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ORIGINAL ARTICLE

Determinants of utilization of cryopreservation of germ cells in adolescent cancer patients in four European countries

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Abstract

Infertility is a relevant late-effect following cancer treatment; yet, a large proportion of survivors cannot recall having been informed of this risk. In an intervention study, we examined if and how supportive patient information material on fertility/fertility-preserving measures influences utilization of cryopreservation in adolescent cancer patients. The control group, recruited 03/2014–01/2016, received the usual patient education at initial diagnosis. The intervention group, recruited 04/2016–10/2017, received patient education supported by a fertility flyer and brochure. Patients and parents were each asked questions on utilization of cryopreservation in a questionnaire 3 and 6 months after initial diagnosis. Patient core and therapy data were obtained from medical records. Overall, cryopreservation rates showed no significant difference between the control (32.7%, $n = 37/113$) and intervention group (36.6%, $n = 37/101$). In the control group, cryopreservation was associated with gender (OR 0.100, CI 0.023–0.427), age (OR 1.559, CI 1.077–2.258) and recalling information on fertility protection (OR 33.663, CI 2.100–539.574); in the intervention group, cryopreservation was related to gender (OR 0.093, CI 0.026–0.330) and the estimated infertility risk (OR 43.665, CI 2.157–883.974).

Conclusion: Cryopreservation rates did not overall increase following the intervention; however, the individual risk seemed to be brought into attention more: Those at risk, including younger patients, cryopreserved at higher rates.

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What is Known:
•Infertility is a relevant late-effect following adolescent cancer.
•Guidelines recommend to offer fertility protection before cancer treatment.
•A relevant proportion of adolescents with cancer are not aware of this risk.
•Fertility protection seems under-used in cancer patients at risk for infertility.

What is New:
•Information material on fertility and protection in adolescents did not increase overall rates of cryopreservation.
•Cryopreservation rates were improved according to individual risk for infertility.
•Our flyers and brochures on fertility in cancer patients are available in various languages.

Keywords Patient education · Childhood and adolescent cancer · Fertility impairment · Fertility protection · Cryopreservation · Patient empowerment

Introduction

Fertility impairment is a relevant late-effect following chemotherapy and/or radiotherapy in adolescence. However, not all survivors are aware of this risk or of available fertility protection [1]. Previous studies have emphasized the necessity of adequate and early counselling of patients and their parents on the potential risk for fertility impairment [1–3]. Especially patients of younger age and female patients in general seem to recall having received such information to a lower rate than older or male patients [4]. While established fertility protection exists for adolescent patients, there are limited options for prepubertal and peripubertal children [5, 6]. Additionally, within Europe, there are inequities regarding availability and insurance coverage of fertility protection [7, 8].

Efforts of research in the field of fertility following cancer treatment in adolescence have led to improved and more specific guidelines for fertility protection [5, 9]. For male adolescents, current guidelines recommend to offer sperm banking prophylactically before any potentially gonadotoxic therapy [5]. Sperm banking is well established and easy to conduct [10]. Overall, rates of sperm banking for adolescents prior to cancer treatment are still considered low [4, 11, 12]. However, Klosky et al. reported of adolescents' perceived benefits of sperm banking [13]. For female adolescent cancer patients, there are various options of fertility protection [14]. Most of them have limitations in the paediatric oncologic setting and are more complex to be organized and conducted [5, 6]. Oocytes can be collected for cryopreservation and future reproductive treatment following 2 weeks of hormonal stimulation [5]. For most adolescent cancers, treatment cannot be delayed to this extend. In this case, ovarian tissue can be collected surgically and cryopreserved before cancer treatment [15]. The birth of at least 130 healthy babies has been reported following autologous transplantation of ovarian tissue after cancer treatment [16]. However, ovarian tissue may contain malignant cells, with transplantation posing a risk of inducing a relapse in both, patients with systemic malignancies or solid tumours [17–19]. In a recent European study, only 17% of female adolescents used cryopreservation [4].

Adequate education on fertility impairment and prevention options is important to enable cancer patients to self-determine their fertility protection. Informed patients are more likely to have their fertility status tested after cancer treatment and therefore improve their chances of having children through early family planning [1]. Having an own child is relevant for a high quality of life following childhood cancer treatment with parenthood being connected to normality, gratitude and happiness by former patients [2]. Within the framework of *PanCareLIFE*, a project funded by the *European Union's Seventh Framework Programme for research, technological development and demonstration* (grant agreement no. 602030), we conducted the multicentre intervention study *Patient education* [4, 20].

Objectives

The present study examined if and how supportive patient information material on the risk of fertility impairment following cancer treatment and on available fertility protection, embedded in the education of the attending physician, influences utilization of fertility protection in adolescent cancer patients.

Methods

Study design and methods

The intervention study *Patient education* was conducted in two study phases (see Fig. 1). Between March 2014 and January 2016, newly diagnosed adolescent cancer patients were recruited for the *control group* and from April 2016 to October 2017 for the *intervention group*. Patients in the control group received the standard patient education on the risk of fertility impairment and fertility protection according to European therapy optimizing studies. Further details on

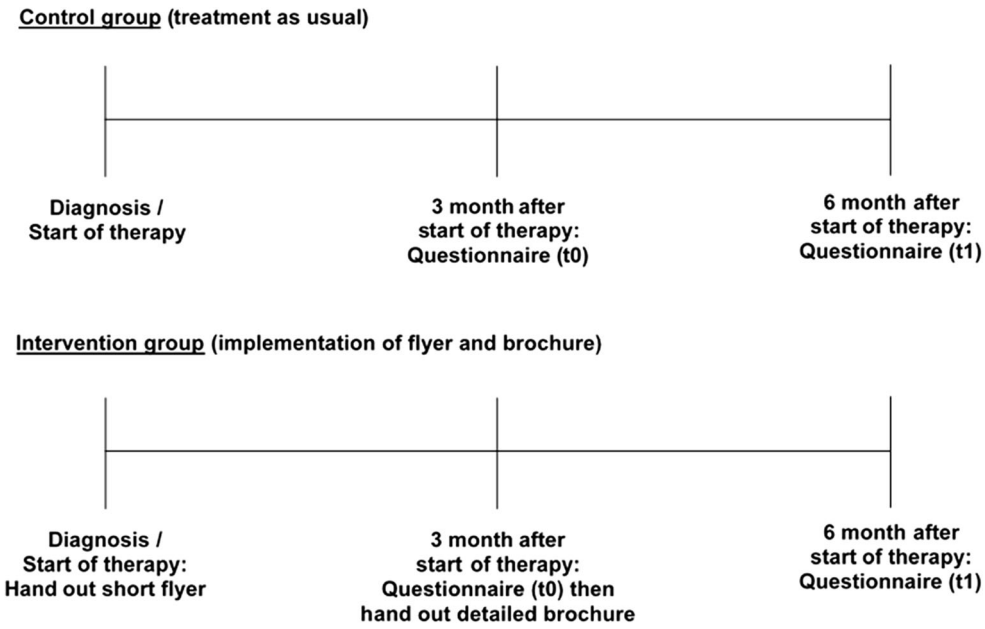


Fig. 1 Study design *Patient education* multicenter intervention study

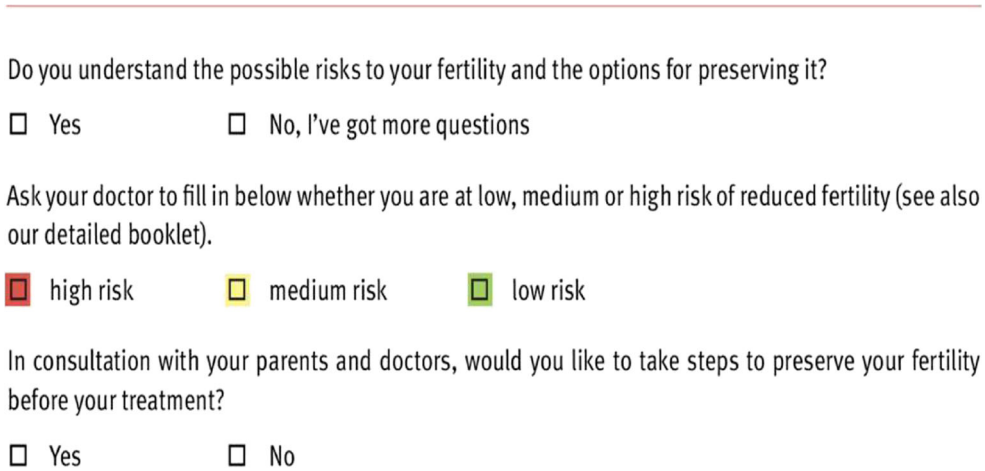
the first study phase have been previously published [4]. In the intervention group, patient education at initial diagnosis was supported by a flyer on fertility impairment. This flyer included a paragraph in which the physician estimated the patient's individual fertility risk based on a list of potentially gonadotoxic protocols in our brochures, and patients stated whether they had further questions and wished to protect their fertility (see Fig. 2). Three months after the start of treatment, patients and parents received the gender-specific patient brochure on fertility following cancer treatment. Written informed consent of patients and their parents in both study groups was obtained for participation. Following, participating patients and their parents were asked to each complete a questionnaire three (t0) and 6 months (t1) after onset of cancer treatment. Full patient flyer, brochures and questionnaires are available at: https://kinderonkologie.charite.de/forschung/ag_borgmann_staudt/pancarelife_interventionstudy_patient_education_2013_2018/. To examine utilization of fertility preservation, relevant answers were obtained from the questionnaire and patient core and clinical data from medical records (Fig. 1, Fig. 2).

Ethics and data protection

The coordinating study centre Charité-Universitätsmedizin Berlin received approval from their local ethics committee on 04/04/2014 (EA2/155/11). All data providers received approval for the study from their respective ethics committees. Patient data was pseudonymized. Only data providers were able to assign patient names to the respective identification number. Patient names were not transmitted to the coordinating study centre.

Patient recruitment and eligibility criteria

The following paediatric oncology departments participated in both study phases: Medical University of Graz (Austria); University Hospital Brno and University Hospital Motol


Do you understand the possible risks to your fertility and the options for preserving it?

☐ Yes ☐ No, I've got more questions

Ask your doctor to fill in below whether you are at low, medium or high risk of reduced fertility (see also our detailed booklet).

☐ high risk ☐ medium risk ☐ low risk

In consultation with your parents and doctors, would you like to take steps to preserve your fertility before your treatment?

☐ Yes ☐ No

Fig 2 Extract, patient information flyer on fertility risk and protection in adolescent cancer patients supporting shared and informed decision making

(Czech Republic); University Duesseldorf, University Ulm, University Hospital Muenster, Charité-Universitätsmedizin Berlin, University Luebeck and Helios-Klinikum Berlin-Buch (Germany) and University Children's Hospital Bialystok and University Gdansk (Poland).

All newly diagnosed adolescent patients who required chemotherapy and/or radiotherapy were eligible for participation. Patients with tumour relapse, secondary malignancies or an unfavourable prognosis at diagnosis were excluded, as well as patients with cognitive impairment and those who were unable to understand the written national language.

Statistics

Data analysis was conducted with the SPSS Statistics Software, Version 24. Univariate analysis was assessed by using chi-squared tests. Effect sizes (Phi, Cramer's V) were calculated to estimate the practical relevance of the results. Cohen (1988) defined effect sizes (Phi, Cramer's V) > 0.10 as small, > 0.30 as medium and > 0.50 as large [21]. For multivariate analyses, binary logistic regression was performed to estimate odds ratios (OR) with 95% confidence intervals. According to a power analysis conducted with GPower [22], a total sample size of $n = 184$ was required to show an OR of ≥ 1.7 on a significance level of 5% with a power of 80%. The educational status of the parents was determined according to the International Standard Classification of Education (ISCED 1997) and classified into three educational status groups [23].

Results

Patient characteristics

Overall, 134 patients were eligible for participation in the intervention phase, of whom 101 (75.4%) participated in the first questionnaire survey at t0 and 98 (73.1%) followed-up at t1. Participation was declined by 16 patients, 5 were unable to participate due to treatment and 12 were excluded due to other social or ethical reasons.

The non-responder analyses revealed no significant differences regarding responders' and non-responders' gender, age at diagnosis and distribution of cancer diagnoses (Table 1). Data on the control group has been published previously [4]. No significant differences between participants of the control and intervention groups could be found regarding gender, age at diagnosis and distribution of cancer diagnoses or for the attending clinic (Table 1, Table 2).

Utilization of fertility preservation

Within the control group, 32.7% ($n = 37/113$) of the participants and 36.6% ($n = 37/101$) of participants of the intervention group used cryopreservation. The rates of cryopreservation showed no statistically significant differences between the groups according to treatment. Overall, univariate analysis showed that cryopreservation was mainly associated with gender and patient information. In the control group, gender, age

Table 1 Non-responders' characteristics in control and intervention group

		Control group		Intervention group		Total	
Non-responder (patients, time-point t0)		Frequency	Percent of control	Frequency	Percent of intervention	Frequency	Percent of total
Gender	Female	10	34.5	15	45.5	25	40.3
	Male	19	65.5	18	54.5	37	59.7
Age group	13–15 years	17	58.6	19	57.6	36	58.1
	16–17 years	12	41.4	13	39.4	25	40.3
	18 years and older	0	0.0	1	3.0	1	1.6
Diagnose main groups	Leukaemia	19	65.5	24	72.7	43	69.4
	Brain tumours	3	10.3	0	0.0	3	4.8
	Solid tumours	7	24.1	9	27.3	16	25.8
Diagnose (details)	Leukaemia	7	24.1	12	36.4	19	30.6
	Lymphoma	12	41.4	12	36.4	24	38.7
	Brain tumours	3	10.3	0	0.0	3	4.8
	Bone tumours	2	6.9	6	18.2	8	12.9
	Soft tissue sarcoma	1	3.4	3	9.1	4	6.5
	Liver tumour	0	0.0	0	0.0	0	0.0
	Germ cell tumour	2	6.9	0	0.0	2	3.2
	Carcinoma	2	6.9	0	0.0	2	3.2
	other	0	0.0	0	0.0	0	0.0

Table 2 Participants' characteristics in control and intervention group

		Control group		Intervention group		Total	
		Frequency	Response (%)	Frequency	Response (%)	Frequency	Response (%)
Survey participation	Patient Q1	113	79.6	101	75.4	214	77.5
	Patient Q2	106	74.6	98	73.1	204	73.9
	Parent Q1	111	78.2	99	73.9	210	76.1
	Parent Q2	103	72.5	95	70.9	198	71.7
Participants (patients) t0		Frequency	Percent of control	Frequency	Percent of intervention	Frequency	Percent of total
Gender	Female	53	46.90	43	42.60	96	44.90
	Male	60	53.10	58	57.40	118	55.10
Age group	13–15 years	52	46	46	45.50	98	45.80
	16–17 years	52	46	51	50.50	103	48.10
	18 years and older	9	8	4	4	13	6.10
Country of attending clinic	Austria	10	8.80	7	6.90	17	7.90
	Czech Republic	48	42.50	42	41.60	90	42.10
	Germany	42	37.20	40	39.60	82	38.20
	Poland	13	11.50	12	11.90	25	11.70
Diagnose (main groups)	Leukaemia	62	55.40	65	64.40	127	59.60
	Brain tumours	5	4.50	5	5.00	10	4.70
	Solid tumours	45	40.20	31	30.70	76	35.70
Diagnose (details)	Leukaemia	18	15.90	20	19.80	38	17.80
	Lymphoma	44	38.90	45	44.60	89	41.60
	Brain tumours	5	4.40	5	5.00	10	4.70
	Bone tumours	22	19.50	13	12.90	35	16.40
	Soft tissue sarcoma	8	7.10	6	5.90	14	6.50
	Liver tumour	1	0.90	1	1.00	2	0.90
	Germ cell tumour	13	11.50	10	9.90	23	10.70
	Carcinoma	1	0.90	1	1.00	2	0.90
	other	1	0.90	0	0.00	1	0.50

and patient information on fertility protection were associated with utilization of cryopreservation. In the intervention group, cryopreservation was associated with gender, the subjective assessment of the fertility risk and the information on risks before treatment (Table 3).

Binary logistic regression was performed for multivariate analyses for determinants of cryopreservation. Included were patient's gender, age at time of questionnaire completion, cancer diagnosis, country of attending clinic, estimated risk for fertility, whether or not the patient received information on infertility risks and protection as part of education with or without intervention. Table 3 shows the results of binary logistic regression (Table 4).

In total, patient's gender (OR 0.141, CI 0.061–0.325) and age (OR 1.302, CI 1.021–1.66) as well as having received information on prophylactic measures (OR 10.687, CI 2.056–55.548) were predictors for utilization of cryopreservation. Female patients only had a 14% chance to cryopreserve compared to male patients. With rising age, the likeliness to cryopreserve increased by more than 30% per year. Patients who received information on prophylactic measures had a 10 times higher chance to cryopreserve than those who did not.

Sub-group analysis of the control group showed a 10% chance of using cryopreservation for female compared to male patients (OR 0.100, CI 0.023–0.427). With rising age, the likeliness to cryopreserve in the control group increased by almost 56% per year (OR 1.559, CI 1.077–2.258). The likeliness to cryopreserve was associated with having received information on fertility-preserving measures (OR 33.663, CI 2.100–539.574).

Utilization of cryopreservation was less likely in female patients in the intervention group (OR 0.093, CI 0.026–0.330) and was also associated with the estimated fertility risk (OR 43.665, CI 2.157–883.974). Thus, the chance to use cryopreservation of patients rating their fertility risk as high was more than 43 times greater than of those with low risk estimation in the intervention group.

Table 3 Utilization of cryopreservation—results of univariate analysis

		Control group				Intervention group				Total			
		Freq.	Percent	*p* value	Effect	Freq.	Percent	*p* value	Effect	Freq.	Percent	*p* value	Effect
Gender	Female	9	17.0	< 0.001	0.316	6	14.0	< 0.001	0.405	15	15.6		0.359
	Male	28	46.7			31	53.4			59	50.0	< 0.001	
Age group	13–15 years	10	20.0	0.031	0.248	12	30.0	n.s.	–	22	24.4	0.024	0.187
	16–17 years	21	41.2			20	40.0			41	40.6		
	18 years and older	6	50.0			5	45.5			11	47.8		
Country of attending clinic	Austria	3	30.0	n.s.	–	3	42.9	n.s.	–	6	35.3	n.s.	–
	Czech Republic	17	35.4			12	28.6			29	32.2		
	Germany	15	35.7			17	42.5			32	39.0		
	Poland	2	15.4			5	41.7%			7	28.0		
Diagnose (main groups)	Leukaemia	18	29.0	n.s.	–	21	32.3%	n.s.	–	39	30.7	n.s.	–
	Brain tumours	1	20.0			2	40.0			3	70.0		
	Solid tumours	17	37.8			14	45.2			31	40.8		
Risk for infertility	High	11	42.3	n.s.	–	5	83.3	0.030	0.270	16	50.0	0.046	0.174
	Medium	17	36.2			23	36.5			40	36.4		
	Low	8	23.5			7	25.9			15	24.6		
Information on prophylactic measures	Yes	36	43.9	< 0.001		34	39.5	0.068	0.183	70	41.7		
	No/do not know	1	3.3		0.382	2	14.3			3	6.8	< 0.001	0.297
Risk information before treatment, including fertility impairment	Yes	35	39.3	0.007	0.256	33	41.8	0.020	0.238	68	40.5	< 0.001	0.248
	No/do not know	2	9.1			2	11.8			4	10.3		

Effect size (Phi, Cramer-V): > 0.10 = small; > 0.30 = medium; > 0.50 = large

n.s. (not significant); Effect size (Phi, Cramer-V): >0.10=small; >0.30=medium;>0.50=large

Table 4 Results of binary logistic regression of predictors for utilization of cryopreservation

	Control group[1]			Intervention group[2]			Total[3]		
	p value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI
Gender of patient (female)	*0.002*	*0.100*	*0.023–0.427*	*<0.001*	*0.093*	*0.026–0.330*	*0.000*	*0.141*	*0.061–0.325*
Age of patient (in years)	*0.019*	*1.559*	*1.077–2.258*	0.892	1.027	0.696–1.516	*0.034*	*1.302*	*1.021–1.660*
Diagnosis (brain tumours)	0.865	0.765	0.035–16.917	0.694	1.688	0.124–22.936	0.888	0.875	0.138–5.546
Diagnosis (solid tumours)	0.610	0.733	0.223–2.415	0.970	1.024	0.305–3.432	0.951	0.976	0.448–2.124
Country of attending clinic (cz)	0.095	0.337	0.094–1.210	0.473	0.635	0.184–2.193	0.052	0.445	0.196–1.008
Country of attending clinic (pl)	0.094	0.156	0.018–1.369	0.798	1.267	0.207–7.771	0.228	0.461	0.131–1.623
Country of attending clinic (at)	0.140	0.237	0.035–1.602	0.682	1.550	0.190–12.642	0.332	0.513	0.134–1.974
Estimated risk for fertility (medium)	0.188	2.400	0.652–8.826	0.162	2.503	0.691–9.071	0.061	2.302	0.963–5.504
Estimated risk for fertility (high)	0.807	1.196	0.284–5.032	*0.014*	*43.665*	*2.157–883.974*	0.134	2.413	0.763–7.637
Information on prophylactic measures (yes)	*0.013*	*33.663*	*2.100–539.574*	0.101	10.712	0.629–182.396	*0.005*	*10.687*	*2.056–55.548*
Risk information before treatment - including fertility impairment (yes)	0.707	0.599	0.041–8.710	0.147	4.608	0.585–36.329	0.374	1.850	0.477–7.184
Treatment (Intervention group)	–	–	–	–	–	–	0.680	0.857	0.412–1.784

Gender of patient: male; diagnosis: systemic haematological malignancies (leukaemia and lymphoma); country of attending clinic: Germany; Estimated risk for fertility: low; information on prophylactic measures: no/ don't know; risk information before treatment: no/ don't know; treatment: without intervention (control group)

[1] Control group: $n = 105/113$ (92.9%);

[2] Intervention group: $n = 91/101$ (90.1%);

[3] Total: $n = 196/214$ (91.6%);

italic: significant results

Availability of fertility protection

All data providers gave information on availability of fertility protection in their countries: Cryopreservation of oocytes was only available in Germany, and ovarian tissue cryopreservation only in Austria and Germany. Ovariopexy was only conducted in the Czech Republic and Germany. Sperm banking was available in all countries; testicular tissue cryopreservation was only available in Germany.

Out of 36 female patients who stated that they were planning to use fertility protection, 25 (69.4%) did not in the end. For 16/25 (64.0%) patients, ovarian tissue cryopreservation, and for 19/25 (76.0%), oocyte cryopreservation, was not available in their country. Overall, 6/25 (24.0%) female patients could not receive an ovariopexy, as this procedure was not available in their country. Out of 63 male patients who stated that they were planning to use fertility protection, 20 (31.7%) did not. For 14/20 (70.0%) patients, testicular tissue cryopreservation was not available in their country (Table 5).

Discussion

Patient Education is a first study to systematically collect data on utilization of fertility protection in adolescent cancer patients in four European countries. Participation rate was high for both control and intervention group, showing the significance of the topic to families affected. Additional information material embedded in patient education did not increase the overall rate of cryopreservation but multivariate sub-group analysis revealed different sets of predictors for the use of cryopreservation in both study groups: While in the control group, the use of

Table 5 Number of patients with unavailability of fertility protection according to country of treatment

	Czech Republic		Poland		Austria		Germany	
	n	%	*n*	%	*n*	%	*n*	%
Cryopreservation of ovarian tissue	13	52.0	3	12.0	–	–	–	–
Cryopreservation of egg cells	13	52.0	3	12.0	3	12.0	–	–
Cryopreservation of testicular tissue	12	60.0	1	5.0	1	5.0	–	–
Cryopreservation of sperm cells	–	–	–	–	–	–	–	–
Ovariopexy	–	–	3	12.0	3	12.0	–	–

cryopreservation was associated with gender, age and having received information on fertility-preserving measures, cryopreservation in the intervention group was related to gender and the estimated risk for fertility. Compared to patient education as usual, the additional use of flyers and gender-specific brochures seems to bring those at risk into attention more and also increase the willingness to use cryopreservation even among younger patients.

Providers' perception of the parents' and patients' interests in fertility preservation often does not align with their actual attitudes and concerns. Especially patients of younger age and female patients are prone to recall having received fertility education to a lower rate than older or male patients [4], suggesting that providers may distinguish before even discussing potential options with patients. Even though fertility protection in female patients might be more complex, well-established options exist and there has been progress for prepubertal children [6]. Unfortunately, these misperceptions as well as lack of time and knowledge on the side of the educating physician may result in superficial discussions of future fertility [24, 25]. Knowing that time can be short in daily clinical routine, we developed detailed gender-specific brochures on fertility impairment following cancer in adolescence and fertility-preserving options as well as an additional informative flyer. Within the brochure, a table classifying therapy optimization trial protocols and their sub-treatment groups into low, elevated or high risk for fertility impairment gives the physicians a quick overview to estimate the patient's individual fertility risk. Prior to cancer treatment, the physician will visualize the estimated risk to the adolescents and their parents by marking the low (green), elevated (yellow) or high (red) risk on the fertility flyer with a cross. Additionally, the families are asked to state whether or not they have further questions in regard to fertility and if they wish to proceed with fertility protection measures, supporting a shared and informed decision making.

Insurance coverage of fertility protection is unequal among participating study centres with varying options for additional private funding support [7, 8]. We collected information on which fertility protection was available in the participating countries in our study. The biggest proportion of patients, who did not receive fertility protection even they would have liked to, were those treated in the Czech Republic: Almost half the patients could not be offered procedures due to lack of availability. In contrast, all patients who desired could undergo fertility protection in Germany. However, also in Germany, the costs for these interventions were not funded for by health insurance: However, only recently, in March 2019, a law was passed now making fertility protection for cancer patients part of German health insurance coverage.

To avoid selection bias, inclusion and exclusion criteria were applied to all newly diagnosed adolescent cancer patients. Non-participants were comparable to participants regarding gender, age and cancer diagnosis. Patient education as usual was conducted according to the therapy optimization trial protocols. However, form and extend of content of presentation of patient information could differ from centre to centre and among providers. We provided information material to the centres (short manual and instruction slides) to support further standardizing the usual patient education. Physicians, who treated and educated the study participants may have discussed fertility issues particularly well, having been aware of the ongoing study. Therefore, the results for the control group and intervention group participants may not differ as much as the onset of the study might have been a first intervention already. The prevalence of utilization of cryopreservation could therefore be higher in the participating centres than usual. In addition, participating centres had different fertility preservation measures available. For this reason, the country of the attending clinic was included in the multivariate analysis as a potential confounder as particularly patients' age and gender appeared to be influencing factors for the utilization of cryopreservation. Due to a small case number, some of the results of logistic regression showed broad confidence intervals, which suggests uncertain estimates.

Conclusion

Although no significant difference in the utilization of cryopreservation between the control and intervention groups was detected regarding treatment, sub-group analysis showed differences between the groups regarding determinants of cryopreservation utilization. The additional use of flyers and gender-specific brochures increased the willingness to cryopreserve also among younger patients. At the same time, the individual fertility risk seemed to be brought into attention more. Our results emphasize the importance of patient information for increasing the likelihood to use fertility protection where adequate. Country-specific differences in availability, affordability and feasibility of fertility protection indicate that in addition to appropriate patient information, further aspects affect utilization of fertility protection. Patient information should not only inform on available measures, but also on the respective social conditions which could impede utilization.

Authors' contributions MB: study concept and design, data acquisition, data interpretation, manuscript preparation, editing, revision and proof. RS: study concept and design, data acquisition, quality control of data and algorhythms; data analysis and interpretation; statistical analysis, manuscript editing, revisiona and proof. JB: study concept and design, manuscript editing. UD: data acquisition, manuscript editing. HC: data acquisition, manuscript editing. MJFG: manuscript editing. TK: data acquisition, manuscript editing. EK: study concept and design, data acquisition, quality control of data and algorhythms, manuscript editing. JK: data acquisition, manuscript editing. MK: data acquisition, manuscript editing. HL: data acquisition, manuscript editing. TL: data acquisition, manuscript editing. MSZ: data acquisition, manuscript editing. JS: data acquisition,

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The coordinating study centre Charité-Universitätsmedizin Berlin received approval from their local ethics committee on 04/04/2014 (EA2/155/11). All data providers received approval for the study from their respective ethics committees.

Informed consent Informed consent was obtained from all participants included in the study.

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