients: a systematic review. Reprod Biomed Online 2016;33(1):29-38, doi:10.1016/j.rbmo.2016.04.002

36. Cobo A, Garcia-Velasco J, Domingo J, et al. Elective and Onco-fertility preservation: factors related to IVF outcomes. Hum Reprod 2018;33(12):2222-2231, doi:10.1093/humrep/dey321

37. Lotz L, Bender-Liebenthron J, Dittrich R, et al. Determinants of transplantation success with cryopreserved ovarian tissue: data from 196 women of the FertiPROTEKT network. Hum Reprod 2022;37(12):2787-2796, doi:10.1093/humrep/deac225

38. Shapira M, Dolmans MM, Silber S, et al. Evaluation of ovarian tissue transplantation: results from three clinical centers. Fertil Steril 2020;114(2):388-397, doi:10.1016/j.fertnstert.2020.03.037