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MEDICINOS FAKULTETAS

Magistro baigiamasis darbas

Onkologine liga sergančių vaikų konsultavimo apie vaisingumo išsaugojimą kokybės vertinimas

Evaluation of the Quality Counselling on Fertility Preservation in Childhood Cancer Patients

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Vaikų ligų klinika

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Santrauka

Įvadas. Penkerių metų išgyvenamumas susirgus onkologine liga vaikystėje siekia 80 proc., tačiau daugelis išgyvenusiųjų susiduria su atokiosiomis gydymo pasekmėmis, kurių viena pagrindinių – nevaisingumas. Daugelio pasveikusiųjų nuomone, gydymo metu buvo suteikta nepakankamai informacijos apie gydymo poveikį vaisingumui.

Darbo tikslas – įvertinti onkologine liga sergančių vaikų vaisingumo konsultavimo kokybę.

Tiriamieji ir tyrimo metodai. Onkologine liga sirgusių vaikų tėvai (nepriklausomai nuo vaiko amžiaus) arba 12-17,9 metų vaikai, gydyti nuo 2021 m. liepos 1 d. iki 2022 m. liepos 1 d., buvo pakviesti užpildyti vaisingumo konsultavimo vertinimo klausimyną. Užpildžius klausimyną, respondentai priskirti didelei arba mažai nevaisingumo rizikai naudojant tam skirtą metodiką („*triage*"). Taikyti aprašomosios statistikos metodai.

Rezultatai. Iš viso 48 tėvai ir 13 vaikų užpildė klausimyną. Mažai nevaisingumo rizikai priskirti 36 (59 proc.), didelei – 25 (41 proc.) respondentai. Dauguma didelės nevaisingumo rizikos respondentų (21 iš 25, 84 proc.) nekonsultuoti vaisingumo specialisto. Šeši berniukai (4 didelės rizikos, 2 – mažos) prieš onkologinės ligos gydymą konsultuoti vaisingumo specialisto, mergaitės konsultuotos nebuvo. Trims didelės nevaisingumo rizikos berniukams užšaldyta sperma. Tik 17 (27,9 proc., 9 didelės rizikos, 8 – mažos) respondentų teisingai įvardino savo nevaisingumo riziką. Visi konsultuoti berniukai (n=6) sutiko, jog buvo minėtas vaisingumo pažeidimas, palyginus su 49,1 proc. (n=27) nekonsultuotų respondentų. Visi konsultuoti respondentai sutiko, jog žino pakankamai apie vaisingumą (palyginus su 42 proc. nekonsultuotų) bei žino savo vaisingumo išsaugojimo galimybes (palyginus su 38,8 proc. nekonsultuotų).

Išvados. Vaisingumo specialisto konsultuoti respondentai turėjo daugiau žinių apie vaisingumą nei informuoti tik gydytojo vaikų onkohematologo. Taikant „*triage*" metodiką nustatyta, jog dauguma didelės nevaisingumo rizikos respondentų nenukreipti specialisto konsultacijai. Vaisingumo konsultavimą tikslinga tobulinti.

Raktažodžiai. Anketinė apklausa; gonadotoksiškumas; onkologija; pediatrija; vaisingumas

Summary

Background. While the five-year survival rate of childhood cancer exceeds 80%, many survivors develop late effects including infertility. However, most survivors perceive the information regarding fertility as insufficient.

The aim of the study was to evaluate the quality of fertility care in childhood cancer patients.

Material and methods. All parents or patients aged 12-17.9 years treated from July 1, 2021 until July 1, 2022 were invited to complete oncofertility-care-evaluation-questionnaire. After completing the questionnaire, respondents were triaged to low or high risk of gonadal damage using a gonadal damage risk stratification tool (triage). Data was assessed using descriptive statistics.

Results. Questionnaires were completed by 48 parents and 13 children. Triage resulted in 36 (59%) low gonadal damage risk and 25 (41%) high risk respondents. Most high risk respondents (21/25, 84%) were not counseled by a fertility specialist. Six boys (4 high risk, 2 low risk) were counseled, none of the girls was counseled. Three high risk boys underwent sperm cryopreservation. Only 17 (27.9%, 9 high risk, 8 low risk) respondents correctly estimated their risk. All counseled boys (n=6) agreed the risk for fertility impairment had been mentioned compared to 49.1% (n=27) of uncounseled. All counseled respondents agreed they knew enough about fertility (vs 42%) and all knew their fertility preservation options (vs 38.8%).

Conclusions. Respondents counseled by a fertility specialist were provided more information on fertility than uncounseled. Gonadal damage risk stratification revealed a lack of high risk respondents counseling. Based on the current experience oncofertility care will be improved.

Keywords. Childhood cancer; fertility counseling; late effects; questionnaire; reproductive health

SANTRUMPOS

CED – Ciklofosfamido ekvivalentinė dozė

CNS – centrinė nervų sistema

ELI – Elektroninė ligos istorija

IGHG – Tarptautinė vaikų vėžio atokiųjų pasekmių stebėsenos gairių derinimo grupė (angl. *International Late Effects of Childhood Cancer Guideline Harmonization Group*)

IKP – interkvartilinis plotis

KKLT – Kraujodaros kamieninių ląstelių transplantacija

PMC – *Princess Máxima Center*

ĮVADAS

Penkerių metų išgyvenamumas, susirgus onkologine liga vaikystėje, Lietuvoje, kaip ir kitose Vakarų Europos šalyse, siekia 80 proc. [1]. Pagerėjus gydymo galimybėms ir augant išgyvenusiųjų skaičiui svarbu ne tik ieškoti priemonių įveikti onkologinę ligą, bet ir užtikrinti pasveikusiųjų gyvenimo kokybę. Deja, daugeliui išgyvenusiųjų išsivysto atokiosios pasekmės, susijusios su pačia onkologine liga ir / ar jos gydymu. Viena pagrindinių pasekmių – nevaisingumas [2–4]. Yra žinoma, jog sumažėjęs vaisingumas, ankstyva menopauzė ir nevaisingumas reikšmingai blogina jaunų moterų, persirgusių onkologine liga vaikystėje, gyvenimo kokybę, sukelia psichosocialinių sunkumų [5,6]. Onkologine liga vaikystėje sirgę vyrai dėl didelių dozių chemoterapijos ar radioterapijos į sėklides ar galvos sritį gali susidurti su nevaisingumu dėl hipogonadizmo ir sutrikusios spermatogenezės [7].

Daugelis autorių rekomenduoja vaisingumo klausimus aptarti prieš skiriant onkologinės ligos gydymą [8–11]. Remiantis naujausiomis rekomendacijomis, parengtomis tarptautinės vaikų vėžio atokiųjų pasekmių stebėsenos gairių derinimo grupės (angl. *International Late Effects of Childhood Cancer Guideline Harmonization Group*, IGHG), visi pacientai turėtų būti informuojami apie gonadotoksinio pažeidimo riziką, turi būti pasiūlytos vaisingumo išsaugojimo galimybės [7,12]. Vis dėlto pritaikyti šias rekomendacijas klinikinėje praktikoje gali būti sudėtinga, tą parodė *Princess Máxima Center* (PMC, Nyderlandai) atliktas tyrimas, vertinantis vaisingumo priežiūros plano, skirto mergaitėms, kurioms diagnozuota onkologinė liga, taikymą [13]. Šis planas gali pasitarnauti kaip IGHG rekomendacijų įdiegimo pavyzdys.

Literatūros duomenimis konsultavimas vaisingumo klausimais turi teigiamą įtaką gyvenimo kokybei po onkologinės ligos gydymo, nepriklausomai nuo sprendimo dėl vaisingumo išsaugojimo [14,15]. Dauguma suaugusiųjų, vaikystėje sirgusių onkologine liga, teigia, jog nebuvo suteiktas tinkamas vaisingumo konsultavimas bei nežino, ar gydymas pakenkė jų vaisingumui [16,17]. Suaugusieji, persirgę onkologine liga vaikystėje, nori tapti tėvais, tačiau stokoja informacijos apie savo vaisingumo būklę [17]. Tą patvirtino mūsų atliktas skerspjūvio tyrimas – rezultatai atskleidė, jog daugelis pilnamečių pasveikusiųjų nurodė, kad gydymo metu nepateikta pakankamai informacijos apie gydymo poveikį vaisingumui ir vaisingumo išsaugojimą [18].

Šiuo metu onkologine liga sergančių vaikų vaisingumo konsultavimas Lietuvoje vykdomas nenuosekliai, vaisingumo išsaugojimas galimas po specialisto konsultacijos, tačiau nėra vieningos

reprodukcinės sveikatos priežiūros sistemos. Tikėtina, jog daugeliui vaikų, kuriems kyla vaisingumo pažeidimo rizika, nesuteikiamas tinkamas vaisingumo konsultavimas. Iki šiol nebuvo įrankių įvertinti, kaip onkologine liga sergantys vaikai ir jų tėvai vertina vaisingumo konsultavimo kokybę. Tuo tikslu bendradarbiaujant su PMC (vykdant Horizon 2020 mokslinių tyrimų ir inovacijų finansavimo programos projektą, siekiantį pagerinti vaikų, sergančių piktybiniais navikais, išgyvenamumą Lietuvoje, angl. *Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania,* TREL, https://cordis.europa.eu/project/id/952438), sukūrėme validuotus vaisingumo vertinimo klausimynus, taikomus PMC ir Vilniaus Universiteto Ligoninėje Santaros Klinikose (VULSK) Vaikų onkohematologijos centre [19].

Darbo tikslas – įvertinti onkologine liga sergančių vaikų vaisingumo konsultavimo kokybę VULSK.

Darbo uždaviniai:

1) Nustatyti vaisingumo konsultavimo vertinimo skirtumus tarp vaisingumo specialisto konsultuotų ir gydytojo vaikų onkohematologo informuotų respondentų;
2) Įvertinti respondentų nevaisingumo riziką taikant tam skirtą metodiką („*triage*“);
3) Nustatyti pačių respondentų subjektyviai įvertintos ir taikant metodiką įvertintos nevaisingumo rizikos skirtumus.

TIRIAMIEJI IR TYRIMO METODAI

Atliktas skerspjūvio tyrimas taikant anketinę apklausą. Tyrime pakviesti dalyvauti visi onkologine liga (TLK-10-AM C00-96) sergančių vaikų tėvai (nepriklausomai nuo vaiko amžiaus) ir 12-17,9 m. vaikai, gydyti VULSK nuo 2021 m. liepos 1 d. iki 2022 m. liepos 1 d. Tiriamųjų grupę sudarė naujai diagnozuoti pacientai bei tyrimo metu gydyti pacientai, kuriems liga diagnozuota prieš pradedant tyrimą. Pakviestieji sutiko dalyvauti tyrime pasirašydami informuoto asmens sutikimo formą.

Tyrimo dalyviai suskirstyti į dvi grupes – konsultuotus vaisingumo specialisto ir informuotus apie vaisingumą gydytojo vaikų onkohematologo. Laikyta, jog visi specialisto nekonsultuoti tyrimo dalyviai buvo informuoti vaikų onkohematologo – visiems pacientams gydymo pradžioje pateikta trumpa rašytinė informacija apie šalutinius gydymo poveikius, įskaitant nevaisingumą (nenurodant konkrečios paciento nevaisingumo rizikos). Visais atvejais vaisingumo specialisto konsultavimas ir

vaisingumo išsaugojimas atliktas Santaros Vaisingumo Centre prieš onkologinės ligos gydymą. Berniukai ir jų tėvai konsultuoti gydytojo embriologo prieš ir po spermos surinkimo procedūros. Sperma surinkta masturbacijos būdu. Esant pakankamai gerai jos kokybei, atlikta spermos krioprezervacija. Mergaitės VULSK vaisingumo klausimais konsultuojamos gydytojos akušerės-ginekologės. Tyrimo metu vaisingumo išsaugojimas atliktas tik 14 metų ir vyresniems vaikams, nes vaisingumo išsaugojimo paslaugos jaunesniems vaikams buvo draudžiamos Lietuvos Respublikos pagalbinio apvaisinimo įstatymo [20].

Visi tyrimo dalyviai užpildė TREL projekto metu sukurtus validuotus vaisingumo konsultavimo vertinimo klausimynus [19]. Vienas klausimynas taikytas tyrimo dalyviams, informuotiems gydytojo vaikų onkohematologo (Priedai 1,2), kitas – konsultuotiems vaisingumo specialisto (Priedai 3,4). Sudarant vaisingumo konsultavimo vertinimo klausimynus, remtasi validuotais klausimynais, skirtais suaugusiesiems (Priedai 5,6) [21–24]. Pritaikant klausimynus tarptautiniam naudojimui, klausimai iš olandų kalbos išversti į anglų, o iš anglų – į lietuvių kalbą (Priedai 5,6). Validuojant klausimynus atliktas vertimas iš lietuvių kalbos į anglų, nenustatyta reikšmingų skirtumų, palyginus su pirmine versija anglų kalba. Klausimynus Lietuvoje įvertino du gydytojai vaikų onkohematologai, gydytoja ginekologė ir dviejų pacientų tėvai, kurie visi laisvai kalbėjo angliškai. Galiausiai olandiška versija palyginta su lietuviška vertėjo pagalba [19].

Klausimynas pacientams, informuotiems gydytojo vaikų onkohematologo, turėjo 27 uždarus klausimus, buvo suskirstytas į keturias dalis: „Bendrieji klausimai“, „Klausimai, susiję su pokalbiu su gydytoja onkohematologe“, „Klausimai po pokalbio apie vaisingumą“ ir keturis atvirus klausimus (Priedai 1,2). Klausimyne konsultuotiems pacientams papildomai išskirti klausimai, susiję su specialisto konsultacija. Šis klausimynas turėjo 39 uždarus klausimus ir buvo suskirstytas į penkias dalis: „Bendrieji klausimai“, „Klausimai, susiję su pokalbiu su gydytoja vaikų onkohematologe“, „Klausimai, susiję su ginekologo/urologo/embriologo konsultacija“, „Klausimai, susiję su abiem pokalbiais dėl vaisingumo“ ir keturis atvirus klausimus (Priedai 3,4). Devyniolika klausimų sutapo tarp abiejų klausimynų. Klausimai pateikti teiginių forma, atsakant buvo prašoma nurodyti, kaip stipriai sutinkama su kiekvienu teiginiu. Atsakymų variantai pateikti penkių balų *Likert* skale nuo „Visiškai nesutinku“ iki „Visiškai sutinku“. Klausimynus pildė arba tėvai, arba vaikai – tai reiškia vieną užpildytą klausimyną vienam pacientui. Jei vaikui buvo 12 metų ir daugiau, buvo siekiama, jog klausimyną pildytų pats vaikas, jam atsisakius – paprašyta klausimyną užpildyti tėvų. Klausimynai

tėvams ir vaikams nesiskyrė, išskyrus klausimų formuluočių adaptavimą tėvams (Priedai 1,3) ir vaikams (Priedai 2,4).

Respondentai atsakė, kokia, jų nuomone, yra jų pačių ar jų vaiko nevaisingumo rizika po onkologinės ligos gydymo. Įvardinta rizika palyginta su nevaisingumo rizika, nustatyta darbo autorės taikant tam skirtą metodiką (aprašyta žemiau). Apskaičiuotas dažnis respondentų, vienodai stipriai pritarusių klausimynuose pateiktiems teiginiams (pagal penkių balų *Likert* skalę). Atsakymų pasiskirstymas į vienodus klausimus tarp dviejų grupių respondentų – konsultuotų vaisingumo specialisto ir informuotų gydytojo vaikų onkohematologo – pateiktas grafiškai.

Kiekvieno respondento nevaisingumo rizika įvertinta tam skirta metodika („*triage*“) (7 priedas). Metodika buvo pritaikyta naudojimui VULSK adaptuojant PMC publikuotą nevaisingumo rizikos vertinimo metodiką [13]. Nevaisingumo rizika vertinta remiantis ciklofosfamido ekvivalentine doze (CED, angl. *Cyclophosphamide Equivalent Dose)*, atspindinčia gonadų pažeidimo riziką [25]. CED apskaičiuojama pagal formulę: CED (mg/m^2) = 1,0 (suminė ciklofosfamido dozė (mg/m^2)) + 0,244 (suminė ifosfamido dozė (mg/m^2)) + 0,857 (suminė prokarbazino dozė (mg/m^2)) + 14,286 (suminė chlorambucilo dozė (mg/m^2)) + 15,0 (suminė karmustino dozė (mg/m^2)) + 16,0 (suminė lomustino dozė (mg/m^2)) + 40 (suminė melfalano dozė (mg/m^2)) + 50 (suminė *Thiotepa* dozė (mg/m^2)) + 100 (suminė azoto garstyčių darinių dozė (mg/m^2)) + 8,823 (suminė busulfano dozė (mg/m^2)) [25].

Gonadotoksinio pažeidimo rizika suskirstyta į mažą ir didelę pagal naujausias rekomendacijas [7,12]. Didele mergaičių nevaisingumo rizika laikyta, kai apskaičiuota CED ≥6000 mg/m^2, maža – kai CED <6000 mg/m^2 [12]. Didelė nevaisingumo rizika berniukams kyla, kai CED ≥4000 mg/m^2, maža – kai CED <4000 mg/m^2 [7]. Kamieninių kraujodaros ląstelių transplantacija (KKLT), viso kūno apšvita, radioterapija į kiaušidžių ar sėklidžių sritį lemia didelę nevaisingumo riziką mergaitėms ir berniukams [7,12]. PMC publikuota metodika skirta tik mergaitėms [13]. Metodiką adaptavus, įtraukta berniukų nevaisingumo rizika pagal IGHG gaires [7]. Originalioje metodikoje nurodyta vidutinė nevaisingumo rizika mergaitėms (4000-6000 mg/m^2), tačiau metodiką adaptavus, remiantis naujausiomis gairėmis, išskirtos tik maža ir didelė rizikos [12]. Šiek tiek skirtingi gydymo protokolai taikomi PMC ir VULSK. Metodika („*triage*“) papildyta VULSK naudotais protokolais, netaikomais PMC. Taip pat iš originalios metodikos ištrinti VULSK netaikyti protokolai. Visoms įtrauktų gydymo

protokolų šakoms apskaičiuota CED, nustatyta nevaisingumo rizika mergaitėms ir berniukams. Originalios (išverstos į lietuvių kalbą) ir adaptuotos metodikos palyginimas pateiktas 8 priede.

Respondentų demografinės ir gydymo charakteristikos surinktos iš Elektroninės Ligos Istorijos (ELI). Diagnozės nustatymo data apibrėžta kaip klinikinės diagnozės pagrindimo data, nurodyta ELI. Taikyti aprašomosios statistikos metodai. Kintamųjų pasiskirstymas patikrintas *Shapiro-Wilk* testu, kintamieji išreikšti medianomis, interkvartiliniais pločiais (IKP) bei mažiausiomis ir didžiausiomis reikšmėmis (min-max). Duomenų analizei taikyta SPSS for Windows 17.0 programa.

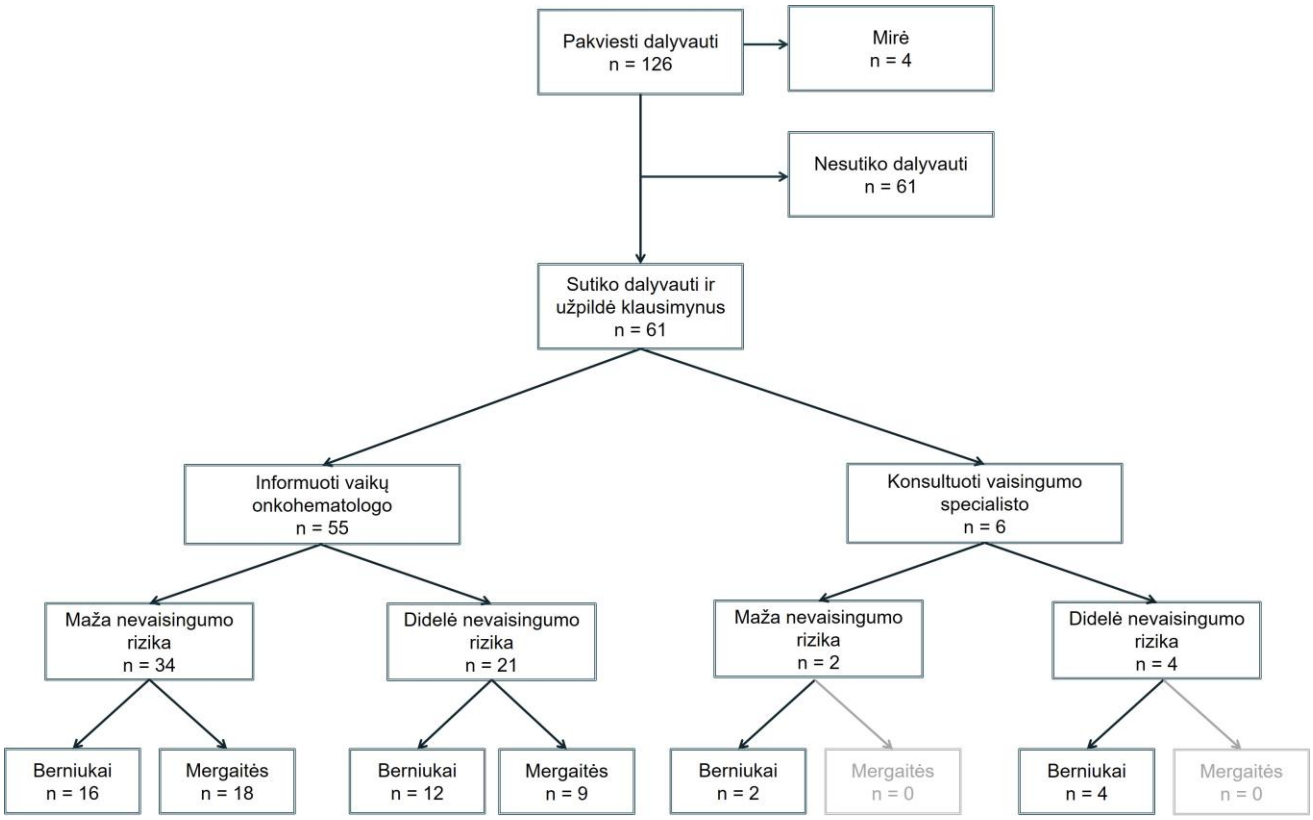
Darbas yra biomedicininio tyrimo „Vaikų vėžio diagnostikos ir stebėsenos optimizavimas vykdant TREL projektą“ dalis. Tyrimui išduotas Vilniaus Regioninio Bioetikos Komiteto leidimas Nr. 2020/10-1274-753 (9 priedas). Darbo autorė tyrime dalyvauja kaip „Kiti tyrime dalyvaujantys asmenys“.

TYRIMO REZULTATAI

Iš 126 pakviestų dalyvauti tyrime pacientų, 4 mirė (1 paveikslas). Iš likusių 122 pakviestųjų, sutiko dalyvauti lygiai pusė (61, 50 proc.). Iš jų 28 (45,9 proc.) diagnozuoti prieš pradedant tyrimą (iki 2021 m. liepos 1 d.), 33 (54,1 proc.) – tyrimo metu. Atsisakiusių dalyvauti tyrime pacientų medicininiai duomenys nebuvo analizuojami, dėl to šių pacientų charakteristikos nepateiktos, nenustatyta nevaisingumo rizika. Nesutikę dalyvauti tyrime pacientai nenurodė atsisakymo priežasties.

Vaisingumo konsultavimo vertinimo klausimynus užpildė 48 tėvai ir 13 vaikų. Klausimynus pacientams, informuotiems tik gydytojo vaikų onkohematologo, užpildė 48 tėvai ir 7 vaikai, o klausimynus, skirtus konsultuotiems vaisingumo specialisto pacientams, užpildė 6 berniukai. Didelei nevaisingumo rizikai priskirti 25 respondentai – 16 berniukų ir 9 mergaitės. Dauguma didelės rizikos respondentų (21 iš 25, 84 proc.) nekonsultuoti vaisingumo specialisto. Iš jų 15 (71,4 proc.) buvo jaunesni nei 14 metų amžiaus, todėl vaisingumo išsaugojimas dėl įstatyminių apribojimų nepasiūlytas [20]. Vaisingumo išsaugojimo paslaugos nesuteiktos šešiems didelės nevaisingumo rizikos pacientams, vyresniems nei 14 metų amžiaus. Du iš jų diagnozuoti prieš pradedant vykdyti tyrimą, o trys didelės rizikos berniukai ir viena mergaitė – tyrimo metu. Iš konsultuotų berniukų keturi priskirti didelei nevaisingumo rizikai, du – mažai. Trims konsultuotiems didelės nevaisingumo rizikos

berniukams diagnozuota normospermija ir atlikta spermos krioprezervacija. Vienam didelės nevaisingumo rizikos berniukui diagnozuota azoospermija, dėl to spermos krioprezervacija neatlikta. Dviem mažai nevaisingumo rizikai priskirtiems berniukams nepavyko surinkti spermos mėginio.



1 pav. Tyrimo schema

Vidutinis tiriamųjų amžius diagnozės metu – 8 metai (nuo 3 mėn. iki 17 m.) (1 lentelė). Vidutinis laikas nuo diagnozės nustatymo datos iki klausimyno pildymo tik gydytojo vaikų onkohematologo informuotų respondentų – 16 mėnesių (nuo 2 dienų iki 60 mėnesių), o konsultuotų vaisingumo specialisto – 3,5 (0,16-11) mėnesio. Dažniausia diagnozė – ūminė limfoblastinė leukemija (ŪLL) (21 iš 61, 34,4 proc.). Daugumai didelės nevaisingumo rizikos respondentų diagnozuoti solidiniai navikai (12 iš 25, 48 proc.). Iš trijų nekonsultuotų didelės rizikos berniukų, diagnozuotų tyrimo metu, dviem diagnozuota Hodžkino limfoma, vienam – sėklidės mišrus germinacinis navikas. Trims iš keturių konsultuotų didelės rizikos berniukų diagnozuoti solidiniai navikai, vienam didelei nevaisingumo rizikai priskirtam berniukui – ūminė mieloblastinė leukemija (ŪML), jis gydytas taikant alogeninę KKLT. Iš viso 11 iš 25 (44 proc.) didelės rizikos respondentų taikyta KKLT.

1 lentelė. Tyrimo dalyvių charakteristika

Charakteristika	**Informuoti gydytojo vaikų onkohematologo (n=55)**			**Konsultuoti vaisingumo specialisto (n=6)**			**Iš viso (n=61)**		
Nevaisingumo rizika	Maža	Didelė	Viso	Maža	Didelė	Viso	Maža	Didelė	Viso
Amžius diagnozės metu (metais) Mediana (min-max, [IKP])	7 (1-17 , [4-10])	6 (0,4-16, [3-13])	7 (0,4-17, [4-11])	15 (17, [14])	17 (15-17, [16-17])	17 (14-17, [15-17])	8 (1-17, [4-11])	7 (0,4-17, [4-14])	8 (0,4-17, [4-14])
Amžius įtraukimo į tyrimą metu (metais) Mediana (min-max, [IKP])	9 (2-18, [6-12])	8 (0,7-18, [5-15])	8 (0,7-18, [7-12])	16 (17, [14])	17 (16-17, [17])	17 (14-17, [16-17])	9 (2-18, [6-12])	9 (0,7-18, [5-15])	9 (0,7-18, [5-15])
Laikas nuo diagnozės iki įtraukimo į tyrimą (mėnesiais) Mediana (min-max, [IKP])	15 (0,6-37, [8-22])	18 (0,07-60, [4-28])	16 (0,07-60, [7-23])	3 (4, [1])	5 (0,16-11, [2-8])	3,5 (0,16-11, [2-6])	14 (0,6-37, [7-21])	12 (0,07-60, ([4-22])	13 (0,06-60, [6-23])
Diagnozė n (proc.)									
Hematologinės ligos	**22 (64,7)**	**9 (42,9)**	**31 (56,4)**	**2 (100)**	**1 (25)**	**3 (50)**	**24 (66,7)**	**10 (40)**	**34 (55,7)**
Ūminė limfoblastinė leukemija	18 (52,9)	3 (14,3)	21 (38,2)	-	-	-	18 (50)	3 (12)	21 (34,4)
Ūminė mieloblastinė leukemija	1 (2,9)	-	1 (1,8)	-	1 (25)	1 (16,7)	1 (2,8)	1 (4)	2 (3,3)
Hodžkino limfoma	1 (2,9)	4 (19)	5 (9,1)	1 (50)	-	1 (16,7)	2 (5,6)	4 (16)	6 (9,8)
Ne Hodžkino limfoma	1 (2,9)	2 (9,5)	3 (5,5)	1 (50)	-	1 (16,7)	2 (5,6)	2 (8)	4 (6,6)
Langerhanso ląstelių histiocitozė	1 (2,9)	-	1 (1,8)	-	-	-	1 (2,8)	-	1 (1,6)
Solidiniai navikai	**9 (26,5)**	**9 (42,9)**	**18 (32,7)**	**-**	**3 (75)**	**3 (50)**	**9 (25)**	**12 (48)**	**21 (34,4)**
Centrinės nervų sistemos navikai	3 (8,8)	3 (14,3)	6 (10,9)	-	-	-	3 (8,3)	3 (12)	6 (9,8)
Neuroblastoma	2 (5,9)	2 (9,5)	4 (7,3)	-	-	-	2 (5,6)	2 (8)	4 (6,6)
Inkstų navikai	4 (11,8)	1 (4,8)	5 (9,1)	-	-	-	4 (11,1)	1 (4)	5 (8,2)
Osteosarkoma	2 (5,9)	-	2 (3,6)	-	-	-	2 (5,6)	-	2 (3,3)

Ewing sarkoma	-	1 (4,8)	1 (1,8)	-	1 (25)	1 (16,7)	-	2 (8)	2 (3,3)
Minkštųjų audinių sarkoma	1 (2,9)	3 (14,3)	4 (7,3)	-	1 (25)	1 (16,7)	1 (2,8)	4 (16)	5 (8,2)
Germinogeninių ląstelių navikai	-	1 (4,8)	1 (1,8)	-	1 (25)	1 (16,7)	-	2 (8)	2 (3,3)
Retinoblastoma	-	1 (4,8)	1 (1,8)	-	-	-	-	1 (4)	1 (1,6)
Iš viso	**34**	**21**	**55**	**2**	**4**	**6**	**36**	**25**	**61**

Paklausus, kokia nevaisingumo rizika kilo po onkologinės ligos gydymo, daugiau nei pusė visų respondentų atsakė, jog nežino (36 iš 61, 59 proc.) (2 lentelė). Palyginus su nevaisingumo rizika, nustatyta darbo autorės taikant tam skirtą metodiką („*triage*“), teisingai savo nevaisingumo riziką įvardino 17 iš 61 (27,9 proc.) visų respondentų. Iš visų didelei nevaisingumo rizikai priskirtų respondentų, vos daugiau nei trečdalis (9 iš 25, 36 proc.) teisingai įvardino savo riziką. Tik trys iš šešių konsultuotų respondentų žinojo savo nevaisingumo riziką.

2 lentelė. Nevaisingumo rizikos vertinimo naudojantis tam skirta metodika („*triage*“) palyginimas su respondentų įvardinta nevaisingumo rizika

Charakteristika	**Informuoti vaikų onkohematologo (n=55)**		**Konsultuoti vaisingumo specialisto (n=6)**	
Nevaisingumo rizika pagal „*triage*“* / **Nevaisingumo rizika pagal respondentus****	Maža	Didelė	Maža	Didelė
Maža	7	2	1	1
Didelė	2	7	-	2
Nežinau	22	12	1	1
Neatsakė	3	-	-	-

* - įvertinta darbo autorės

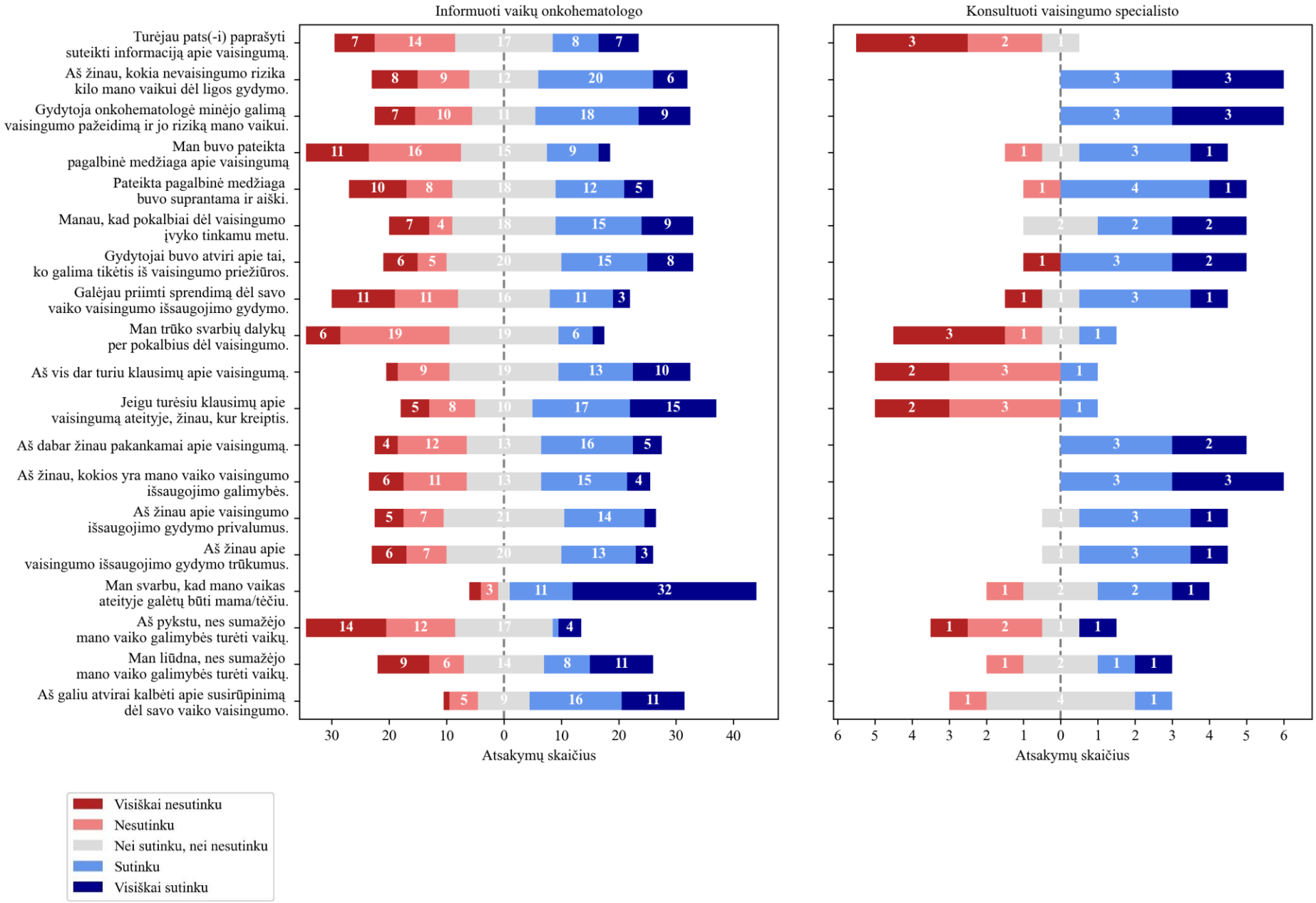
** - pagal 48 tėvus ir 13 vaikų, kurie pildė vaisingumo konsultavimo vertinimo klausimyną

Palyginus atsakymus į vienodus vaisingumo konsultavimo vertinimo klausimynų klausimus tarp specialisto konsultuotų ir informuotų tik gydytojo vaikų onkohematologo respondentų, galima pastebėti, jog konsultuoti respondentai labiau patenkinti vaisingumo priežiūra bei jiems pateikta daugiau informacijos vaisingumo klausimais (2 paveikslas).

Visi konsultuoti berniukai (n=6) sutiko, jog gydytoja onkohematologė minėjo galimą vaisingumo pažeidimą, palyginus su 49,1 proc. (n=27) respondentų, informuotų tik gydytojo vaikų onkohematologo. Visi konsultuoti respondentai manė, jog žino pakankamai apie vaisingumą (palyginus su n=21, 42 proc. nekonsultuotų respondentų) bei žino savo vaisingumo išsaugojimo galimybes (palyginus su n=19, 38,8 proc. nekonsultuotų respondentų). Tik 10 iš 55 (19,2 proc.) nekonsultuotų respondentų buvo pateikta pagalbinė medžiaga apie vaisingumą (palyginus su 4 iš 6 konsultuotųjų). Respondentų atsakymai į visus klausimynų klausimus pateikti 10 ir 11 prieduose.

Kiek daugiau nei pusė (31 iš 61, 50,8 proc.) respondentų pateikė atsakymus į atvirą klausimą „Kaip manote, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?” Dauguma atsakiusiųjų (27 iš 31, 87,1 proc.) teisingai nurodė, jog galimas vaisingumo pažeidimas turėtų būti aptartas prieš

onkologinės ligos gydymą. Keturių (12,9 proc.) (2 – didelės nevaisingumo rizikos, 2 – mažos rizikos) respondentų nuomone, tinkamiausias laikas pokalbiui – baigus gydymą. Daugelis (17 iš 55, 30,9 proc.) nekonsultuotų respondentų teigė, jog pokalbio apie vaisingumą nebuvo.



2 pav. Atsakymų tarp vienodų klausimų pasiskirstymas tarp informuotų apie vaisingumą gydytojo vaikų onkohematologo ir konsultuotų vaisingumo specialisto respondentų

TYRIMO REZULTATŲ APTARIMAS

Didėjant suaugusiųjų, persirgusių onkologine liga vaikystėje, skaičiui, svarbu siekti geros pasveikusiųjų gyvenimo kokybės, kuriai didelę įtaką daro galimybė turėti vaikų. Vaisingumo konsultavimas ir išsaugojimas Lietuvoje naujos temos – Lietuvos Respublikos Pagalbinio apvaisinimo įstatymas priimtas tik 2017 metais [20]. Dėl to metodikos, kuri leistų sistemingai konsultuoti onkologine liga sergančius vaikus vaisingumo klausimais, Lietuvoje iki šiol nebuvo. Palyginimui, vaisingumo priežiūros planas klinikinėje praktikoje PMC (Nyderlandai) taikomas nuo 2019 metų [13]. Planas sudarytas iš penkių žingsnių: 1) visų naujų pacientų identifikavimas; 2) jų nevaisingumo rizikos nustatymas naudojantis tam skirta metodika („*triage*“); 3) pacientų informavimas apie galimą vaisingumo pažeidimą, suteikiamas gydytojo vaikų onkohematologo; 4) vaisingumo specialisto konsultacija; 5) vaisingumo išsaugojimas [13]. Rekomenduojama visus vaisingumo priežiūros plano žingsnius atlikti prieš pradedant onkologinės ligos gydymą [7,12,13].

Vaikų vėžys priskiriamas retų ligų grupei [26]. Kiekvienais metais VULSK onkologinė liga diagnozuojama apie 50-60 vaikų [19]. Siekiant kuo reprezentatyvesnės tiriamųjų imties, tyrime pasiūlyta dalyvauti naujai diagnozuotiems ir anksčiau pradėjusiems gydymą pacientams, gydytiems tyrimo metu. Šiame tyrime respondentų gonadotoksinio pažeidimo rizika įvertinta po vaisingumo konsultavimo klausimynų pildymo (1 paveikslas). Rekomenduojama nustatyti pacientų nevaisingumo riziką prieš pradedant onkologinės ligos gydymą [7,12,27]. Tačiau tam tikrais atvejais, dėl labai spartaus onkologinės ligos progreso, informuoti pacientus apie vaisingumo pažeidimo riziką ir nukreipti konsultacijai prieš pradedant gydymą neįmanoma, nes reikia skubiai gydyti onkologinę ligą [13]. Taip pat pacientams, sergantiems ŪLL, ŪML, ne Hodžkino limfoma bei metastazavusiais solidiniais navikais nevaisingumo rizikos įvertinimą bei vaisingumo išsaugojimą siūloma atidėti iki gydymo šakos priskyrimo arba pasiekus remisiją – dėl potencialios rizikos vėliau autotransplantuoti vėžines ląsteles [28,29]. Pacientams, sergantiems inkstų navikais, rekomenduojama nevaisingumo riziką vertinti po nefrektomijos, kuri, pagal *International Society of Paediatric Oncology Renal Tumour Study Group* gydymo protokolą, taikomą VULSK, atliekama 4–6 savaitės nuo gydymo chemoterapija pradžios [13,30]. Nevaisingumo rizika gali kisti gydymo eigoje pasikeitus gydymo taktikai, dėl to reikalinga dokumentuoti ir koordinuoti vaisingumo priežiūros vykdymą, pakartotinai nustatyti gonadotoksinio pažeidimo riziką, pavyzdžiui, PMC tai atlieka vaisingumo koordinatorė [13].

Tyrimas atskleidė, jog dauguma (84 proc.) didelės nevaisingumo rizikos respondentų nekonsultuoti vaisingumo specialisto (1 paveikslas). Iš dalies tai susiję, kaip minėta aukščiau, su Pagalbinio apvaisinimo įstatymu, tyrimo metu ribojusiu vaisingumo išsaugojimo paslaugas jaunesniems nei 14 metų amžiaus vaikams [20]. Nuo 2022 m. liepos 1 d. priimtos įstatymo pataisos, leidžiančios atlikti vaisingumo išsaugojimą susirgus onkologine liga nepriklausomai nuo vaiko amžiaus [20]. Tikėtina, kad tai prisidės prie augančio pacientų konsultacijų vaisingumo klausimais ir vaisingumo išsaugojimo procedūrų skaičiaus. Antra, pokalbio metu, kuomet pacientas ir jo artimieji informuojami apie onkologinės ligos diagnozę ir numatomą gydymą, pašnekovai patiria didžiulį stresą. Yra žinoma, jog stresą keliančiose situacijose pacientai neįsimena visos gydytojų pateikiamos informacijos, studijų duomenimis, gali būti atsimenama tik iki 20 proc. informacijos [31,32]. Taigi, gydytojams vaikų onkohematologams būtina atkreipti dėmesį, jog, kalbant apie ligos prognozę, derėtų daugiau laiko skirti vaisingumo klausimams aptarti.

Rekomenduojama atlikti vaisingumo išsaugojimą didelės ir mažos nevaisingumo rizikos berniukams, nes spermos krioprezervacija yra neinvazyvus, greitas, pigus metodas, neatitolinantis onkologinės ligos gydymo [33,34]. Spermos krioprezervacija gali būti taikoma lytiškai subrendusiems ir brėstantiems berniukams [35]. Susirgusiems onkologine liga prieš lytinį brendimą berniukams vaisingumo išsaugojimo galimybės ribotos – sėklidės audinio krioprezervacija vis dar laikoma eksperimentine technologija [35]. Šio tyrimo metu vaisingumo išsaugojimas nepasiūlytas trims vyresniems nei 14 metų berniukams, diagnozuotiems pradėjus tyrimą. Vis dėlto, net atlikus šiems pacientams vaisingumo išsaugojimą prieš gydymą, kiltų klausimas dėl tolimesnio lytinių ląstelių panaudojimo – kaip minėta, sergant tam tikromis ligomis išlieka tikimybė išsaugoti ne tik sveikas, bet ir vėžines ląsteles, kas sukeltų riziką palikuonims susirgti onkologine liga [28,29].

Mergaitėms vaisingumo išsaugojimo atlikimas sudėtingesnis nei berniukams – nors kiaušidžių stimuliacija ir kiaušidės audinio išsaugojimas laikomi standartine praktika, tai invazyvūs metodai, reikalaujantys šiek tiek atidėti onkologinės ligos gydymą [12]. Dėl šios priežasties tyrimo metu diagnozuotai didelės nevaisingumo rizikos pacientei nepasiūlytas vaisingumo išsaugojimas. Vis dėlto, nepaisant procedūros sudėtingumo, rekomenduojama informuoti visas pacientes ir jų tėvus, suteikiant galimybę priimti sprendimą [12].

Dažniausios diagnozės tyrimo metu – ŪLL, centrinės nervų sistemos (CNS) navikai ir limfomos (1 lentelė), tai atspindi pasaulinį vaikų vėžio paplitimą [36]. Berniukai dažniau priskirti didelei

nevaisingumo rizikai nei mergaitės. Tai susiję su tuo, jog mažesnė citotoksinių preparatų dozė (CED ≥4000 mg/m^2) sukelia didesnę nevaisingumo riziką berniukams nei mergaitėms (CED ≥6000 mg/m^2) [7,12]. Beveik pusei didelės nevaisingumo rizikos respondentų diagnozuoti solidiniai navikai (n=12, 48 proc.). Daugeliui respondentų taikyta KKLT (n=11, 44 proc.). Įprastai solidiniams navikams gydyti taikomos didesnės citotoksinių preparatų dozės nei hematologinėms ligoms, o kondicionavimas prieš KKLT atliekamas taikant didelių dozių chemoterapiją, kas turi didelę įtaką tolimesniam vaisingumui. Pavyzdžiui, didžiausias priešlaikinio kiaušidžių išsekimo dažnis stebimas tarp neuroblastoma sirgusių suaugusių moterų, palyginus su kitomis onkologinėmis ligomis sirgusiomis moterimis [37]. Mergaitėms, gydytoms KKLT, sutrinka makšties vystymasis, mažėja gimdos tūris [38]. Daugeliui suaugusių vyrų, prieš brendimą gydytų KKLT, diagnozuojama azoospermija [39], didžiausias spermijų sumažėjimo dažnis – CNS navikais sirgusių vyrų grupėje [40]. Vis dėlto, studijų duomenimis, įmanoma pastoti ir išnešioti vaisių net po gydymo didelių dozių chemoterapija ar viso kūno apšvita [41].

Tik 27,9 proc. visų respondentų teisingai įvardino savo nevaisingumo riziką (2 lentelė). Kaip jau minėta aukščiau, stresą keliančiose situacijose atsimenama ne daugiau nei 20 proc. informacijos [31,32]. Tikėtina, jog tarp atsakiusiųjų, jog gydytojas onkohematologas neminėjo gydymo poveikio vaisingumui, yra dalis nepamenančių šios informacijos. Be to, tyrimas parodė, jog tik 19,2 proc. respondentų, informuotų gydytojo onkohematologo, buvo pateikta pagalbinė medžiaga apie vaisingumą (2 paveikslas). Galima daryti prielaidą, jog nepakanka glaustai paminėti vaisingumo pažeidimą greta kitų šalutinių gydymo poveikių. Dėl šios priežasties, siekiant kokybiško informavimo, parengėme informacines skrajutes pacientams, nurodančias nevaisingumo riziką (12 priedas). Jas tikslinga pateikti kiekvienam pacientui. Daugumos respondentų nuomone, vaisingumo pažeidimą derėtų paminėti prieš pradedant gydymą, kas sutampa su rekomendacijomis [7,12]. Vis dėlto, kaip minėta, ne visada tai įmanoma atlikti prieš gydymą [28–30]. Tokiu atveju derėtų pateikti apibendrinančio pobūdžio informaciją apie gonadotoksinį gydymo poveikį.

Nors publikuotos rekomendacijos dėl vaisingumo išsaugojimo susirgus onkologine liga, trūksta vieningos nuomonės, kaip suteikti konsultavimą [42]. Pagal IGHG gaires, konsultuoti vaisingumo klausimais gali gydytojas vaikų onkohematologas, gydytojas endokrinologas, vaisingumo specialistas arba slaugytoja [12]. Šio tyrimo rezultatai atskleidė, jog vaisingumo specialisto konsultuoti respondentai pozityviau vertino pateiktą informaciją bei savo žinias apie vaisingumą nei informuoti tik gydytojo vaikų onkohematologo (2 paveikslas). Paminėtina, jog konsultuoti respondentai įtraukti į tyrimą praėjus mažiau laiko nuo diagnozės nustatymo nei nekonsultuoti respondentai (palyginimui,

vidutiniškai 16 ir 3,5 mėn.) (1 lentelė). Dėl žemo konsultuotų respondentų skaičiaus ir nevienodo laiko tarpo nuo diagnozės nustatymo iki įtraukimo į tyrimą, šiuos rezultatus derėtų interpretuoti rezervuotai.

Tyrimų, nagrinėjančių vaisingumą susirgus onkologine liga, Lietuvoje atlikta nedaug, onkologine liga sergančių vaikų vaisingumo konsultavimo kokybė iki šiol netirta. Lietuvių autorių atlikta literatūros apžvalga apie onkologinės ligos gydymo poveikį mergaičių vaisingumui ir vaisingumo išsaugojimo būdus [43]. Taip pat tirtos tėvų žinios ir požiūris į onkologine liga sergančių mergaičių vaisingumo išsaugojimą, rezultatai parodė, jog žinios nepakankamos [44]. Publikuotas sėkmingas pagalbinio apvaisinimo atvejis moters, kuriai dėl Hodžkino limfomos gydymo paauglystėje išsaugotas vaisingumas atlikus kiaušidžių transpoziciją [45]. Taip pat analizuota onkologine liga sirgusių suaugusių vyrų sperma, nustatyta, jog sergantiems sėklidžių vėžiu vyrams spermatogenezės pažeidimas pasireiškė spermatozoidų koncentracijos mažėjimu, o hematologinių pacientų – judrumo sutrikimais [46]. Mūsų ankstesnis tyrimas parodė, jog Lietuvoje daugelis suaugusiųjų, vaikystėje persirgusių onkologine liga, gavo nepakankamai informacijos apie galimą vaisingumo pažeidimą dėl onkologinės ligos gydymo [18]. Tyrimo rezultatai sutapo su užsienio autorių duomenimis – dauguma išgyvenusiųjų manė, jog jiems nepakanka žinių apie vaisingumą bei jaudinasi dėl to, ar jiems pavyks tapti tėvais [16,17,47]. Tobulėjant vėžio gydymo metodams vaisingumo tema išlieka aktuali, pavyzdžiui, kol kas nėra rekomendacijų dėl vaisingumo išsaugojimo ir nėštumo planavimo taikant CAR T-ląstelių terapiją, nežinoma, kaip šis gydymo būdas veikia vaisingumą [48]. Taip pat trūksta duomenų dėl taikinių terapijos poveikio reprodukcinei sistemai [49].

Kaip vieną šio tyrimo ribotumų galima išskirti mažą konsultuotų respondentų skaičių. Dėl šios priežasties tarp specialisto konsultuotų ir informuotų gydytojo vaikų onkohematologo respondentų grupių atlikta tik aprašomojo pobūdžio palyginamoji analizė, statistinių testų rezultatai, tikėtina, būtų nepatikimi. Dėl mažos imties, siekiant išvengti atsitiktinių radinių, atsakymų į klausimynus rezultatai nepalyginti tarp berniukų ir mergaičių. Į atskiras grupes neišskirti tėvų ir vaikų pildyti klausimynai – kadangi vyresni nei 12 metų vaikai turėjo įstatyminę teisę išreikšti savo nuomonę, vaikų pildytų klausimynų atsakymai laikyti lygiaverčiais pildytiems tėvų. Be to, dėl mažo vaikų, užpildžiusių klausimynus, skaičiaus, būtų netikslinga jų atsakymus lyginti su tėvų atsakymais. Tęsiant tyrimą, derėtų palyginti vaikų ir tėvų atsakymus, norint išsiaiškinti, ar skiriasi konsultavimo kokybės vertinimas tarp šių grupių. Daugiau nei pusė pakviestų dalyvauti tyrime pacientų dalyvauti atsisakė. Tai kelia klausimą dėl atsakymų šališkumo – pavyzdžiui, gali būti, jog nesutikę dalyvauti tyrime pacientai ir jų tėvai konsultavimą vertino geriau nei tyrimo dalyviai. Būtų naudinga palyginti sutikusių ir atsisakiusių

dalyvauti tyrime pacientų charakteristikas, tačiau, nesant informuoto asmens sutikimo, analizuoti atsisakiusiųjų duomenis nebuvo galimybės. Tęsiant tyrimą, atsisakančių dalyvauti pacientų tikslinga paprašyti nurodyti atsisakymo priežastį.

Šis tyrimas – tai pirmasis tokio pobūdžio tyrimas, nagrinėjantis vėžiu sergančių vaikų vaisingumo konsultavimo kokybę VULSK, tyrimo rezultatai bus naudingi tolimesnėms mokslinėms studijoms. Tyrimo rezultatai turi ne tik mokslinę reikšmę nagrinėjant atokiąsias vėžio gydymo išeitis, bet ir svarbūs klinikinėje praktikoje, konsultuojant onkologine liga sergančius vaikus vaisingumo klausimais – gydytojams vaikų onkohematologams, ginekologams, urologams, embriologams. Tyrimas bus tęsiamas, ketinama dokumentuoti kiekvieno paciento vaisingumo priežiūrą, atlikti vaisingumo konsultavimo fakto analizę. Apklausa taikant validuotus vaisingumo konsultavimo vertinimo klausimynus bus tęsiama, planuojama analizuoti vaisingumo priežiūrą pacientų, diagnozuotų po 2022 m. liepos 1 d. Bus palyginta vaisingumo konsultavimo kokybė prieš ir po nevaisingumo rizikos vertinimo metodikos įdiegimo, tikimasi teigiamų pokyčių. Planuojama palyginti berniukų ir mergaičių konsultavimo kokybę, siekiant vienodai efektyvaus konsultavimo tarp lyčių.

IŠVADOS

1. Vaisingumo specialisto konsultuotiems respondentams pateikta daugiau informacijos apie vaisingumą nei informuotiems tik gydytojo vaikų onkohematologo.
2. Taikant metodiką („*triage*“) įvertinta nevaisingumo rizika leido identifikuoti pacientus, kurie turėtų būti nukreipiami vaisingumo specialisto konsultacijai.
3. Dauguma respondentų savo nevaisingumo riziką subjektyviai įvertino neteisingai.

PASIŪLYMAI

1. Pacientų nevaisingumo rizikos vertinimui ir didelės rizikos pacientų identifikavimui siūloma į klinikinę praktiką įdiegti nevaisingumo rizikos vertinimo metodiką („*triage*“).
2. Kokybiškesnės reprodukcinės sveikatos priežiūros užtikrinimui kiekvienam pacientui rekomenduojama pateikti informacines skrajutes apie nevaisingumo riziką.

Atliekant šį tyrimą parengtos ir atspausdintos mokslinės publikacijos:
(Informacija pateikta iš eLABa)

1. **Stukaitė-Ruibienė, Eglė**; Jurkonis, Mantas; Adomaitis, Robertas; Bumbulienė, Žana; Gudlevičienė, Živilė; Verkauskas, Gilvydas; Žagminas, Kęstutis; Vaičiūnienė, Rasa; Rascon, Jelena. A crosscut survey on reproductive health in Lithuanian childhood cancer survivors // Ginekologia polska. Gdańsk : Via Medica. ISSN 0017-0011. eISSN 2543-6767. 2021, vol. 92, no. 4, p. 262-270. DOI: 10.5603/GP.a2021.0027. [DB: Science Citation Index Expanded (Web of Science), Index Copernicus] [IF: 1.216; AIF: 3.486; Q4 (2021 InCities JCR SCIE)van der Perk, M. E. Madeleine;
2. **Stukaitė-Ruibienė, Eglė**; Bumbulienė, Žana; Vaitkevičienė, Goda Elizabeta; Bos, Annelies M. E.; van den Heuvel-Eibrink, Marry M.; Rascon, Jelena. Development of a questionnaire to evaluate female fertility care in pediatric oncology, a TREL initiative // BMC cancer. London : BioMed Central Ltd. eISSN 1471-2407. 2022, vol. 22, art. no. 450, p. [1-6]. DOI: 10.1186/s12885-022-09450-2. [DB: MEDLINE, Scopus, Science Citation Index Expanded (Web of Science)]
3. **Stukaitė-Ruibienė, Eglė**; van der Perk, M.E.M.; Bumbulienė, Žana; Vaitkevičienė, Goda Elizabeta; van den Heuvel-Eibrink, M.M.; Rascon, Jelena. Evaluation of the quality of fertility counseling in childhood cancer patients // NOPHO 39th annual meeting: Together towards individually targeted treatment, 6.-7. and 9.-10.5.2022, virtual, Kuopio, Finland : program and abstracts. Kuopio. 2022, p. 63.
4. **Stukaitė-Ruibienė, Eglė**; van der Perk, M.E.M.; Bumbulienė, Žana; Vaitkevičienė, Goda Elizabeta; van den Heuvel-Eibrink, M.M.; Rascon, Jelena. Implementation of the infertility risk triage and perception of the quality of fertility counseling in childhood cancer patients // 5th Baltic Paediatric Congress & 23rd Estonian Paediatric Association Congress, 2-4 June 2022, Tallinn, Estonia : programme and abstract book. Tallinn. 2022, p. 71-72.
5. **Stukaitė-Ruibienė, Eglė**; van der Perk, M.E.M.; Vaitkevičienė, Goda Elizabeta; Bumbulienė, Žana; van den Heuvel-Eibrink, M.M.; Rascon, Jelena. Assessment of fertility care in childhood cancer patients // Acta medica Lituanica. Vilnius : Vilniaus universiteto leidykla. ISSN 1392-0138. eISSN 2029-4174. 2022, vol. 29, no. 2, suppl. p. 15. DOI: 10.15388/Amed.Supp.2022.292.2. [DB: Dimensions, PubMed]

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PRIEDAI

1 priedas. Vaisingumo konsultavimo vertinimo klausimynas pacientų tėvams, informuotiems apie vaisingumą gydytojo vaikų onkohematologo

TREL Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania

Ver. 3.0 2021-06-18

Vilniaus universiteto ligoninėje Santaros klinikose vyksta Horizon 2020 „Mokslinių tyrimų ir švietimo bendradarbiavimo projektas, siekiant pagerinti vaikų, sergančių piktybiniais navikais, išgyvenamumą Lietuvoje (TREL) Nr.952438". Projekto tikslas – pagerinti vaikų, sergančių onkologinėmis ligomis išgyvenamumą ir gyvenimo kokybę pasveikus.

Pasveikus nuo onkologinės ligos gali nukentėti vaisingumas – t .y. galimybė susilaukti vaikų. Vienas iš projekto tikslų – įvertinti, ar pacientų tėvai/globėjai ir patys pacientai tinkamai informuojami apie nevaisingumo riziką.

Prieš kurį laiką Jūsų vaikui buvo diagnozuota onkologinė liga. Prašytume pasidalinti savo patirtimi užpildant šį klausimyną, siekiant pagerinti konsultavimo dėl vaisingumo kokybę.

Aš esu: (pažymėkite [x])

Vaiko mama ☐ Vaiko tėtis ☐

Auginu:

Mergaitę ☐ Berniuką ☐

Jūsų vaiko nevaisingumo rizika po onkologinės ligos gydymo:

Maža ☐ Didelė ☐ Nežinau ☐

Žemiau esantys teiginiai apibūdina konsultaciją dėl Jūsų vaiko vaisingumo. Pasirinkite vieną variantą prie kiekvieno teiginio. Nurodykite, kaip stipriai sutinkate su pateiktu teiginiu, apibraukdami skaičių prie atsakymo (1- visiškai nesutinku, 5 – visiškai sutinku).

Bendri klausimai

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
1	Aš žinau, kad nuo onkologinės ligos pasveiksta 80 proc. vaikų.	1	2	3	4	5
2	Aš žinau, kad onkologinės ligos gydymas gali pakenkti mano vaiko vaisingumui – t. y. galimybei susilaukti vaikų baigus gydymą.	1	2	3	4	5
3	Turėjau galimybę aptarti vaisingumo klausimus su medicinos personalu (gydytojais, slaugytojomis, psichologe).	1	2	3	4	5
4	Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.	1	2	3	4	5
5	Informaciją apie vaisingumą gavau ne iš medikų (interneto, bendraujant su kitais tėvais ir pan.).	1	2	3	4	5
6	Aš žinau, kokia nevaisingumo rizika kilo mano vaikui dėl ligos gydymo.	1	2	3	4	5

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Klausimai, susiję su pokalbiu su gydytoja onkohematologe

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
7	Gydytoja onkohematologė minėjo galimą vaisingumo pažeidimą ir jo riziką mano vaikui.	1	2	3	4	5
8	Pokalbių metu pateikta informacija apie vaisingumą buvo suprantama ir aiški.	1	2	3	4	5
9	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
10	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5
11	Galėjau įsiterpti ir išsakyti savo nuomonę pokalbių dėl vaisingumo metu.	1	2	3	4	5
12	Manau, kad pokalbiai dėl vaisingumo įvyko tinkamu metu.	1	2	3	4	5
13	Manau, kad pokalbiai dėl vaisingumo įvyko tinkamoje aplinkoje.	1	2	3	4	5
14	Manau, kad gydytojai apie vaisingumą kalbėjo tinkamu tonu.	1	2	3	4	5
15	Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.	1	2	3	4	5
16	Galėjau priimti sprendimą dėl savo vaiko vaisingumo išsaugojimo gydymo.	1	2	3	4	5
17	Man trūko svarbių dalykų per pokalbius dėl vaisingumo.	1	2	3	4	5
18	Aš vis dar turiu klausimų apie vaisingumą.	1	2	3	4	5
19	Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.	1	2	3	4	5

Klausimai po pokalbio apie vaisingumą

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
20	Aš dabar žinau pakankamai apie vaisingumą.	1	2	3	4	5
21	Aš žinau, kokios yra mano vaiko vaisingumo išsaugojimo galimybės.	1	2	3	4	5
22	Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.	1	2	3	4	5
23	Aš žinau apie vaisingumo išsaugojimo gydymo trūkumus.	1	2	3	4	5
24	Man svarbu, kad mano vaikas ateityje galėtų būti mama/tėčiu.	1	2	3	4	5
25	Aš pykstu, nes sumažėjo mano vaiko galimybės turėti vaikų.	1	2	3	4	5
26	Man liūdna, nes sumažėjo mano vaiko galimybės turėti vaikų.	1	2	3	4	5
27	Aš galiu atvirai kalbėti apie susirūpinimą dėl savo vaiko vaisingumo.	1	2	3	4	5

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Ar yra dalykų, kurių jums trūko per pokalbius ar konsultacijas dėl vaisingumo?

Kaip manote, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

Kaip manote, kas praėjo gerai per Jūsų vaiko vaisingumo priežiūrą?

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Ar turite kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

Ačiū už skirtą laiką!

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2 priedas. Vaisingumo konsultavimo vertinimo klausimynas vaikams, informuotiems apie vaisingumą gydytojo vaikų onkohematologo

TREL

Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania

Ver. 3.0 2021-06-18

Vilniaus universiteto ligoninėje Santaros klinikose vyksta Horizon 2020 „Mokslinių tyrimų ir švietimo bendradarbiavimo projektas, siekiant pagerinti vaikų, sergančių piktybiniais navikais, išgyvenamumą Lietuvoje (TREL) Nr.952438". Projekto tikslas – pagerinti vaikų, sergančių onkologinėmis ligomis išgyvenamumą ir gyvenimo kokybę pasveikus.

Pasveikus nuo onkologinės ligos gali nukentėti vaisingumas – t .y. galimybė susilaukti vaikų. Vienas iš projekto tikslų – įvertinti, ar pacientų tėvai/globėjai ir patys pacientai tinkamai informuojami apie nevaisingumo riziką.

Prieš kurį laiką Tau buvo diagnozuota onkologinė liga. Prašytume pasidalinti savo patirtimi užpildant šį klausimyną, siekiant pagerinti konsultavimo dėl vaisingumo kokybę.

Aš esu: (pažymėk [X])

Mergaitė ☐ Berniukas ☐

Tavo nevaisingumo rizika po onkologinės ligos gydymo:

Maža ☐ Didelė ☐ Nežinau ☐

Žemiau esantys teiginiai apibūdina konsultaciją dėl Tavo vaisingumo. Pasirink vieną variantą prie kiekvieno teiginio. Nurodyk, kaip stipriai sutinki su pateiktu teiginiu, apibraukiant skaičių prie atsakymo (1- visiškai nesutinku, 5 – visiškai sutinku).

Bendri klausimai

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
1	Aš žinau, kad nuo onkologinės ligos pasveiksta 80 proc. vaikų.	1	2	3	4	5
2	Aš žinau, kad onkologinės ligos gydymas gali pakenkti mano vaisingumui – t. y. galimybei susilaukti vaikų baigus gydymą.	1	2	3	4	5
3	Turėjau galimybę aptarti vaisingumo klausimus su medicinos personalu (gydytojais, slaugytojomis, psichologe).	1	2	3	4	5
4	Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.	1	2	3	4	5
5	Informaciją apie vaisingumą gavau ne iš medikų (interneto, bendraujant su kitais vaikais ir pan.).	1	2	3	4	5
6	Aš žinau, kokia nevaisingumo rizika man kilo dėl ligos gydymo.	1	2	3	4	5

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Klausimai, susiję su pokalbiu su gydytoja onkohematologe

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
7	Gydytoja onkohematologė minėjo galimą vaisingumo pažeidimą ir jo riziką.	1	2	3	4	5
8	Pokalbių metu pateikta informacija apie vaisingumą buvo suprantama ir aiški.	1	2	3	4	5
9	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
10	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5
11	Galėjau įsiterpti ir išsakyti savo nuomonę pokalbių dėl vaisingumo metu.	1	2	3	4	5
12	Manau, kad pokalbiai dėl vaisingumo įvyko tinkamu metu.	1	2	3	4	5
13	Manau, kad pokalbiai dėl vaisingumo įvyko tinkamoje aplinkoje.	1	2	3	4	5
14	Manau, kad gydytojai apie vaisingumą kalbėjo tinkamu tonu.	1	2	3	4	5
15	Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.	1	2	3	4	5
16	Galėjau priimti sprendimą dėl savo vaisingumo išsaugojimo gydymo.	1	2	3	4	5
17	Man trūko svarbių dalykų per pokalbius dėl vaisingumo.	1	2	3	4	5
18	Aš vis dar turiu klausimų apie vaisingumą.	1	2	3	4	5
19	Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.	1	2	3	4	5

Klausimai po pokalbio apie vaisingumą

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
20	Aš dabar žinau pakankamai apie vaisingumą.	1	2	3	4	5
21	Aš žinau, kokios yra mano vaisingumo išsaugojimo galimybės.	1	2	3	4	5
22	Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.	1	2	3	4	5
23	Aš žinau apie vaisingumo išsaugojimo gydymo trūkumus.	1	2	3	4	5
24	Man svarbu, kad ateityje galėčiau būti mama/tėčiu.	1	2	3	4	5
25	Aš pykstu, nes sumažėjo mano galimybės turėti vaikų	1	2	3	4	5
26	Man liūdna, nes sumažėjo mano galimybės turėti vaikų	1	2	3	4	5
27	Aš galiu atvirai kalbėti apie susirūpinimą dėl savo vaisingumo.	1	2	3	4	5

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Ar yra dalykų, kurių Tau trūko per pokalbius ar konsultacijas dėl vaisingumo?

Kaip manai, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

Kaip manai, kas praėjo gerai per Tavo vaisingumo priežiūrą?

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Ar turi kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

Ačiū už skirtą laiką!

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

3 priedas. Vaisingumo konsultavimo vertinimo klausimynas pacientų tėvams, konsultuotiems vaisingumo specialisto

Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania

TREL

Versija 3.0 2021-06-14

Vilniaus universiteto ligoninėje Santaros klinikose vyksta Horizon 2020 „Mokslinių tyrimų ir švietimo bendradarbiavimo projektas, siekiant pagerinti vaikų, sergančių piktybiniais navikais, išgyvenamumą Lietuvoje (TREL) Nr.952438". Projekto tikslas – pagerinti vaikų, sergančių onkologinėmis ligomis išgyvenamumą ir gyvenimo kokybę pasveikus.

Pasveikus nuo onkologinės ligos gali nukentėti vaisingumas – t .y. galimybė susilaukti vaikų. Vienas iš projekto tikslų – įvertinti, ar pacientų tėvai/globėjai ir patys pacientai tinkamai informuojami apie nevaisingumo riziką.

Prieš kurį laiką Jūsų vaikui buvo diagnozuota onkologinė liga. Prašytume pasidalinti savo patirtimi užpildant šį klausimyną, siekiant pagerinti konsultavimo dėl vaisingumo kokybę.

Aš esu: (pažymėkite [x])

Vaiko mama ☐ Vaiko tėtis ☐

Auginu:

Mergaitę ☐ Berniuką ☐

Jūsų vaiko nevaisingumo rizika po onkologinės ligos gydymo:

Maža ☐ Didelė ☐ Nežinau ☐

Žemiau esantys teiginiai apibūdina konsultaciją dėl Jūsų vaiko vaisingumo. Pasirinkite vieną variantą prie kiekvieno teiginio. Nurodykite, kaip stipriai sutinkate su pateiktu teiginiu, apibraukdami skaičių prie atsakymo (1- visiškai nesutinku, 5 – visiškai sutinku).

Bendri klausimai:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
1	Mūsų gydytoja paminėjo vaisingumą pirmoje konsultacijoje, kai buvo aptarta mano vaiko diagnozė.	1	2	3	4	5
2	Kai sužinojau apie diagnozę ir gydymą, susirūpinau dėl savo vaiko vaisingumo.	1	2	3	4	5
3	Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.	1	2	3	4	5

Klausimai, susiję su pokalbiu su gydytoja vaikų onkohematologe:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
4	Jaučiau, kad tuo metu buvo svarbu gauti informaciją apie vaisingumą.	1	2	3	4	5
5	Manau, kad pokalbis apie vaisingumą įvyko tinkamu metu.	1	2	3	4	5

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6	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
7	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5
8	Informacija apie nevaisingumą man buvo suprantama.	1	2	3	4	5
9	Man trūko svarbių dalykų per pokalbį dėl vaisingumo.	1	2	3	4	5

Klausimai, susiję su ginekologo/urologo/embriologo konsultacija:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
10	Manau, kad konsultacija įvyko tinkamu metu.	1	2	3	4	5
11	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
12	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5
13	Aš žinau, kokia yra nevaisingumo rizika mano vaikui pasibaigus gydymui.	1	2	3	4	5
14	Man buvo papasakota, kokie yra galimi būdai vaisingumo išsaugojimui.	1	2	3	4	5
15	Buvo aptarti vaisingumo išsaugojimo gydymo privalumai.	1	2	3	4	5
16	Buvo aptarti vaisingumo išsaugojimo gydymo trūkumai.	1	2	3	4	5
17	Aš galėjau spręsti dėl savo vaiko vaisingumo ateityje.	1	2	3	4	5
18	Informacija apie nevaisingumą man buvo suprantama.	1	2	3	4	5
19	Man buvo išaiškintos mano vaiko vaisingumo išsaugojimo gydymo galimybės.	1	2	3	4	5
20	Išaiškinimas apie vaisingumo išsaugojimo gydymo galimybes buvo suprantamas.	1	2	3	4	5
21	Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.	1	2	3	4	5
22	Man trūko svarbių dalykų per konsultaciją dėl vaisingumo.	1	2	3	4	5
23	Po konsultacijos vis dar turiu klausimų apie vaisingumą.	1	2	3	4	5
24	Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.	1	2	3	4	5
25	Galėjau priimti sprendimą dėl savo vaiko vaisingumo išsaugojimo gydymo.	1	2	3	4	5
26	Galėjau rinktis be spaudimo ar kitų daromos įtakos.	1	2	3	4	5

Klausimai, susiję su abiem pokalbiais dėl vaisingumo:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku

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27	Aš esu gerai informuotas(-a) apie vaisingumą.	1	2	3	4	5
28	Aš dabar žinau pakankamai apie vaisingumą.	1	2	3	4	5
29	Aš žinau, kokia mano vaiko nevaisingumo rizika dėl gydymo.	1	2	3	4	5
30	Aš žinau, kokios yra mano vaiko vaisingumo išsaugojimo galimybės.	1	2	3	4	5
31	Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.	1	2	3	4	5
32	Aš žinau apie vaisingumo išsaugojimo gydymo trūkumus.	1	2	3	4	5
33	Aš pykstu, nes sumažėjo mano vaiko galimybės turėti vaikų.	1	2	3	4	5
34	Man svarbu, kad mano vaikas ateityje galėtų būti mama/tėčiu.	1	2	3	4	5
35	Aš galiu atvirai kalbėti apie savo susirūpinimą dėl savo vaiko vaisingumo.	1	2	3	4	5
36	Man liūdna, nes sumažėjo mano vaiko galimybės turėti vaikų.	1	2	3	4	5
37	Aš priėmiau teisingą sprendimą dėl vaisingumo išsaugojimo.	1	2	3	4	5
38	Aš gailiuosi priimo sprendimo.	1	2	3	4	5
39	Dabar aš priimčiau kitokį sprendimą.	1	2	3	4	5

Ar yra dalykų, kurių jums trūko per pirmą pokalbį ar konsultaciją dėl vaisingumo?

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Kaip manote, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

Kaip manote, kas praėjo gerai per Jūsų vaiko vaisingumo priežiūrą?

Ar turite kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

Ačiū už skirtą laiką!

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

4 priedas. Vaisingumo konsultavimo vertinimo klausimynas vaikams, konsultuotiems vaisingumo specialisto

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Pasveikus nuo onkologinės ligos gali nukentėti vaisingumas – t .y. galimybė susilaukti vaikų. Vienas iš projekto tikslų – įvertinti, ar pacientų tėvai/globėjai ir patys pacientai tinkamai informuojami apie nevaisingumo riziką.

Prieš kurį laiką Tau buvo diagnozuota onkologinė liga. Prašytume pasidalinti savo patirtimi užpildant šį klausimyną, siekiant pagerinti konsultavimo dėl vaisingumo kokybę.

Aš esu: (pažymėk ☒)

Mergaitė ☐ Berniukas ☐

Tavo nevaisingumo rizika po onkologinės ligos gydymo:

Maža ☐ Didelė ☐ Nežinau ☐

Žemiau esantys teiginiai apibūdina konsultaciją dėl Tavo vaisingumo. Pasirink vieną variantą prie kiekvieno teiginio. Nurodyk, kaip stipriai sutinki su pateiktu teiginiu, apibraukiant skaičių prie atsakymo (1- visiškai nesutinku, 5 – visiškai sutinku).

Bendri klausimai:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
1	Mano gydytoja paminėjo vaisingumą pirmoje konsultacijoje, kai buvo aptarta mano diagnozė.	1	2	3	4	5
2	Kai sužinojau apie diagnozę ir gydymą, susirūpinau dėl savo vaisingumo.	1	2	3	4	5
3	Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.	1	2	3	4	5

Klausimai, susiję su pokalbiu su gydytoja vaikų onkohematologe:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
4	Jaučiau, kad tuo metu buvo svarbu gauti informaciją apie vaisingumą.	1	2	3	4	5
5	Manau, kad pokalbis apie vaisingumą įvyko tinkamu metu.	1	2	3	4	5
6	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
7	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5

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8	Informacija apie nevaisingumą man buvo suprantama.	1	2	3	4	5
9	Man trūko svarbių dalykų per pokalbį dėl vaisingumo.	1	2	3	4	5

Klausimai, susiję su ginekologo/urologo/embriologo konsultacija:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
10	Manau, kad konsultacija įvyko tinkamu metu.	1	2	3	4	5
11	Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)	1	2	3	4	5
12	Pateikta pagalbinė medžiaga buvo suprantama ir aiški.	1	2	3	4	5
13	Aš žinau, kokia yra mano nevaisingumo rizika pasibaigus gydymui.	1	2	3	4	5
14	Man buvo papasakota, kokie yra galimi būdai vaisingumo išsaugojimui.	1	2	3	4	5
15	Buvo aptarti vaisingumo išsaugojimo gydymo privalumai.	1	2	3	4	5
16	Buvo aptarti vaisingumo išsaugojimo gydymo trūkumai.	1	2	3	4	5
17	Aš galėjau spręsti dėl savo vaisingumo ateityje.	1	2	3	4	5
18	Informacija apie nevaisingumą man buvo suprantama.	1	2	3	4	5
19	Man buvo išaiškintos mano vaisingumo išsaugojimo gydymo galimybės.	1	2	3	4	5
20	Išaiškinimas apie vaisingumo išsaugojimo gydymo galimybes buvo suprantamas.	1	2	3	4	5
21	Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.	1	2	3	4	5
22	Man trūko svarbių dalykų per konsultaciją dėl vaisingumo.	1	2	3	4	5
23	Po konsultacijos vis dar turiu klausimų apie vaisingumą.	1	2	3	4	5
24	Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.	1	2	3	4	5
25	Galėjau priimti sprendimą dėl savo vaisingumo išsaugojimo gydymo.	1	2	3	4	5
26	Galėjau rinktis be spaudimo ar kitų daromos įtakos.	1	2	3	4	5

Klausimai, susiję su abiem pokalbiais dėl vaisingumo:

		Visiškai nesutinku	Nesutinku	Nei sutinku, nei nesutinku	Sutinku	Visiškai sutinku
27	Aš esu gerai informuotas(-a) apie vaisingumą.	1	2	3	4	5
28	Aš dabar žinau pakankamai apie vaisingumą.	1	2	3	4	5
29	Aš žinau, kokia mano nevaisingumo rizika dėl gydymo.	1	2	3	4	5

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30	Aš žinau, kokios yra mano vaisingumo išsaugojimo galimybės.	1	2	3	4	5
31	Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.	1	2	3	4	5
32	Aš žinau apie vaisingumo išsaugojimo gydymo trūkumus.	1	2	3	4	5
33	Aš pykstu, nes sumažėjo mano galimybės turėti vaikų.	1	2	3	4	5
34	Man svarbu, kad ateityje galėčiau būti mama/tėčiu.	1	2	3	4	5
35	Aš galiu atvirai kalbėti apie susirūpinimą dėl savo vaisingumo.	1	2	3	4	5
36	Man liūdna, nes sumažėjo mano galimybės turėti vaikų.	1	2	3	4	5
37	Aš priėmiau teisingą sprendimą dėl vaisingumo išsaugojimo.	1	2	3	4	5
38	Aš gailiuosi priimo sprendimo.	1	2	3	4	5
39	Dabar aš priimčiau kitokį sprendimą.	1	2	3	4	5

Ar yra dalykų, kurių Tau trūko per pirmą pokalbį ar konsultaciją dėl vaisingumo?

Kaip manai, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

Kaip manai, kas praėjo gerai per Tavo vaisingumo priežiūrą?

Ar turi kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

Ačiū už skirtą laiką!

This project has received funding from the European Union's Horizon 2020 – Work Programme on Spreading Excellence and Widening Participation under grant agreement No 952438. "

5 priedas. Klausimynų vaisingumo specialisto konsultuotiems pacientams sandara *Princess Máxima Center* (PMC) ir Vilniaus Universiteto Ligoninėje Santaros Klinikose (VULSK)

1 dalis. Bendri klausimai

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**PMC klausimynas (anglų kaba)**	**PMC klausimynas (olandų kalba)**	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
Naujas klausimas	My doctor had mentioned fertility at the first consult when the diagnosis of my child was discussed.	1 De behandelaar van mijn kind had vruchtbaarheid bij het eerste gesprek toen de diagnose werd verteld al benoemd.	My doctor had mentioned fertility at the first consult when the diagnosis of my child was discussed.	1 Mūsų gydytoja paminėjo vaisingumą pirmoje konsultacijoje, kai buvo aptarta mano vaiko diagnozė.
Ik maak me zorgen of ik wel kinderen kan krijgen. (ENG Q not published) (RCS-NL VBS: 1) (1)	When I heard the diagnosis and treatment I was worried about my child's fertility.	2 Toen ik de diagnose en behandeling hoorde, maakte ik mij zorgen om vruchtbaarheid van mijn kind.	When I heard the diagnosis and treatment I was worried about my child's fertility.	2 Kai sužinojau apie diagnozę ir gydymą, susirūpinau dėl savo vaiko vaisingumo.
Naujas klausimas	I had to ask for information about fertility myself.	3 Ik heb zelf om informatie over vruchtbaarheid moeten vragen.	I had to ask for information about fertility myself.	3 Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.

2 dalis. Klausimai, susiję su pokalbiu su gydytoja vaikų onkohematologe

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**PMC klausimynas (anglų kalba)**	**PMC klausimynas (olandų kalba)**	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
Naujas klausimas	I felt it was important at that time to receive the information about fertility.	4 Ik vond het belangrijk op dat moment de informatie over vruchtbaarheid te horen.	I felt it was important at that time to receive the information about fertility.	4 Jaučiau, kad tuo metu buvo svarbu gauti informaciją apie vaisingumą.
Naujas klausimas	I thought that the moment this was discussed was a good one.	5 Ik vond het moment dat dit besproken werd een goed moment.	I thought that the moment this was discussed was a good one.	5 Manau, kad pokalbis apie vaisingumą įvyko tinkamu metu.
Did you also receive written information apart from verbal information? (PCQ: 3) (2)	-	-	I received supportive material on fertility (leaflets, books, website links etc.)	6 Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)
Did you also receive written information apart from verbal information? (PCQ: 3) (2) Was the information about the investigations you would undergo comprehensive? (PCQ: 5) (2)	I thought the supporting material used during the explanation was clarifying.	6 Ik vond het ondersteunende materiaal dat tijdens de uitleg gebruikt werd verduidelijkend.	I thought the supporting material used during the explanation was clarifying.	7 Pateikta pagalbinė medžiaga buvo suprantama ir aiški.
Was the information about the investigations you would undergo comprehensive? (PCQ: 5) (2)	The information about infertility was comprehensive and clear.	7 De uitleg over onvruchtbaarheid was duidelijk.	The information about infertility was comprehensive and clear.	8 Informacija apie nevaisingumą man buvo suprantama.

Did you miss any instructions from a nurse? If so, when? (PCQ: 12) (2)	I missed important things during the conversation.	8 Ik heb belangrijke dingen gemist tijdens het gesprek.	I missed important things during the conversation.	9 Man trūko svarbių dalykų per pokalbį dėl vaisingumo.

3 dalis. Klausimai, susiję su ginekologo/urologo/embriologo konsultacija

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**PMC klausimynas (anglų kalba)**	**PMC klausimynas (olandų kalba)**	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
Naujas klausimas	I think the moment of fertility counseling was a good one.	9 Ik vond het moment van counseling een goed moment.	I think the moment of fertility counseling was a good one.	10 Manau, kad konsultacija įvyko tinkamu metu.
Did you also receive written information apart from verbal information? (PCQ: 3) (2)	-	-	I received supportive material on fertility (leaflets, books, website links etc.)	11 Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)
Was the information about the investigations you would undergo comprehensive? (PCQ: 5) (2)	I thought the supporting material used during the explanation was clarifying.	10 Ik vond het ondersteunende materiaal dat tijdens de uitleg gebruikt werd verduidelijkend.	I thought the supporting material used during the explanation was clarifying.	12 Pateikta pagalbinė medžiaga buvo suprantama ir aiški.
Naujas klausimas	I know the risk of infertility after treatment.	11 Ik weet wat het risico voor mijn kind is op onvruchtbaarheid door de behandeling.	I know the risk of infertility after treatment.	13 Aš žinau, kokia yra nevaisingumo rizika mano vaikui pasibaigus gydymui.
Were different treatment options discussed with you? (PCQ: 6) (2)	I was told what treatment options are available to maintain fertility.	12 Mij werd verteld welke mogelijkheden er zijn om vruchtbaarheid van mijn kind te behouden.	I was told what treatment options are available to maintain fertility.	14 Man buvo papasakota, kokie yra galimi būdai vaisingumo išsaugojimui.

Were you informed of any possible side-effects of the medication prescribed to you? (PCS: 9) (2) I know the benefits of each option(DCS: 2) (3)	The benefits of fertility preservation treatments` were discussed.	13 De voordelen van vruchtbaarheidsbehoudende behandelingen zijn besproken.	The benefits of fertility preservation treatments were discussed	15 Buvo aptarti vaisingumo išsaugojimo gydymo privalumai.
I know the risks and side effects of each option. DCS 3. (3)	The disadvantages of fertility preservation treatments were discussed.	14 De nadelen van vruchtbaarheidsbehoudende behandelingen zijn besproken.	The disadvantages of fertility preservation treatments were discussed.	16 Buvo aptarti vaisingumo išsaugojimo gydymo trūkumai.
Ik heb controle gehad over mijn toekomstige vruchtbaarheid. (ENG Q not published) (RCS-NL VBS: 9) (1)	I had control over my child's future fertility.	15 Ik heb controle gehad over de toekomstige vruchtbaarheid van mijn kind.	I had control over my child's future fertility	17 Aš galėjau spręsti dėl savo vaiko vaisingumo ateityje.
Was the information about the investigations you would undergo comprehensive? (PCQ: 5) (2)	The information about infertility was comprehensive.	16 De uitleg over onvruchtbaarheid was duidelijk.	The information about infertility was comprehensive.	18 Informacija apie nevaisingumą man buvo suprantama.
Were different treatment options discussed with you? (PCQ: 6) (2)	The different treatment options were discussed with me.	17 Ik heb uitleg gekregen over de behandelmogelijkheden.	The different treatment options were discussed with me.	19 Man buvo išaiškintos mano vaiko vaisingumo išsaugojimo gydymo galimybės.
Was the information about the treatment you would receive comprehensive? (PCQ: 7) (2)	The information about the treatment options was comprehensive.	18 De uitleg over de behandelmogelijkheden was duidelijk.	The information about the treatment options was comprehensive.	20 Išaiškinimas apie vaisingumo išsaugojimo gydymo galimybes buvo suprantamas.
Were caregivers honest and clear about what to expect from the fertility care service? (PCQ: 14) (2)	My caregivers were honest and clear about what we could expect from the care.	19 Mijn behandelaars waren eerlijk en duidelijk over wat ik kon verwachten van de zorg.	My caregivers were honest and clear about what we could expect from the care.	21 Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.

Did you miss any instructions from anurse? If so, when? (PCQ: 12) (2)	I missed important things during thecounseling.	20 Ik heb belangrijke dingen gemist tijdens het gesprek.	I missed important things during thecounseling	22 Man trūko svarbių dalykų perkonsultaciją dėl vaisingumo.
Naujas klausimas	I still have questions about fertilityafter the counseling.	21 Ik heb na dit gesprek nog steeds vragen over vruchtbaarheid.	I still have questions about fertilityafter the counseling.	23 Po konsultacijos vis dar turiu klausimų apie vaisingumą.
Naujas klausimas	If I have questions about fertility in the future, I know how to request another counseling.	22 Als ik in de toekomst vragen heb over vruchtbaarheid van mijn kind, weet ik hoe ik opnieuw een gesprek kan aanvragen.	If I have questions about fertility in the future, I know how to request another counseling.	24 Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.
Was decision-making shared withyou, if you preferred? (PCQ: 23) (2)	Decision-making was shared with me,concerning my daughters treatment.	23 Er was ruimte om mee te beslissenover mijn dochters behandeling.	Decision-making was shared with me,concerning my child's treatment	25 Galėjau priimti sprendimą dėl savovaiko vaisingumo išsaugojimo gydymo.
I am choosing without pressure fromothers (DCS: 8) (3)	I am choosing without pressure fromothers	24 Ik heb kunnen kiezen zonder drukof beïnvloeding van anderen.	I am choosing without pressure fromothers	26 Galėjau rinktis be spaudimo ar kitųdaromos įtakos.

4 dalis. Klausimai, susiję su abiem pokalbiais dėl vaisingumo

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**PMC klausimynas (anglų kalba)**	**PMC klausimynas (olandų kalba)**	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
I have enough advice to make achoice. (DCS: 9) (3)	I am well informed about fertility.	25 Ik ben goed geïnformeerd over vruchtbaarheid van mijn kind.	I am well informed about fertility.	27 Aš esu gerai informuotas(-a) apie vaisingumą.
I have enough advice to make achoice. (DCS: 9) (3)	I now know enough about women'sfertility.	26 Ik weet nu voldoende overvruchtbaarheid van de vrouw.	I now know enough about fertility.	28 Aš dabar žinau pakankamai apie vaisingumą.

Naujas klausimas	I know the risk of infertility from mychild's treatment.	27 Ik weet wat het risico voor mijn kind is op onvruchtbaarheid door de behandeling.	I know the risk of infertility from mychild's treatment.	29 Aš žinau, kokia mano vaikonevaisingumo rizika dėl gydymo.
I know which options are available tome (DCS: 1) (3)	I know which options are available tomaintain my child's fertility.	28 Ik weet wat de mogelijkheden zijn om de vruchtbaarheid van mijn kind te behouden.	I know which options are available tomaintain my child's fertility	30 Aš žinau, kokios yra mano vaikovaisingumo išsaugojimo galimybės.
I know the benefits of each option(DCS: 2) (3)	I know the benefits of fertilitypreservation treatments.	29 Ik weet welke voordelen er zijn van vruchtbaarheidsbehoudende behandelingen.	I know the benefits of fertilitypreservation treatments.	31 Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.
I know the risk and side effects ofeach option (DCS: 3) (3)	I know the disadvantages of fertilitypreservation treatments.	30 Ik weet welke nadelen er zijn van vruchtbaarheidsbehoudende behandelingen.	I know the disadvantages of fertilitypreserving treatments.	32 Aš žinau apie vaisingumoišsaugojimo gydymo trūkumus.
Ik ben boos omdat bij mij demogelijkheid om kinderen te krijgenis aangetast. (ENG Q not published) (RCS-NL VBS: 5) (1)	I am angry because my child's possibilities to have children has been impaired.	31 Ik ben boos omdat bij mijn kindde mogelijkheid om kinderen te krijgen is aangetast.	I am angry because my child's possibilities to have children has been impaired	33 Aš pykstu, nes sumažėjo manovaiko galimybės turėti vaikų.
Naujas klausimas	I think it's important that my childcan be a mother in the future.	32 Ik vind het belangrijk dat mijnkind later moeder kan zijn.	I think it's important that my childcan be a parent in the future.	34 Man svarbu, kad mano vaikasateityje galėtų būti mama/tėčiu.
Ik kan openlijk praten over mijn zorgen rondom mijn vruchtbaarheid. (ENG Q not published) (RCS-NL VBS: 6) (1)	I can talk openly about my concernsconcerning my child's fertility.	33 Ik kan openlijk praten over mijn zorgen rondom de vruchtbaarheid van mijn kind.	I can talk openly about my concernsconcerning my child's fertility.	35 Aš galiu atvirai kalbėti apie susirūpinimą dėl savo vaikovaisingumo.
Ik ben verdrietig omdat bij mij demogelijkheid om kinderen te krijgenis aangetast (ENG Q not published) (RCS-NL VBS:	I am sad because my child's possibilities to have children has been impaired.	34 Ik ben verdrietig omdat bij mijn kind de mogelijkheid om kinderen te krijgen is aangetast.	I am sad because my child's possibilities to have children has been impaired.	36 Man liūdna, nes sumažėjo manovaiko galimybės turėti vaikų

8) (1)				
It was the right decision. (Regret scale DRS: 1) (4)	I made the right decision about fertility preservation.	35 Ik heb de juiste beslissing gemaakt over vruchtbaarheidsbehoud.	I made the right decision about fertility preservation.	37 Aš priėmiau teisingą sprendimą dėl vaisingumo išsaugojimo.
I regret the choice that was made. (Regret scale DRS: 2) (4)	I regret the decision I made.	36 Ik heb spijt van de beslissing die ik heb gemaakt.	I regret the decision I made	38 Aš gailiuosi priimo sprendimo.
I would go for the same choice if I had to do it over again. (Regret scale DRS: 3) (4)	I would go for a different choice if I had to do it over again.	37 Ik zou nu een andere beslissing maken.	I would go for a different choice if I had to do it over again.	39 Dabar aš priimčiau kitokį sprendimą.

5 dalis. Atviri klausimai

1. Eng: Are there things you missed during the first conversation regarding fertility or counseling? NL: Zijn er dingen die u heeft gemist tijdens de gesprekken?
   LT: Ar yra dalykų, kurių jums trūko per pirmą pokalbį ar konsultaciją dėl vaisingumo?

2. Eng: What time do you think is the best time to have a conversation about fertility?
   NL: Welk moment is volgens u het beste moment voor een gesprek over vruchtbaarheid?
   LT: Kaip manote, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

3. Eng: What do you think went well during fertility care?
   NL: Wat vond u goed gaan tijdens de zorg rondom vruchtbaarheid?
   LT: Kaip manote, kas praėjo gerai per Jūsų vaiko vaisingumo priežiūrą?

4. Eng: Do you have any other additions or tips for fertility care?
   NL: Heeft u nog meer aanvullingen of tips voor de zorg rondom vruchtbaarheid?
   LT: Ar turite kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

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6 priedas. Klausimyno nekonsultuotiems vaisingumo specialisto pacientams sandara Vilniaus Universiteto Ligoninėje Santaros Klinikose (VULSK)

1 dalis. Bendri klausimai

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
Naujas klausimas	1 I know that 80 percent of children diagnosed with childhood cancer are curable.	1 Aš žinau, kad nuo onkologinės ligos pasveiksta 80 proc. vaikų.
Naujas klausimas	2 I know that childhood cancer treatment could affect my child's fertility (a possibility to have children after the treatment).	2 Aš žinau, kad onkologinės ligos gydymas gali pakenkti mano vaiko vaisingumui – t. y. galimybei susilaukti vaikų baigus gydymą.
Naujas klausimas	3 I had a possibility to discuss questions regarding fertility with healthcare personnel (doctors, nurses, psychologist).	3 Turėjau galimybę aptarti vaisingumo klausimus su medicinos personalu (gydytojais, slaugytojomis, psichologe).
Naujas klausimas	4 I had to ask for information about fertility myself.	4 Turėjau pats(-i) paprašyti suteikti informaciją apie vaisingumą.
Naujas klausimas	5 I got information about fertility not from healthcare personnel but from other sources (Internet, other parents etc.)	5 Informaciją apie vaisingumą gavau ne iš medikų (interneto, bendraujant su kitais tėvais ir pan.).
Naujas klausimas	6 I know the risk for my child's infertility after the treatment.	6 Aš žinau, kokia nevaisingumo rizika kilo mano vaikui dėl ligos gydymo.

2 dalis. Klausimai, susiję su pokalbiu su gydytoja onkohematologe

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
Naujas klausimas	7 Pediatric oncologist mentioned a possibility and risk forfertility impairment for my child	7 Gydytoja onkohematologė minėjo galimą vaisingumo pažeidimą ir jo riziką mano vaikui
Was the information about the investigations you wouldundergo comprehensive? (PCQ: 5) (2)	8 Information regarding fertility provided was understandable and clear.	8 Pokalbių metu pateikta informacija apie vaisingumą buvosuprantama ir aiški.
Did you also receive written information apart from verbalinformation? (PCQ: 3) (2)	9 I received supportive material on fertility (leaflets, books,website links etc.)	9 Man buvo pateikta pagalbinė medžiaga apie vaisingumą (lankstinukai, knygos, nuorodos internete ar kt.)
Was the information about the investigations you wouldundergo comprehensive? (PCQ: 5) (2)	10 I thought the supporting material used during the explanation was clarifying.	10 Pateikta pagalbinė medžiaga buvo suprantama ir aiški.
Was decision-making shared with you, if you preferred?(PCQ: 23) (2)	11 There was room for me to have a say during a conversation about my child's fertility.	11 Galėjau įsiterpti ir išsakyti savo nuomonę pokalbių dėl vaisingumo metu.
Naujas klausimas	12 I thought that the moment this was discussed was a goodone.	12 Manau, kad pokalbiai dėl vaisingumo įvyko tinkamu metu.
Naujas klausimas	13 I think the space was suitable for fertility discussion.	13 Manau, kad pokalbiai dėl vaisingumo įvyko tinkamoje aplinkoje.
How often did your physician have empathy for your emotionsand your current situation? (PCQ: 26) (5)	14 I think practitioners used suitable voice tone during fertility discussion.	14 Manau, kad gydytojai apie vaisingumą kalbėjo tinkamu tonu.
Were caregivers honest and clear about what to expect fromthe fertility care service? (PCQ: 14) (2)	15 My caregivers were honest and clear about what we could expect from the care.	15 Gydytojai buvo atviri apie tai, ko galima tikėtis iš vaisingumo priežiūros.
Was decision-making shared with you, if you preferred?(PCQ: 23) (2)	16 Decision-making was shared with me, concerning my child's treatment	16 Galėjau priimti sprendimą dėl savo vaiko vaisingumo išsaugojimo gydymo.
Did you miss any instructions from a nurse? If so, when?(PCQ: 12) (2)	17 I missed important things during the conversation.	17 Man trūko svarbių dalykų per pokalbius dėl vaisingumo.

Naujas klausimas	18 I still have questions about fertility after the conversation.	18 Aš vis dar turiu klausimų apie vaisingumą.
Naujas klausimas	19 If I have questions about fertility in the future, I know how to request another conversation.	19 Jeigu turėsiu klausimų apie vaisingumą ateityje, žinau, kur kreiptis.

3 dalis. Klausimai po pokalbio apie vaisingumą

Klausimų atitikmuo validuotuose klausimynuose, skirtuose suaugusiesiems (originalia kalba)	**VULSK klausimynas (anglų kalba)**	**VULSK klausimynas (lietuvių kalba)**
I have enough advice to make a choice. (DCS: 9) (3)	20 I now know enough about fertility.	20 Aš dabar žinau pakankamai apie vaisingumą.
I know which options are available to me (DCS: 1) (3)	21 I know which options are available to maintain my child's fertility	21 Aš žinau, kokios yra mano vaiko vaisingumo išsaugojimo galimybės.
I know the benefits of each option (DCS: 2) (3)	22 I know the benefits of fertility preservation treatment.	22 Aš žinau apie vaisingumo išsaugojimo gydymo privalumus.
I know the risk and side effects of each option (DCS: 3) (3)	23 I know the disadvantages of fertility preserving treatment.	23 Aš žinau apie vaisingumo išsaugojimo gydymo trūkumus.
Naujas klausimas	24 I think it's important that my child can be a parent in the future.	24 Man svarbu, kad mano vaikas ateityje galėtų būti mama/tėčiu.
Ik ben boos omdat bij mij de mogelijkheid om kinderen te krijgen is aangetast. (ENG Q not published) (RCS-NL VBS: 5) (1)	25 I am angry because my child's possibilities to have children has been impaired	25 Aš pykstu, nes sumažėjo mano vaiko galimybės turėti vaikų.
Ik ben verdrietig omdat bij mij de mogelijkheid om kinderen te krijgen is aangetast (ENG Q not published)	26 I am sad because my child's possibilities to have children has been impaired.	26 Man liūdna, nes sumažėjo mano vaiko galimybės turėti vaikų

(RCS-NL VBS: 8) (1)		
Ik kan openlijk praten over mijn zorgen rondom mijn vruchtbaarheid. (ENG Q not published) (RCS-NL VBS: 6) (1)	27 I can talk openly about my concerns concerning my child's fertility.	27 Aš galiu atvirai kalbėti apie susirūpinimą dėl savo vaiko vaisingumo.

4 dalis. Atviri klausimai

1. Eng: Are there things you missed during the first conversation regarding fertility or counseling?
   LT: Ar yra dalykų, kurių jums trūko per pokalbius dėl vaisingumo?

2. Eng: What time do you think is the best time to have a conversation about fertility?
   LT: Kaip manote, kada yra tinkamiausias laikas pokalbiui apie vaisingumą?

3. Eng: What do you think went well during fertility care?
   LT: Kaip manote, kas praėjo gerai per Jūsų vaiko vaisingumo priežiūrą?

4. Eng: Do you have any other additions or tips for fertility care?
   LT: Ar turite kitų pastebėjimų ar patarimų dėl vaisingumo priežiūros?

Literatūros šaltiniai

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7 priedas. Nevaisingumo rizikos vertinimo metodika („*triage*“)*

Onkologinė liga	Protokolas	Gydymo šaka	CED mg/m²**	Mergaitės nevaisingumo rizika pagal CED***	Berniuko nevaisingumo rizika pagal CED****
Hematologinės ligos					
Leukemijos					
ŪLL (ūminė limfoblastinė leukemija)	Interfant06	Vidutinė/didelė rizika be KKLT*****	3000	Maža	Maža
		Vidutinė/didelė rizika + KKLT	3000 + KKLT	Didelė	Didelė
	Interfant21	Vidutinė-maža rizika	3000	Maža	Maža
		Vidutinė-didelė rizika	1000	Maža	Maža
		Didelė rizika	KKLT	Didelė	Didelė
	EsPhALL	Šaka A	9000	Didelė	Didelė
		Šaka B	3000	Maža	Maža
		Didelė rizika	3976 + KKLT	Didelė	Didelė
		Didelė rizika	5976 + KKLT	Didelė	Didelė
	ALLTogether	R1 standartinė, eksperimentinė	0	Maža	Maža
		R2 standartinė, eksp, šaka A, eksp. šaka B	3000	Maža	Maža
		R3 standartinė, eksp. InO: vidutinė-didelė rizika	2000	Maža	Maža
		ABL didelė rizika alo-KKLT (≥ 1-3 NOPHO blokai)	2000 + KKLT	Didelė	Didelė
		ABL vidutinė-didelė	2000	Maža	Maža
		Didelė rizika BCP KKLT 3 blokai	4200 + KKLT	Didelė	Didelė
		Didelė rizika BCP chemo 6 blokai	7400	Didelė	Didelė
		Didelė rizika T-ląstelių be Nelarabino + didelės rizikos blokai	4200	Maža	Didelė
		Didelė rizika T-ląstelių su Nelarabinu	1000	Maža	Maža
		Didelė rizika T-ląstelių su Nelarabinu + didelės rizikos blokai	3200	Maža	Maža
		Didelė rizika T-ląstelių su Nelarabinu papildomai	2000	Maža	Maža

		Didelė rizika T-ląstelių su Nelarabinu papildomai + didelės rizikos blokai	4200	Maža	Didelė
		DS-standartinė rizika	1000	Maža	Maža
		DS-vidutinė rizika, DS-didelė rizika	3000	Maža	Maža
ŪML (ūminė mieloidinė leukemija)	Nopho DBH AML 2012	Standartinė rizika	0	Maža	Maža
		Didelė rizika	0 + KKLT	Didelė	Didelė
Ūminė promielocitinė leukemija	ICC APL 01	Standartinė rizika MLL- / Standartinė rizika MLL+ / Didelė rizika	0	Maža	Maža
	ICC APL 02	Standartinė rizika, didelė rizika	0	Maža	Maža
Limfomos					
Hodžkino limfoma	EuroNet-PHL-C2	TL1	1000	Maža	Maža
		TL2	2000	Maža	Maža
		TL2 intensyvinta	2500	Maža	Maža
		TL3	4000	Maža	Didelė
		TL3 intensyvinta	5000	Maža	Didelė
NHL (Ne Hodžkino limfoma)	Euro LB-02	T-ląstelių LL stadijos I-II	2000	Maža	Maža
		T-ląstelių LL stadijos III-IV	3000	Maža	Maža
		Ne T-ląstelių LL stadijos I-II	2000	Maža	Maža
		Ne T-ląstelių LL stadijos III-IV	3000	Maža	Maža
LBL (Limfoblastinė limfoma)	EICNHL	Standartinės rizikos grupė, I ir II stadijos pB-LBL	2000	Maža	Maža
		Didelės rizikos grupė, III and IV stadijos pB-LBL ir T-LBL (visų stadijų)	3000	Maža	Maža
	LBL 2018	Standartinės rizikos grupė (I/II pB-LBL stadijos I/II)	2000	Maža	Maža
		Standartinės rizikos grupė (T-LBL N/F mut.)	3000	Maža	Maža
		Didelės rizikos grupė - standartinė šaka	3000	Maža	Maža
		Didelės rizikos grupė - intensyvi šaka	4976	Maža	Didelė
Anaplastinė didelių ląstelių limfoma	EICNHL	Izoliuota odos forma	0	Maža	Maža

		Sisteminė forma: visiškai pašalinta	3352	Maža	Didelė
		Sisteminė forma: visos kitos stadijos	6328	Didelė	Didelė
		Pacientai su CNS+	4352	Maža	Maža
	ALCL	Maža rizika	3352	Maža	Maža
		Standartinė rizika šakos 1 ir 3, didelė rizika šakos 1, 2, 3, 4	6328	Didelė	Didelė
B-NHL/B-ŪLL	NHL-BFM	R1	1976	Maža	Maža
		R2	4352	Maža	Didelė
		R3-R4-CNS-	4352	Maža	Didelė
		R4-CNS+	4352	Maža	Didelė
	EICNHL	A	3000	Maža	Maža
		B I	3300	Maža	Maža
		B II (didelė rizika)	3300	Maža	Maža
		C1	5800	Maža	Didelė
		C3	5800	Maža	Didelė
	Inter-B-NHL ritux	Grupė B didelė rizika	3300	Maža	Maža
		Grupė C1	5800	Maža	Didelė
		Grupė C3	5800	Maža	Didelė
		PMLBL	4500	Maža	Didelė
Kita					
LLH (langerhanso ląstelių histiocitozė)	LCH IV	Gydymo šaka 1 grupė 1 (MS-LLH) šaka A / B / C / D	0	Maža	Maža
		Gydymo šaka 1 grupė 2 (SS-LLH)	0	Maža	Maža
		Gydymo šaka 2	0	Maža	Maža
		Gydymo šaka V be klinikinės neurodegeneracijos	0	Maža	Maža
		Gydymo šaka V su klinikine neurodegeneracija	0	Maža	Maža
Solidiniai navikai					
Neuroblastoma					
	SIOPEN European Low and Intermediate Risk	Maža rizika grupė 1	0	Maža	Maža
		Maža rizika grupė 2 2xVP/CARBO	0	Maža	Maža
		Maža rizika grupė 2 2xVP/CARBO +2x CADO	3000	Maža	Maža

	Neuroblastoma (LINES)	Maža rizika grupė 3 4x VP/CARBO	0	Maža	Maža
		Maža rizika grupė 3 2x VP/CARBO + 2x CADO	3000	Maža	Maža
		Maža rizika grupė 4	0	Maža	Maža
		Maža rizika grupė 5 2xVP/CARBO	0	Maža	Maža
		Maža rizika grupė 5 2xVP/CARBO +2x CADO	3000	Maža	Maža
		Maža rizika grupė 6 4x VP/CARBO	0	Maža	Maža
		Maža rizika grupė 6 2x VP/CARBO + 2x CADO	3000	Maža	Maža
		Vidutinė rizika grupė 7 4x VP/CARBO	0	Maža	Maža
		Vidutinė rizika grupė 7 2x VP/CARBO + 2x CADO	3000	Maža	Maža
		Vidutinė rizika grupė 8 2x VP/CARBO + 2x CADO + 1xVP/CARBO + 1xCADO	4500	Maža	Didelė
		Vidutinė rizika grupė 8 2x VP/CARBO + 2x CADO + 2xCADO	6000	Didelė	Didelė
		Vidutinė rizika grupė 9 2x VP/CARBO + 2x CADO + 1xVP/CARBO + 1xCADO	4500	Maža	Didelė
		Vidutinė rizika grupė 10 4x VP/CARBO	0	Maža	Maža
		Vidutinė rizika grupė 10 2x VP/CARBO + 2xCADO	3000	Maža	Maža
		Vidutinė rizika grupė 10 2x VP/CARBO + 4x CADO	6000	Didelė	Didelė
		Vidutinė rizika grupė 10 4x VP/CARBO + 4x CADO	6000	Didelė	Didelė
	HR-NBL-1.8/SIOPEN	BuMel bet koks svoris	>12000	Didelė	Didelė
Kauliniai navikai					
Ewing sarkoma	Ewing 2008	R1 mot.	25176	Didelė	Didelė
		R3	25176	Didelė	Didelė
		R3 + TreoMel arba BuMel	30776	Didelė	Didelė
	Ewing 2012	Šaka A R2 VAC	25140	Didelė	Didelė
		BuMel bet koks svoris	>23000	Didelė	Didelė
		Šaka A R2 VAI	24888	Didelė	Didelė

		Šaka B R2 IEVC	23772	Didelė	Didelė
		Šaka B R2 BuMel bet koks svoris	>23000	Didelė	Didelė
Osteosarkoma	EURAMOS 1	MAP	0	Maža	Maža
		MAPIE	14640	Didelė	Didelė
Inkstų navikai					
	UMBRELLA 2016/SIOP 2001	AV + AVD, AV + AV1, AV + AV2	0	Maža	Maža
		AV + didelė rizika	8100	Didelė	Didelė
Minkštųjų audinių ir ekstrakaulinės sarkomos					
Minkštųjų audinių sarkomos	EpSSG RMS 2005	Maža rizika pogrupis A	0	Maža	Maža
		Standartinė rizika pogrupis B	5800	Maža	Didelė
		Standartinė rizika pogrupis C (9x ifosfamidas)	13176	Didelė	Didelė
		Standartinė rizika pogrupis C (5x ifosfamidas)	7320	Didelė	Didelė
		Standartinė rizika pogrupis D (9x ifosfamidas)	13176	Didelė	Didelė
		Didelė rizika ir grupė A + grupė C	13176	Didelė	Didelė
		Didelė rizika ir grupė A + grupė D	17376	Didelė	Didelė
		Didelė rizika ir grupė B + grupė C	13176	Didelė	Didelė
		Didelė rizika ir grupė B + grupė D	17376	Didelė	Didelė
	CWS-guidance-2014	RMS maža rizika pogrupis A	0	Maža	Maža
		RMS standartinė rizika pogrupis B	5856	Maža	Didelė
		RMS standartinė rizika pogrupis C be RT	13176	Didelė	Didelė
		RMS standartinė rizika pogrupis C su RT	7320	Didelė	Didelė
		RMS standartinė rizika pogrupis D	13176	Didelė	Didelė
		RMS didelė rizika pogrupis E, F, G	13176	Didelė	Didelė
		RMS labai didelė rizika pogrupis H	13176	Didelė	Didelė
		"*RMS-like*" (SySa, STET (EES, pNET), UDS)	13176	Didelė	Didelė
		"*Non-RMS-like*" (NRTS) maža rizika	0	Maža	Maža

		"*Non-RMS-like*" (NRTS) vidutinė rizika	0	Maža	Maža
		"*Non-RMS-like*" (NRTS) didelė rizika	13176	Didelė	Didelė
		Metastatiniai minkštųjų audinių navikai	13176	Didelė	Didelė
		CWS angiosarkomai	6000	Didelė	Didelė
Atipiniai terato/rabdo navikai	EURHAB	3x DOX, 3x ICE, 3xVCA	8892	Didelė	Didelė
		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa	50928	Didelė	Didelė
		3x DOX, 3x ICE, 3xVCA + RT	8892	Didelė	Didelė
		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa + RT	50928	Didelė	Didelė
NRSTS (Ne-Rabdomiosarkomos)	EpSSG NRSTS 2005	3x ifosfamidas	6588	Didelė	Didelė
		4x ifosfamidas	8784	Didelė	Didelė
		5x ifosfamidas	10980	Didelė	Didelė
		6x ifosfamidas	13176	Didelė	Didelė
Germinogeninių ląstelių navikai					
Intrakranijiniai germinogeninių ląstelių navikai	SIOP CNS GCT II	CCLG	4392	Maža	Didelė
		NGGCT	7320	Didelė	Didelė
		2xPEI+2X HD-PEI (didelės rizikos ne-germinoma)	8540	Didelė	Didelė
Ekstrakranijiniai germinogeniniai navikai	PEB+JEB blokai	Maža rizika	0	Maža	Maža
		Vidutinė rizika	0 (cis/karboplatina)	Maža	Maža
		Didelė rizika	0 (cis/karboplatina)	Maža	Maža
Kepenų navikai					
Hepatoceliulinė karcinoma	PHITT	Grupė A1 labai maža rizika	0	Maža	Maža
		Grupė A2 labai maža rizika	0 (cisplatina)	Maža	Maža
		Grupė B1 maža rizika / B2	0 (cisplatina)	Maža	Maža

		Grupė C vidutinė rizika SIOPEL3HR / C5VD/ CDDP-M	0 (cisplatina)	Maža	Maža
		Grupė D1 didelė rizika HB SIOPEL4, D2 didelė rizika CDCE, CDVI	0 (cis/karboplatina)	Maža	Maža
		Grupė E1 pašalinta HCC	0	Maža	Maža
		Grupė E2 pašalinta HCC PLADO	0 (cisplatina)	Maža	Maža
		Grupė F nepašalinta/metastatinė PLADO sorafenibas, GEMOX	0 (cisplatina)	Maža	Maža
CNS navikai					
Optinė glioma	SIOP LGG 2004	Vinkristinas, karboplatina, etoposidas. (Jei alergija: cyclo)	0	Maža	Maža
Aukšto laipsnio glioma, tilto glioma	ACNS0126	Temozolamidas	0	Nežinoma	Nežinoma
Meduloblastoma	PNET 5	MB-SR / MB-WNT-HR(>16 metų)	17600	Didelė	Didelė
		MB-WNT-HR (<16 metų)	13200	Didelė	Didelė
		MB-SHH-TP53: Jokių alkilinančių preparatų	0	Maža	Maža
	SR ACNS0331	Ciklofosfamidas, lomustinas	13200	Didelė	Didelė
	HR ACNS0332	Ciklofosfamidas	12000	Didelė	Didelė
	HIT-MED Guidance	3x SKK	7200	Didelė	Didelė
		3x SKK+ 2x mSKK	12000	Didelė	Didelė
		3x intensyvi indukcija + 1st HDCT + 2nd HDCT + 6x palaikomasis gydymas	4500+intensyvi indukcija	Didelė	Didelė
		RT + 8x palaikomasis gydymas	0 (cisplatina)	Maža	Maža
		2x SKK + RT + 4x palaikomasis gydymas	4800	Maža	Didelė
Ependimoma	HIT-MED Guidance	3x SKK+2x mSKK	12000	Didelė	Didelė
		Vietiškai RT	0	Maža	Maža
		2x mSKK + RT	4800	Maža	Didelė
Pineoblastoma	HIT-MED Guidance	CARBO/ETO-96 val. indukcija + 1st HDCT + 2nd HDCT + 6x palaikomasis gydymas)	4500	Maža	Didelė
		RT + 8x palaikomasis gydymas	0 (cisplatina)	Maža	Maža

		2x SKK + RT + 4x palaikomasis gydymas	4800	Maža	Didelė
HGG	Infant HGG 2013/HIT SKK	IIs IIIs/1 IIIs/2 IVs	7200	Didelė	Didelė
Retinoblastoma					
Retinoblastoma	RB SFCE 2008-A	Maža rizika	0	Maža	Maža
		Vidutinė rizika pogrupis 1	1500	Maža	Maža
		Vidutinė rizika pogrupis 2	0	Maža	Maža
		Didelė rizika	3000 + KKLT	Didelė	Didelė

* - parengta remiantis *Princess Máxima Center* publikuota nevaisingumo rizikos vertinimo metodika (1).

Rizikos laipsnis nustatytas remiantis 2021 m. *International Guideline Harmonization Group* (IGHG) rekomendacijomis (2,3).

Rizikos įvertinimas pacientams su inkstų navikais atidedamas po operacinio gydymo, kai žinomas tolimesnis gydymas, įskaitant radioterapijos dozę. Pacientams su ŪLL ir NHL rizikos įvertinimas atidedamas po indukcijos iki gydymo šakos priskyrimo pasiekus visišką remisiją. Kai kurie didelės nevaisingumo rizikos pacientai su abdominaliniais navikais konsultuojami vėlesniu laikotarpiu dėl skubios operacijos reikalingumo.

** - CED (*Cyclophosphamide Equivalent Dose*) (mg/m^2) = 1,0 (suminė ciklofosfamido dozė (mg/m^2)) + 0.244 (suminė ifosfamido dozė (mg/m^2)) + 0,857 (suminė prokarbazino dozė (mg/m^2)) + 14,286 (suminė chlorambucilo dozė (mg/m^2)) + 15,0 (suminė karmustino dozė (mg/m^2)) + 16,0 (suminė lomustino dozė (mg/m^2)) + 40 (suminė melfalano dozė (mg/m^2)) + 50 (suminė *Thiotepa* dozė (mg/m^2)) + 100 (suminė azoto garstyčių darinių dozė (mg/m^2)) + 8,823 (suminė busulfano dozė (mg/m^2)) (4).

***** - Didelė mergaičių nevaisingumo rizika, kai CED ≥6000 mg/m^2, radioterapija (RT) į kiaušides, alogeninė kamieninių kraujodaros ląstelių transplantacija (alo-KKLT) – stipriai rekomenduojama kiaušialąsčių krioprezervacija, vidutiniškai rekomenduojama kiaušidžių audinio krioprezervacija.**

Jei taikoma mažų dozių chemoterapija (CED <6000 mg/m^2), kranialinė RT, vienpusė ovarektomija – vidutiniškai rekomenduojama kiaušialąsčių krioprezervacija.

****** - Didelė berniukų nevaisingumo rizika, kai CED ≥4000 mg/m^2 , RT į sėklides, alo-KKLT – stipriai rekomenduojama spermos krioprezervacija.**

Jei taikoma mažų dozių chemoterapija (CED <4000 mg/m^2), cisplatina, orchiektomija, kranialinė RT – stipriai rekomenduojama spermos krioprezervacija.

***** - KKLT – kamieninių kraujodaros ląstelių transplantacija

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8 priedas. Originalios (parengtos *Princess Máxima Center*) ir adaptuotos taikymui VULSK nevaisingumo rizikos vertinimo metodikų palyginimas

Originali metodika (parengta *Princess Máxima Center*)					**Adaptuota taikymui VULSK metodika**					**Skirtumai nuo originalios metodikos**
Onkologinė liga	Protokolas	Gydymo šaka	CED mg/m^2	Mergaitės nevaisingumo rizika	Onkologinė liga	Protokolas	Gydymo šaka	CED mg/m^2	Mergaitės nevaisingumo rizika pagal CED	Berniuko nevaisingumo rizika pagal CED	Pridėta berniuko nevaisingumo rizika pagal CED.
Hematologinės ligos					**Hematologinės ligos**						-
ŪLL (ūminė limfoblastinė leukemija)	ALL-11	Standartinė rizika, vidutinė rizika	2000	Maža	ŪLL (ūminė limfoblastinė leukemija)	-	-	-	-	-	ALL-11 gydymo protokolas netaikomas Vilniaus Universiteto Ligoninėje Santaros Klinikose (VULSK), todėl ištrintas.
		Didelė rizika 1-3 +KKLT	5600 + KKLT	Didelė		-	-	-	-	-	
		Didelė rizika 1-6 + II	9300	Didelė		-	-	-	-	-	
	Interfant06	Vidutinė/didelė rizika be KKLT	3000	Maža		Interfant06	Vidutinė/didelė rizika be KKLT	3000	Maža	Maža	-
		Vidutinė/didelė rizika + KKLT	3000+ KKLT	Didelė			Vidutinė/didelė rizika + KKLT	3000 + KKLT	Didelė	Didelė	
	-	-	-	-		Interfant21	Vidutinė-maža rizika	3000	Maža	Maža	Įtrauktas Interfant 21 gydymo protokolas.
	-	-	-	-			Vidutinė-didelė rizika	1000	Maža	Maža	
	-	-	-	-			Didelė rizika	KKLT	Didelė	Didelė	
	EsPhALL	Šaka A	9000	Didelė		EsPhALL	Šaka A	9000	Didelė	Didelė	-
		Šaka B	3000	Maža			Šaka B	3000	Maža	Maža	
		Didelė rizika	3976 + KKLT	Didelė			Didelė rizika	3976 + KKLT	Didelė	Didelė	

	Didelė rizika	5976 + KKLT	Didelė		Didelė rizika	5976 + KKLT	Didelė	Didelė	
IntReALL	Standartinė rizika Šaka A	1976	Maža	-	-	-	-	-	IntReALL gydymo protokolas netaikomas VULSK, todėl ištrintas.
	Standartinė rizika Šaka A su KKLT	1976 + KKLT	Didelė	-	-	-	-	-	
	Standartinė rizika Šaka B	3400	Maža	-	-	-	-	-	
	Standartinė rizika Šaka B su KKLT	3400 + KKLT	Didelė	-	-	-	-	-	
	Didelė rizika	1976 + KKLT	Didelė		-	-	-	-	
ALLToget her	R1 standartinė, eksperimentinė	0	Maža	ALLToget her	R1 standartinė, eksperimentinė	0	Maža	Maža	-
	R2 standartinė, eksp, šaka A, eksp. šaka B	3000	Maža		R2 standartinė, eksp, šaka A, eksp. šaka B	3000	Maža	Maža	
	R3 standartinė, eksp. InO: vidutinė-didelė rizika	2000	Maža		R3 standartinė, eksp. InO: vidutinė-didelė rizika	2000	Maža	Maža	
	ABL didelė rizika alo-KKLT (≥ 1-3 NOPHO blokai)	2000 +KKLT	Didelė		ABL didelė rizika alo-KKLT (≥ 1-3 NOPHO blokai)	2000 + KKLT	Didelė	Didelė	
	ABL Vidutinė-didelė	2000	Maža		ABL Vidutinė-didelė	2000	Maža	Maža	
	Didelė rizika BCP KKLT 3 blokai	4200 +KKLT	Didelė		Didelė rizika BCP KKLT 3 blokai	4200 + KKLT	Didelė	Didelė	
	Didelė rizika BCP chemo 6 blokai	7400	Didelė		Didelė rizika BCP chemo 6 blokai	7400	Didelė	Didelė	

		Didelė rizika T-ląstelių be Nelarabino + didelės rizikos blokai	4200	Vidutinė*			Didelė rizika T-ląstelių be Nelarabino + didelės rizikos blokai	4200	Maža	Didelė	
		Didelė rizika T-ląstelių su Nelarabinu	1000	Maža			Didelė rizika T-ląstelių su Nelarabinu	1000	Maža	Maža	
		Didelė rizika T-ląstelių su Nelarabinu + didelės rizikos blokai	3200	Maža			Didelė rizika T-ląstelių su Nelarabinu + didelės rizikos blokai	3200	Maža	Maža	
		Didelė rizika T-ląstelių su Nelarabinu papildomai	2000	Maža			Didelė rizika T-ląstelių su Nelarabinu papildomai	2000	Maža	Maža	
		Didelė rizika T-ląstelių su Nelarabinu papildomai + didelės rizikos blokai	4200	Vidutinė*			Didelė rizika T-ląstelių su Nelarabinu papildomai + didelės rizikos blokai	4200	Maža	Didelė	
		DS-standartinė rizika	1000	Maža			DS-standartinė rizika	1000	Maža	Maža	
		DS-vidutinė rizika, DS-didelė rizika	3000	Maža			DS-vidutinė rizika, DS-didelė rizika	3000	Maža	Maža	
LLH (langerhanso ląstelių histiocitozė)	LCH IV	Gydymo šaka 1 grupė 1 (MS-LLH) šaka A / B / C / D	0	Maža	LLH (langerhanso ląstelių histiocitozė)	LCH IV	Gydymo šaka 1 grupė 1 (MS-LLH) šaka A / B / C / D	0	Maža	Maža	-
		Gydymo šaka 1 grupė 2 (SS-LLH)	0	Maža			Gydymo šaka 1 grupė 2 (SS-LLH)	0	Maža	Maža	
		Gydymo šaka 2	0	Maža			Gydymo šaka 2	0	Maža	Maža	

		Gydymo šaka V be klinikinės neurodegeneracijos	0	Maža			Gydymo šaka V be klinikinės neurodegeneracijos	0	Maža	Maža	
		Gydymo šaka V su klinikine neurodegeneracija	0	Maža			Gydymo šaka V su klinikine neurodegeneracija	0	Maža	Maža	
Hodžkino limfoma	EuroNet-PHL-C2	TL1	1000	Maža	Hodžkino limfoma	EuroNet-PHL-C2	TL1	1000	Maža	Maža	-
		TL2	2000	Maža			TL2	2000	Maža	Maža	
		TL2 intensyvinta	2500	Maža			TL2 intensyvinta	2500	Maža	Maža	
		TL3	4000	Vidutinė*			TL3	4000	Maža	Didelė	
		TL3 intensyvinta	5000	Vidutinė*			TL3 intensyvinta	5000	Maža	Didelė	
NHL (Ne Hodžkino limfoma)	Euro LB-02	T-ląstelių LL stadijos I-II	2000	Maža	NHL (Ne Hodžkino limfoma)	Euro LB-02	T-ląstelių LL stadijos I-II	2000	Maža	Maža	-
		T-ląstelių LL stadijos III-IV	3000	Maža			T-ląstelių LL stadijos III-IV	3000	Maža	Maža	
		Ne T-ląstelių LL stadijos I-II	2000	Maža			Ne T-ląstelių LL stadijos I-II	2000	Maža	Maža	
		Ne T-ląstelių LL stadijos III-IV	3000	Maža			Ne T-ląstelių LL stadijos III-IV	3000	Maža	Maža	
-	-	-	-	-	LBL (Limfoblastinė limfoma)	EICNHL	Standartinės rizikos grupė I ir II stadijos pB-LBL	2000	Maža	Maža	Įtrauktas EICNHL gydymo protokolas limfoblastinei limfomai.
-	-	-	-	-			Didelės rizikos grupė, III ir IV stadijos pB-LBL ir T-LBL (visų stadijų)	3000	Maža	Maža	
-	-	-	-	-		LBL 2018	Standartinės rizikos grupė	2000	Maža	Maža	Įtrauktas LBL 2018 gydymo protokolas

							(I/II pB-LBL stadijos I/II)				limfoblastinei limfomai.
-	-	-	-	-			Standartinės rizikos grupė (T-LBL N/F mut.)	3000	Maža	Maža	
-	-	-	-	-			Didelės rizikos grupė - standartinė šaka	3000	Maža	Maža	
							Didelės rizikos grupė - intensyvi šaka	4976	Maža	Didelė	
B-NHL/B-ŪLL	SKION B-NHL/B-ALL 2008	Grupė A	3000	Maža	B-NHL/B-ŪLL	-	-	-	-	-	SKION B-NHL/B-ALL 2008 gydymo protokolas netaikomas VULSK, todėl ištrintas.
		Grupė B	3300	Maža		-	-	-	-	-	
		Grupė C1	6800	Didelė		-	-	-	-	-	
		Grupė C2	6800	Didelė		-	-	-	-	-	
	-	-	-	-		NHL-BFM	R1	1976	Maža	Maža	Įtrauktas NHL-BFM gydymo protokolas, skirtas B-NHL/B-ŪLL.
	-	-	-	-			R2	4352	Maža	Didelė	
	-	-	-	-			R3-R4-CNS-	4352	Maža	Didelė	
	-	-	-	-			R4-CNS+	4352	Maža	Didelė	
	-	-	-	-		EICNHL	A	3000	Maža	Maža	Įtrauktas EICNHL gydymo protokolas, skirtas B-NHL/B-ŪLL.
	-	-	-	-			B I	3300	Maža	Maža	
	-	-	-	-			B II (didelė rizika)	3300	Maža	Maža	
	-	-	-	-			C1	5800	Maža	Didelė	
	-	-	-	-			C3	5800	Maža	Didelė	
	Inter-B-NHL ritux	Grupė B didelė rizika	3300	Maža		Inter-B-NHL ritux	Grupė B didelė rizika	3300	Maža	Maža	-

		Grupė C1	5800	Vidutinė*			Grupė C1	5800	Maža	Didelė	
		Grupė C3	5800	Vidutinė*			Grupė C3	5800	Maža	Didelė	
		PMLBL	4500	Vidutinė*			PMLBL	4500	Maža	Didelė	
Anaplastinė didelių ląstelių limfoma	ALCL	Maža rizika	3352	Maža	Anaplastinė didelių ląstelių limfoma	ALCL	Maža rizika	3352	Maža	Maža	-
		Standartinė rizika šakos 1 ir 3, didelė rizika šakos 1, 2, 3, 4	6328	Didelė			Standartinė rizika šakos 1 ir 3, didelė rizika šakos 1, 2, 3, 4	6328	Didelė	Didelė	
	-	-	-	-		EICNHL	Izoliuota odos forma	0	Maža	Maža	Įtrauktas EICNHL gydymo protokolas anaplastinei didelių ląstelių limfomai.
	-	-	-	-			Sisteminė forma: visiškai pašalinta	3352	Maža	Didelė	
	-	-	-	-			Sisteminė forma: visos kitos stadijos	6328	Didelė	Didelė	
	-	-	-	-			Pacientai su CNS+	4352	Maža	Maža	
ŪML (ūminė mieloidinė leukemija)	Nopho DBH AML 2012	Standartinė rizika	0	Maža	ŪML (ūminė mieloidinė leukemija)	Nopho DBH AML 2012	Standartinė rizika	0	Maža	Maža	-
		Didelė rizika	0+KKLT	Didelė			Didelė rizika	0+KKLT	Didelė	Didelė	
Ūminė promielocitinė leukemija	ICC APL 01	Standartinė rizika MLL- / Standartinė rizika MLL+ / Didelė rizika	0	Maža	Ūminė promielocitinė leukemija	ICC APL 01	Standartinė rizika MLL- / Standartinė rizika MLL+ / Didelė rizika	0	Maža	Maža	-

	ICC APL 02	Standartinė rizika, didelė rizika	0	Maža		ICC APL 02	Standartinė rizika, didelė rizika	0	Maža	Maža	
Solidiniai navikai					Solidiniai navikai						-
Neuroblastoma	DCOG NBL 2009	OG be N4	0	Maža	Neuroblastoma	-	-	-	-	-	DCOG NBL 2009 ir DCOG NBL 2009 <1 m. protokolai netaikomi VULSK, todėl ištrinti.
		OG su 1x N4	2100	Maža		-	-	-	-	-	
		OG su 2x N4	4200	Vidutinė*		-	-	-	-	-	
		OG su 3x N4	6300	Didelė		-	-	-	-	-	
		OG su 4x N4	8400	Didelė		-	-	-	-	-	
		Maža rizika be N4	10290	Didelė		-	-	-	-	-	
		Maža rizika su N4	18690	Didelė		-	-	-	-	-	
		Didelė rizika be N4	12690	Didelė		-	-	-	-	-	
		Didelė rizika su N4	21090	Didelė		-	-	-	-	-	
	DCOG NBL 2009 <1 m.	OG su 1x N4 <1 m.	/kg	Maža		-	-	-	-	-	
		OG su 2x N4 <1 m. 3x N4 <1 m., 4x N4 <1 m.	/kg	Vidutinė*		-	-	-	-	-	
		Maža rizika be N4 <1 m., su N4 <1 m.	/kg	Didelė		-	-	-	-	-	
		Didelė rizika be N4 <1 m., su N4 <1 m.	/kg	Didelė		-	-	-	-	-	
	-	-	-	-		SIOPEN European	Maža rizika grupė 1	0	Maža	Maža	Įtrauktas SIOPEN European Low and

-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
-	-	-	-						
				Low and Intermediate Risk Neuroblastoma (LINES)	Maža rizika grupė 2 2xVP/CARBO	0	Maža	Maža	Intermediate Risk Neuroblastoma (LINES) gydymo protokolas.
					Maža rizika grupė 2 2xVP/CARBO +2x CADO	3000	Maža	Maža	
					Maža rizika grupė 3 4x VP/CARBO	0	Maža	Maža	
					Maža rizika grupė 3 2x VP/CARBO + 2x CADO	3000	Maža	Maža	
					Maža rizika grupė 4	0	Maža	Maža	
					Maža rizika grupė 5 2xVP/CARBO	0	Maža	Maža	
					Maža rizika grupė 5 2xVP/CARBO +2x CADO	3000	Maža	Maža	
					Maža rizika grupė 6 4x VP/CARBO	0	Maža	Maža	
					Maža rizika grupė 6 2x VP/CARBO + 2x CADO	3000	Maža	Maža	
					Vidutinė rizika grupė 7 4x VP/CARBO	0	Maža	Maža	
					Vidutinė rizika grupė 7 2x	3000	Maža	Maža	

						VP/CARBO + 2x CADO				
						Vidutinė rizika grupė 8 2x VP/CARBO + 2x CADO + 1xVP/CARBO + 1xCADO	4500	Maža	Didelė	
-	-	-	-							
						Vidutinė rizika grupė 8 2x VP/CARBO + 2x CADO + 2xCADO	6000	Didelė	Didelė	
-	-	-	-							
						Vidutinė rizika grupė 9 2x VP/CARBO + 2x CADO + 1xVP/CARBO + 1xCADO	4500	Maža	Didelė	
-	-	-	-							
						Vidutinė rizika grupė 10 4x VP/CARBO	0	Maža	Maža	
-	-	-	-							
						Vidutinė rizika grupė 10 2x VP/CARBO + 2xCADO	3000	Maža	Maža	
-	-	-	-							
						Vidutinė rizika grupė 10 2x VP/CARBO + 4x CADO	6000	Didelė	Didelė	
-	-	-	-							
						Vidutinė rizika grupė 10 4x VP/CARBO + 4x CADO	6000	Didelė	Didelė	
-	-	-	-		HR-NBL-1.8/SIOPEN	BuMel bet koks svoris	>12000	Didelė	Didelė	Įtrauktas HR-NBL-1.8/SIOPEN gydymo protokolas.

Ewing sarkoma	Ewing 2008	R1 mot.	25176	Didelė	*Ewing* sarkoma	Ewing 2008	R1 mot.	25176	Didelė	Didelė	
		R3	25176	Didelė			R3	25176	Didelė	Didelė	-
		R3 + TreoMel arba BuMel	30776	Didelė			R3 + TreoMel arba BuMel	30776	Didelė	Didelė	
	-	-	-	-		Ewing 2012	Šaka A R2 VAC	25140	Didelė	Didelė	
	-	-	-	-			BuMel bet koks svoris	>23000	Didelė	Didelė	
	-	-	-	-			Šaka A R2 VAI	24888	Didelė	Didelė	Įtrauktas Ewing 2012 gydymo protokolas.
	-	-	-	-			Šaka B R2 IEVC	23772	Didelė	Didelė	
	-	-	-	-			Šaka B R2 BuMel bet koks svoris	>23000	Didelė	Didelė	
Osteosarkoma	EURAMOS 1	MAP	0	Maža	Osteosarkoma	EURAMOS 1	MAP	0	Maža	Maža	-
		MAPIE	14640	Didelė			MAPIE	14640	Didelė	Didelė	
Inkstų navikai	UMBRELLA 2016/SIOP 2001	AV + AVD, AV + AV1, AV + AV2	0	Maža	Inkstų navikai	UMBRELLA 2016/SIOP 2001	AV + AVD, AV + AV1, AV + AV2	0	Maža	Maža	-
		AV + didelė rizika	8100	Didelė			AV + didelė rizika	8100	Didelė	Didelė	
Inkstų/minkštųjų audinių rabdo-navikai	EpSSG NRSTS 2005	Ciklofosfamidas	17000	Didelė	-	-	-	-	-	-	EpSSG NRSTS 2005 gydymo protokolas minkštųjų audinių rabdo- navikams netaikomas VULSK, todėl ištrintas.
	EURHAB	3x DOX, 3x ICE, 3xVCA	8892	Didelė		-	-	-	-	-	EURHAB gydymo protokolas minkštųjų

		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa	50928	Didelė		-	-	-	-	-	audinių rabdo-navikams netaikomas VULSK, todėl ištrintas.
		3x DOX, 3x ICE, 3xVCA + RT	8892	Didelė		-	-	-	-	-	
		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa + RT	50928	Didelė		-	-	-	-	-	
NRSTS (Ne-Rabdomiosarkomos)	EpSSG NRSTS 2005	3x ifosfamidas	6588	Didelė	NRSTS (Ne-Rabdomiosarkomos)	EpSSG NRSTS 2005	3x ifosfamidas	6588	Didelė	Didelė	-
		4x ifosfamidas	8784	Didelė			4x ifosfamidas	8784	Didelė	Didelė	
		5x ifosfamidas	10980	Didelė			5x ifosfamidas	10980	Didelė	Didelė	
		6x ifosfamidas	13176	Didelė			6x ifosfamidas	13176	Didelė	Didelė	
Minkštųjų audinių sarkomos	EpSSG RMS 2005	Maža rizika pogrupis A	0	Maža	Minkštųjų audinių sarkomos	EpSSG RMS 2005	Maža rizika pogrupis A	0	Maža	Maža	-
		Standartinė rizika pogrupis B	5800	Vidutinė*			Standartinė rizika pogrupis B	5800	Maža	Didelė	
		Standartinė rizika pogrupis C (9x ifosfamidas)	13176	Didelė			Standartinė rizika pogrupis C (9x ifosfamidas)	13176	Didelė	Didelė	
		Standartinė rizika pogrupis C (5x ifosfamidas)	7320	Didelė			Standartinė rizika pogrupis C (5x ifosfamidas)	7320	Didelė	Didelė	
		Standartinė rizika pogrupis D (9x ifosfamidas)	13176	Didelė			Standartinė rizika pogrupis D (9x ifosfamidas)	13176	Didelė	Didelė	
		Didelė rizika ir grupė A + grupė C	13176	Didelė			Didelė rizika ir grupė A + grupė C	13176	Didelė	Didelė	

	Didelė rizika ir grupė A + grupė D	17376	Didelė
	Didelė rizika ir grupė B + grupė C	13176	Didelė
	Didelė rizika ir grupė B + grupė D, vidutinė-didelė rizika	17376	Didelė
CWS-guidance-2014	RMS maža rizika pogrupis A	-	-
	RMS standartinė rizika pogrupis B	-	-
	1RMS standartinė rizika pogrupis C be RT	-	-
	RMS standartinė rizika pogrupis C su RT	-	-
	RMS standartinė rizika pogrupis D	-	-
	RMS didelė rizika pogrupiss E, F, G	-	-
	RMS labai didelė rizika pogrupis H	-	-
	"*RMS-like*" (SySa, STET (EES, pNET), UDS)	-	-

	Didelė rizika ir grupė A + grupė D	17376	Didelė	Didelė	
	Didelė rizika ir grupė B + grupė C	13176	Didelė	Didelė	
	Didelė rizika ir grupė B + grupė D, vidutinė-didelė rizika	17376	Didelė	Didelė	
CWS-guidance-2014	RMS maža rizika pogrupis A	0	Maža	Maža	Įtrauktas CWS-guidance-2014 gydymo protokolas.
	RMS standartinė rizika pogrupis B	5856	Maža	Didelė	
	1RMS standartinė rizika pogrupis C be RT	13176	Didelė	Didelė	
	RMS standartinė rizika pogrupis C su RT	7320	Didelė	Didelė	
	RMS standartinė rizika pogrupis D	13176	Didelė	Didelė	
	RMS didelė rizika pogrupiss E, F, G	13176	Didelė	Didelė	
	RMS labai didelė rizika pogrupis H	13176	Didelė	Didelė	
	"*RMS-like*" (SySa, STET (EES, pNET), UDS)	13176	Didelė	Didelė	

		"*Non-RMS-like*" (NRTS) maža rizika	-	-			"Non-RMS-like" (NRTS) maža rizika	0	Maža	Maža	
		"*Non-RMS-like*" (NRTS) vidutinė rizika	-	-			"*Non-RMS-like*" (NRTS) vidutinė rizika	0	Maža	Maža	
		"*Non-RMS-like*" (NRTS) didelė rizika	-	-			"*Non-RMS-like*" (NRTS) didelė rizika	13176	Didelė	Didelė	
		Metastatiniai minkštųjų audinių navikai	-	-			Metastatiniai minkštųjų audinių navikai	13176	Didelė	Didelė	
		CWS angiosarkomai	-	-			CWS angiosarkomai	6000	Didelė	Didelė	
Germinogeninių ląstelių navikai	SIOP CNS GCT II	-	-	-	Germinogeninių ląstelių navikai	SIOP CNS GCT II	CCLG	4392	Maža	Didelė	Įtrauktos SIOP CNS GCT II protokolo CCLG ir 2xPEI+2xHD-PEI gydymo šakos.
		NGGCT	7320	Didelė			NGGCT	7320	Didelė	Didelė	
		-	-	-			2xPEI+2x HD-PEI	8540	Didelė	Didelė	
	-	-	-	-		PEB+JEB blokai	Maža rizika	0	Maža	Maža	Įtraukti PEB + JEB blokai germinogeninių ląstelių navikams.
	-	-	-	-			Vidutinė rizika	0 (cis/karbo platina)	Maža	Maža	
	-	-	-	-			Didelė rizika	0 (cis/karbo platina)	Maža	Maža	
Kepenų navikai	PHITT	Grupė A1 labai maža rizika	0	Maža	Kepenų navikai	PHITT	Grupė A1 labai maža rizika	0	Maža	Maža	-

		Grupė A2 labai maža rizika	0 (cisplatina)	Maža			Grupė A2 labai maža rizika	0 (cisplatina)	Maža	Maža	
		Grupė B1 maža rizika / B2	0 (cisplatina)	Maža			Grupė B1 maža rizika / B2	0 (cisplatina)	Maža	Maža	
		Grupė C vidutinė rizika SIOPEL3HR / C5VD/ CDDP-M	0 (cisplatina)	Maža			Grupė C vidutinė rizika SIOPEL3HR / C5VD/ CDDP-M	0 (cisplatina)	Maža	Maža	
		Grupė D1 didelė rizika HB SIOPEL4, D2 didelė rizika CDCE, CDVI	0 (cis/karb oplatina)	Maža			Grupė D1 didelė rizika HB SIOPEL4, D2 didelė rizika CDCE, CDVI	0 (cis/karbo platina)	Maža	Maža	
		Grupė E1 pašalinta HCC	0	Maža			Grupė E1 pašalinta HCC	0	Maža	Maža	
		Grupė E2 pašalinta HCC PLADO	0 (cisplatina)	Maža			Grupė E2 pašalinta HCC PLADO	0 (cisplatina)	Maža	Maža	
		Grupė F nepašalinta/metastatinė PLADO sorafenibas, GEMOX	0 (cisplatina)	Maža			Grupė F nepašalinta/metastatinė PLADO sorafenibas, GEMOX	0 (cisplatina)	Maža	Maža	
CNS navikai					**CNS navikai**						-
Optinė glioma	SIOP LGG 2004	Vinkristinas, karboplatina, etoposidas. (Jei alergija: cyclo)	0	Maža	Optinė glioma	SIOP LGG 2004	Vinkristinas, karboplatina, etoposidas. (Jei alergija: cyclo)	0	Maža	Maža	-
Intradural-extramedullary tumor	HIT-MED + KKLT		49500	Didelė	-	-	-	-	-	-	HIT-MED + KKLT gydymo protokolas netaikomas VULSK, todėl ištrintas.

Meduloblastoma	SR ACNS0331	Ciklofosfamidas, lomustinas	13200	Didelė	Meduloblastoma	SR ACNS0331	Ciklofosfamidas, lomustinas	13200	Didelė	Didelė	-
	HR ACNS0332	Ciklofosfamidas	12000	Didelė		HR ACNS0332	Ciklofosfamidas	12000	Didelė	Didelė	-
	PNET 5	MB-SR / MB-WNT-HR(>16 metų)	17600	Didelė		PNET 5	MB-SR / MB-WNT-HR(>16 metų)	17600	Didelė	Didelė	-
		MB-WNT-HR (<16 metų)	13200	Didelė			MB-WNT-HR (<16 metų)	13200	Didelė	Didelė	
		MB-SHH-TP53: Jokių alkilinančių preparatų	0	Maža			MB-SHH-TP53: Jokių alkilinančių preparatų	0	Maža	Maža	
	-	-	-	-		HIT-MED Guidance	3x SKK	7200	Didelė	Didelė	Įtrauktas HIT-MED Guidance gydymo protokolas meduloblastomai.
	-	-	-	-			3x SKK+ 2x mSKK	12000	Didelė	Didelė	
	-	-	-	-			3x intensyvi indukcija + 1st HDCT + 2nd HDCT + 6x palaikomasis gydymas	4500+intensyvi indukcija	Didelė	Didelė	
	-	-	-	-			RT + 8x palaikomasis gydymas	0 (cisplatina)	Maža	Maža	
	-	-	-	-			2x SKK + RT + 4x palaikomasis gydymas	4800	Maža	Didelė	
	EURHAB	3x DOX, 3x ICE, 3xVCA	8892	Didelė		EURHAB	3x DOX, 3x ICE, 3xVCA	8892	Didelė	Didelė	-

Atipiniai terato/rabdo navikai		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa	50928	Didelė	Atipiniai terato/rabdo navikai		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa	50928	Didelė	Didelė	
		3x DOX, 3x ICE, 3xVCA + RT	8892	Didelė			3x DOX, 3x ICE, 3xVCA + RT	8892	Didelė	Didelė	
		2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa + RT	50928	Didelė			2x DOX, 2x ICE, 2x VCA + CARBO Tiotepa + RT	50928	Didelė	Didelė	
Disgerminoma	WHO IV SIOP CNS GCT II HR-non-germinoma	PEI	8540	Didelė	-	-	-	-	-	-	WHO IV SIOP CNS GCT II HR-non-germinoma gydymo protokolas netaikomas VULSK, todėl ištrintas.
-	-	-	-	-	Ependimoma	HIT-MED Guidance	3x SKK+2x mSKK	12000	Didelė	Didelė	Įtrauktas HIT-MED Guidance gydymo protokolas ependimomai.
-	-	-	-	-			Vietiškai RT	0	Maža	Maža	
-	-	-	-	-			2x mSKK + RT	4800	Maža	Didelė	
-	-	-	-	-	Pineoblastoma	HIT-MED Guidance	CARBO/ETO-96 val. indukcija + 1st HDCT + 2nd HDCT + 6x palaikomasis gydymas)	4500	Maža	Didelė	Įtrauktas HIT-MED Guidance gydymo protokolas pineoblastomai.
-	-	-	-	-			RT + 8x palaikomasis gydymas	0 (cisplatina)	Maža	Maža	
-	-	-	-	-			2x SKK + RT + 4x palaikomasis gydymas	4800	Maža	Didelė	
Aukšto laipsnio glioma, tilto glioma	ACNS0126	Temozolamidas	0	Nežinoma	Aukšto laipsnio glioma, tilto glioma	ACNS0126	Temozolamidas	0	Nežinoma	Nežinoma	-

HGG	Infant HGG 2013/HIT SKK	IIs IIIs/1 IIIs/2 IVs	7200	Didelė	HGG	Infant HGG 2013/HIT SKK	IIs IIIs/1 IIIs/2 IVs	7200	Didelė	Didelė	-
-	-	-	-	-	Retinoblastoma	RB SFCE 2008-A	Maža rizika	0	Maža	Maža	Įtrauktas RB SFCE 2008-A gydymo protokolas retinoblastomai.
-	-	-	-	-			Vidutinė rizika pogrupis 1	1500	Maža	Maža	
-	-	-	-	-			Vidutinė rizika pogrupis 2	0	Maža	Maža	
-	-	-	-	-			Didelė rizika	3000 + KKLT	Didelė	Didelė	

* - Vidutinė mergaičių rizika ištrinta – remiantis naujausiomis rekomendacijomis, nevaisingumo rizika mergaitėms skirstoma į mažą ir didelę (1).

1. Mulder RL, Font-Gonzalez A, Hudson MM, Santen HM van, Loeffen EAH, Burns KC, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Hšakaonization Grupė. The Lancet Oncology. 2021 Feb 1;22(2):e45–56.

9 priedas. Vilniaus Regioninio Bioetikos Komiteto leidimas tyrimui

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2020 10 27 Nr.2020/10-1274-753

Tyrimo pavadinimas:

Vaikų vėžio diagnostikos ir stebėsenos optimizavimas vykdant TREL projektą

Protokolo Nr.:	TREL-2020
Versija:	2.0
Data:	2020 10 20
Informuoto asmens sutikimo forma:	1.0 (tėvams/globėjams) 2020 08 30 1.0 (12-17 m. amžiaus paaugliams) 2020 08 30
Pagrindinis tyrėjas:	**Jelena Rascon**
Įstaigos pavadinimas:	VšĮ Vilniaus universiteto ligoninė Santaros klinikos
Adresas:	Santariškių g. 2, Vilnius
Leidimas galioja iki:	**2023 12**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2020/10), vykusio 2020 m. spalio 27 d. sprendimu.

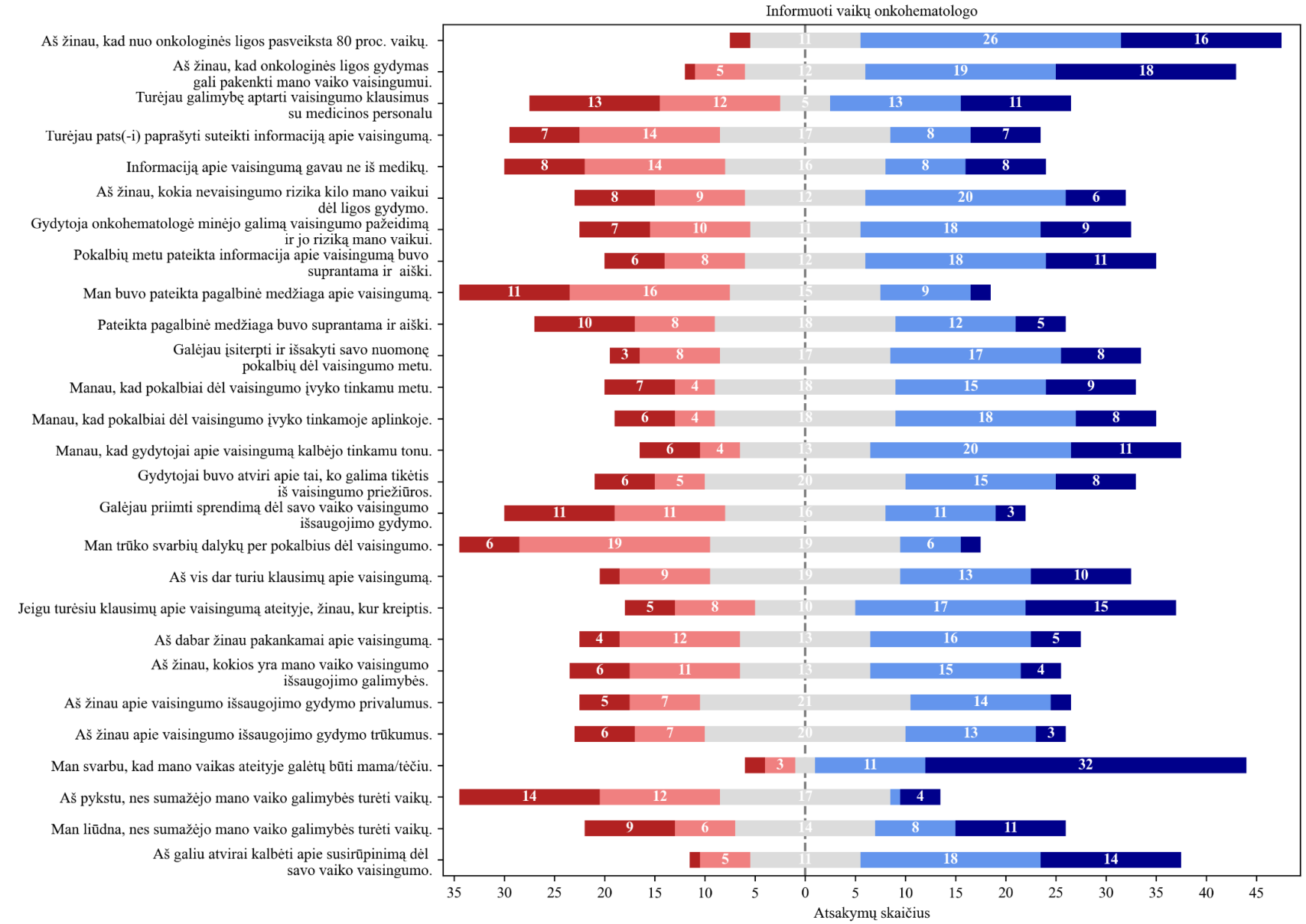
Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga
Universiteto g. 3
01513 Vilnius

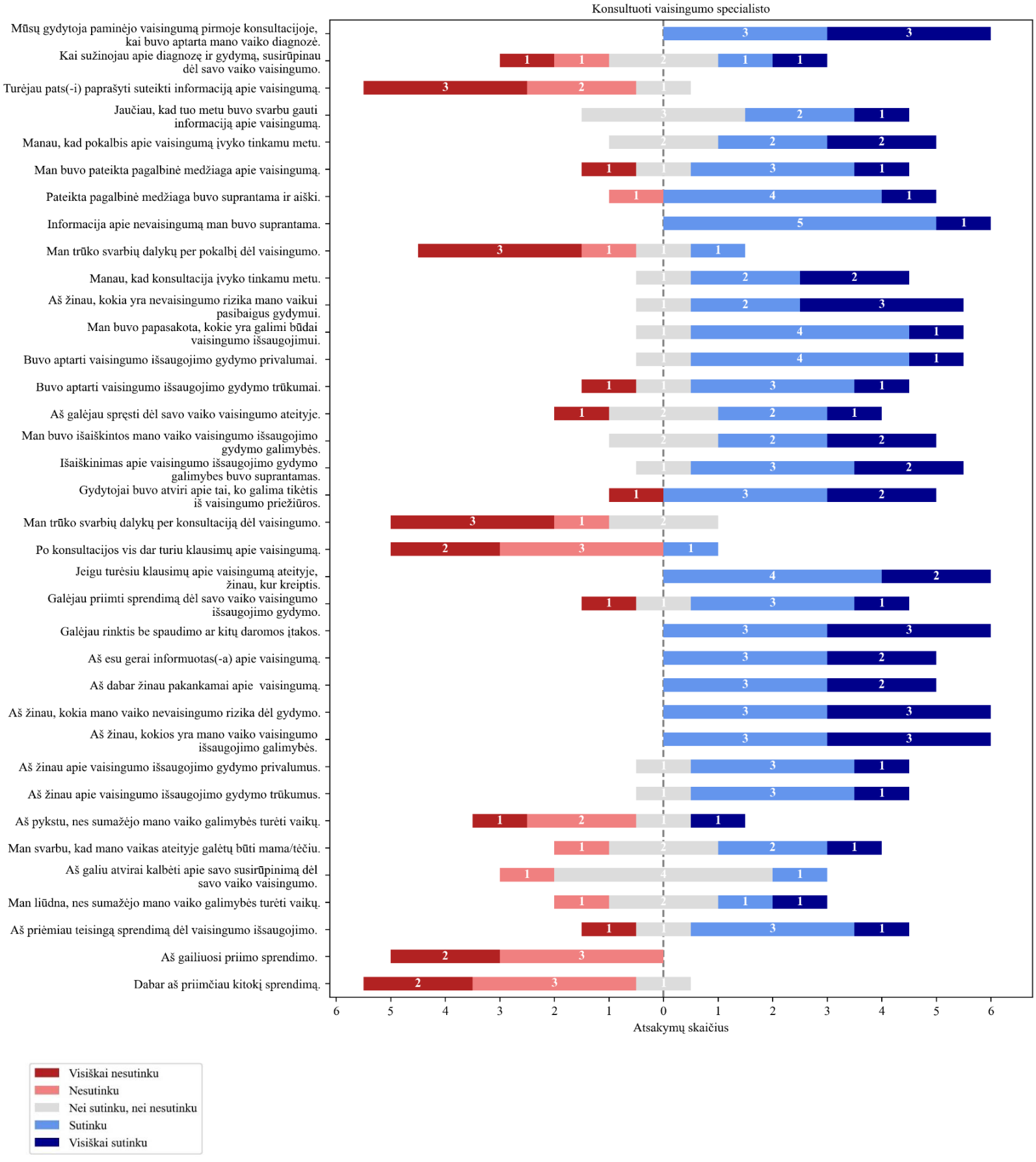
Duomenys kaupiami ir saugomi
Juridinių asmenų registre
Kodas 211950810

Komiteto duomenys:
M. K. Čiurlionio g. 21, LT- 03101 Vilnius
Tel. (8 5) 268 6998, el. p. rbtek@mf.vu.lt

10 priedas. Visi atsakymai į klausimus respondentų, informuotų apie vaisingumą gydytojo vaikų onkohematologo



11 priedas. Visi atsakymai į klausimus respondentų, konsultuotų vaisingumo specialisto



12 priedas. Informacinė skrajutė pacientams apie nevaisingumo riziką po onkologinės ligos gydymo

Twinning in Research and Education to improve survival in Childhood Solid Tumours in Lithuania

TREL

O jei kada nors norėsiu susilaukti vaikų?

Mieli pacientai,

Jūsų ligos gydymo metu, naikinant vėžines ląsteles, taip pat gali būti pažeidžiamos sveikos ląstelės. Kai kuriems pacientams tai reiškia sumažėjusį vaisingumą - galimybę turėti vaikų ateityje, pasveikus nuo onkologinės ligos.

Didelė rizika nevaisingumui:
kamieninių kraujodaros ląstelių transplantacija, viso kūno apšvita, radioterapija į galvos sritį/kiaušides/sėklides, kiaušidės/sėklidės pašalinimas kartu su chemoterapija, didelių dozių chemoterapija, cisplatinos preparatai (berniukams).

Būdai vaisingumo išsaugojimui:
mergaitėms - kiaušidžių audinio krioprezervacija (užšaldymas), kiaušialąsčių krioprezervacija
berniukams - spermos krioprezervacija

Daugiau informacijos galite teirautis savo gydytojo, pageidaujant galite būti nukreipti vaisingumo specialisto konsultacijai ir esant mažai nevaisingumo rizikai.

Mano (mano vaiko)_____
(vardas, pavardė)

vaisingumo pažeidimo rizika yra maža / didelė (pabraukite)

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

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A crosscut survey on reproductive health in Lithuanian childhood cancer survivors

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ABSTRACT

Objectives: Sexual dysfunction was reported to compromise the quality of life in childhood cancer survivors. The aim of our study was to evaluate the reproductive health in long-term pediatric cancer survivors by conducting a crosscut survey.

Material and methods: Childhood cancer survivors over 18 years of age, who were in remission for more than 5 years, were invited to complete a gender-specific questionnaire surveying on their reproductive health. Demographic and treatment data were retrieved from their medical records. Treatment modalities were reviewed for its potential gonadotoxicity.

Results: 34 (17 males and 17 females, respectively) from 346 addressed survivors (9.8%) completed the questionnaire. Median age and follow-up after diagnosis was 27 (18–35) and 14 (3–25) years, respectively. Some respondents reported sexual concerns: 11.8% males experienced problems with penetration, two males (11.8%) who underwent semen analysis were found to be azoospermic. Similarly, 11.8% females reported delayed puberty, the average age of menarche was 14 (12–17) years, 29.4% females reported irregular menstrual cycles. Cyclophosphamide equivalent dose (CED) differed significantly between the patients treated for leukemia, lymphoma and solid tumors (3000 vs 4352 vs 6660 mg/m^2, respectively, $p = 0.014$).

Conclusions: Low prevalence of sexual dysfunction, fertility related disorders or delayed puberty in childhood cancer survivors was found. However, the results should be interpreted with caution taking into account a low response rate.

Key words: late effects; long-term survivors; pediatric cancer; reproductive health; sexual dysfunction

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INTRODUCTION

Over the last few decades, a long-term survival rate after pediatric cancer has improved dramatically and nowadays exceeds 80% in most European countries [1]. High cure rates imply a constantly growing population of childhood cancer survivors. As a consequence, research activities are focused not only on overcoming resistant malignancies but also on the well-being of the cured persons who are at the risk for frailty, and suboptimal quality of life [2].

A healthy reproductive system is a cornerstone of the quality of life in young adult survivors. Sexual dysfunction was reported to be one of the most important side effects of pediatric cancer treatment [3]. Treatment intensity depends on cancer type, localization, spread of the disease (metastases) and other risk factors. Most patients are exposed to combined treatment including chemotherapy, surgery, radiotherapy, less frequently high-dose chemotherapy prior to hematopoietic stem cell transplantation and the immune therapy. All the approaches, used separately or in combination, could potentially have an adverse long-term effect on fertility [4, 5]. It is crucial to inform every patient (parents or guardians in pediatric setting) about the potential adverse effect of cancer treatment on the reproductive health and options for fertility preservation. The majority of childhood cancer survivors perceive they had not been provided sufficient information about reproductive health and had never underwent fertility testing [6, 7].

Studies have shown that in females chemotherapy regimens containing high-dose alkylating agents and abdominal/pelvic radiotherapy affected the gonadal function,

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and were associated with delayed puberty, premature ovarian insufficiency and follicular atresia, premature menopause and infertility [8]. In males, infertility was reported to be related to the use of alkylating agents, testicular radiation, or cranial irradiation [4]. Certain concomitant chemotherapy agents such as cisplatin, carboplatin, increase the risk of infertility in childhood cancer survivors [9–11].

Cumulative exposure to alkylating agents can be quantified using the cyclophosphamide equivalent dose (CED), as described by Green et al. [12] that compares the drugs based on the hematological toxicity. The adoption of the CED allows evaluation of the relationship between hematological toxicity and alkylating agent related late outcomes, such as infertility. The advantage of the CED is its derivation from actual drug doses rather than dependence on a drug dose distribution specific to a single population [12]. CED ≥ 4000 mg/m^2 is associated with a risk of infertility, while CED ≥ 8000 mg/m^2 is most likely to cause infertility leading to premature ovarian insufficiency in females [13] and increased chance of oligospermia and azoospermia in males [14].

The purpose of our study was to evaluate reproductive health in pediatric cancer survivors who were in a long-term remission and were in reproductive age. The research aimed at elucidating personal perception of the study participants with regard to their reproductive health, thus a surveying approach was adopted. Additionally, the exposure to gonadotoxic therapies reviewed was retrospectively.

MATERIAL AND METHODS

A single-center cross-sectional study was carried out from December 2016 to January 2018. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. The study population included childhood cancer survivors treated at the Center for Pediatric Oncology and Hematology, Vilnius University Hospital Santaros Klinikos. The inclusion criteria were defined as 1) age 18+ years as of December 2016; 2) childhood cancer (ICD-O-10 C00-C96) diagnosed in 1982-2011; 3) In remission 5+ years since diagnosis in December 2016. The study was approved by the Vilnius Regional Committee of Biomedical Research (Approval No.158200-16-873-385).

Survivors who met the inclusion criteria were identified at the institutional database. The identified cohort was contacted by regular certificated mail to the postal address available in the medical records: an invitation to participate in the study, an informed consent form, and a questionnaire were sent to each consignee. The respondents who signed the informed consent, completed the questionnaire, and returned it to the study center were included into the final analysis.

Two gender-specific questionnaires were elaborated by a multidisciplinary team of pediatric oncologist, obstetrician-gynecologist, urologist and clinical embryologist. The participants were invited to answer 17–18 questions regarding sexual health, ability to conceive, marital status/partnership (Supp. 1 available on https://journals.viamedica.pl/ginekologia_polska/issue). As a complementary service a consultation of a gender-appropriate reproductive health specialist was offered to all contacted survivors. Additionally, a summary of the study results was offered to be shared upon request.

The answers were collected from the completed questionnaires and analyzed anonymously. Baseline characteristics and treatment-related data (diagnosis, type of chemotherapy drugs used and dosages, information on radiotherapy and surgical treatment) were retrieved from the patients' paper or electronic medical records.

The exposure to alkylating agents was assessed by CED calculation using the equation described by Green et al. [12]: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose, mg/m^2) + 0.244 (cumulative ifosfamide dose, mg/m^2) + 0.857 (cumulative procarbazine dose, mg/m^2) + 14.286 (cumulative chlorambucil dose, mg/m^2) + 15.0 (cumulative BCNU dose, mg/m^2) + 16.0 (cumulative CCNU dose, mg/m^2) + 40 (cumulative melphalan dose, mg/m^2) + 50 (cumulative thioteps dose, mg/m^2) + 100 (cumulative nitrogen mustard dose, mg/m^2) + 8.823 (cumulative busulfan dose, mg/m^2). Cumulative treosulfan dose was not included in the original computation. The dacarbazine cumulative dose was calculated as a single drug — being quite different from other classical alkylating agents, it is not included in CED calculation. In addition, a cumulative dose of platinum compounds (carboplatin and cisplatin) was evaluated. Data on the surgery and radiotherapy for potential involvement of gonadal areas were revised. The data evaluation time-point was January 2018.

Demographic and treatment-related characteristics were assessed using descriptive statistics. The median-test was used to compare the medians of cumulative CED between different types of childhood cancer. SPSS ver. 17 (IBM Corp., Armonk, NY) was used for all quantitative analyses, p-value less than 0.05 was considered to be significant.

RESULTS

In total 346 childhood cancer survivors [195 (56.4%) males and 151 (43.6%) females] matched the inclusion criteria (Supp. 2 available on https://journals.viamedica.pl/ginekologia_polska/issue). In contrast to the expectations, the response rate was very low – only 34 (9.8%) survivors answered the questions. One hundred twenty (34.7%) consignees appeared to be unavailable: in 99 (28.6%) cases the letters were not reclaimed at the post office, in 19 (5.5%)

Table 1. Baseline characteristic of the study participants

Variables	Study participants		
	Males (n = 17)	Females (n = 17)	All (n = 34)
Current age (years)			
Median	27	25	27
(min-max)	(18–35)	(18–31)	(18–35)
Age at cancer diagnosis (years)			
Median	14	14	14
(min-max)	(2–17)	(12–18)	(2–18)
Follow-up time (years)			
Median	13.5	15	14
(min-max)	(3–24)	(5–24)	(3–24)
Cancer type*			
Leukemia, myeloproliferative disorders, myelodysplasia n, (%)	6 (35.3)	7 (36.8)	13 (36.1)
Lymphomas and reticuloendothelial neoplasms n, (%)	7 (41.2)	8 (47)	15 (44.1)
Tumors in the Central Nervous System n, (%)	1 (2.8)	0	1 (2.8)
Neuroblastoma and other peripheral nerve sheath tumors n, (%)	0	2 (10.5)	2 (5.6)
Osteosarcoma and other bone malignancies n, (%)	2 (11.8)	0	2 (5.6)
Other epithelial tumors and melanoma n, (%)	1 (5.9)	0	1 (2.8)

*according to ICCC-3 (International classification of childhood cancer)

cases the postal address was no longer valid, 2 (0.6%) patients had died. However, the majority of the invited survivors 190 (54.9%) received the invitation but refrained from sharing their answers. None of them wished to take the opportunity to see a specialist in reproductive health.

Thirty-four (9.8%) respondents (17 males and 17 females) were included into the final analysis. The median age at the time of evaluation was 27 (18–35) years, meanwhile the one at cancer diagnosis — 13 (2–18) years. The age did not differ between males and females (Tab. 1). Leukemia and lymphoma were the most common types of malignancies among the respondents [13 (36.1%) and 15 (44.1%), respectively] whereas only 6 (17.6%) were affected by solid tumors. All patients were diagnosed with only one type of cancer, there were no cases of a second malignant neoplasm. The distribution of cancer types across survivors who met the inclusion criteria and were invited to participate in the study showed a slight predominance of leukemia as compared to the study cohort: among 346 survivors, 165 (47.7%) were diagnosed with leukemia, 122 (35.3%) with lymphoma, and only 59 (17.1%) with solid tumors (Supp. 2 available on https://journals.viamedica.pl/ginekologia_polska/issue).

Most of the survivors were treated with chemotherapy (n = 33, 97%), radiotherapy was delivered to 18 patients (54.5%), six (17%) patients were operated on, and two patients received an allogeneic hematopoietic stem cell transplantation (HSCT) (Tab. 2). Treatment protocols varied according to the time period of the diagnosis and type of malignancy. The majority of leukemia patients were treated according to Berlin-Frankfurt-Münster (BFM) based protocols while one respondent was cured after being treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) A*cute Lymphoblastic* Leukemia (ALL) 2008 guidelines. The treatment protocols are indicated in the Table 2 and are outlined in details in the Supplement 3 (available on https://journals.viamedica.pl/ginekologia_polska/issue). None of the survivors were irradiated on abdominal field, however nine respondents received cranial irradiation.

Review of the exposure to gonadotoxic drugs revealed significantly higher median cumulative CED in patients treated for solid tumors as compared to those treated for lymphoma and leukemia (6660 vs 4352 vs 3000 mg/m^2, respectively, p = 0.014). According to the expectation in leukemia cohort CED was much higher in the recipients of allogeneic HSCT as compared to non-transplanted patients. Additionally, females affected by Hodgkin lymphomas were treated with dacarbazine (median cumulative dose was 2250 mg/m^2) whereas platinum compounds were frequently added in solid tumors (the respective median cumulative dose for carboplatin and cisplatin was 1500 and 50 mg/m^2, Tab. 2).

Perception of the reproductive health in males

The answers to the questions provided by the male survivors are summarized in Table 3. All 17 respondents were able to get an erection and ejaculate, two survivors (11.8%) reported problems with penetration (both were single at the time of evaluation). Ten young men (58.8%) were married or had a partner, the remaining seven (41.2%) were single at the time of assessment. The average sexual activity was three times per week (ranged from 0 to 10). The majority of males (94.1%) felt normal sexual desire, on a ten-point scale the average libido score was nine (ranged from 3 to 10). Thirteen survivors (76.5%) used contraception, preferably the barrier one. Notwithstanding, 14 out of 17 (82.4%) did

Table 2. Details on exposure to cytotoxic drugs and other gonadotoxic treatment

Cancer type n (%)	Treatment modality			Cumulative dose of gonadotoxic drugs Median* (min-max), mg/m^2			
	Chemotherapy (n)	Radiotherapy (n)	Irradiated area	CED	Dacarbazine	Carboplatin	Cisplatin
Leukemias 13 (38.2)				**3000** (1000–8817)**	n.a.	n.a.	n.a.
ALL 9 (26.5)	#BFM-ALL-90/95/2000 (8) #NOPHO-ALL-2008 (1)	8	Cranial	3000 2000	n.a.	n.a.	n.a.
AML 2 (3.8)	#BFM-AML-98 (2)	0	n.a.	1000	n.a.	n.a.	n.a.
Cx + HSCT 2 (3.8)	#BFM-ALL-2000 + BuCyEto (1) #BFM-AML-98 + CyTreo (1)	0	n.a.	8817 5700***	n.a.	n.a.	n.a.
Lymphomas 15 (44.1)				**4352** (0–5157)**	**2250 (1500–3000)**	**1200**	n.a.
Hodgkin lymphoma 9 (26.5)	2 x OEPA 2 x ABVD (1) #HD-95 (2) #GPOHD-2001 (5) Other**** (1)	5	Chest	4000 (0–5157) 0 4571 2000 (0–4000) 5157	2250 (1500–3000) 1500 n.a. 3000 1500	n.a. n.a. n.a. n.a. 1200	n.a. n.a. n.a. n.a. n.a.
Non-Hodgkin lymphoma 6 (17.6)	#BFM-NHL-95 (6)	1	Chest	0	n.a.	n.a.	n.a.
Solid tumors 6 (17.6)				**6660** (0–35964)**	**4000**	**1500 (0–2100)**	**50 (0–640)**
CNS tumor 1 (2.9)	CPT-SIOP-2009	1	Cranial	6000	n.a.	2100	n.a.
Neuroblastoma 2 (3.8)	#NB-90	1	Chest	9720 (7320–12120)	4000	1500	640
Ewing sarcoma 1 (2.9)	IE plus VAdriaC	1	Femur	35964	n.a.	n.a.	n.a.
Osteosarcoma 1 (2.9)	COSS96+4 x BCD	n.a.	Fibula	1200	n.a.	750	100
Adenocarcinoma 1 (2.9)	No chemotherapy	n.a.	None	n.a.	n.a.	n.a.	n.a.

#for the protocol details refer to supplemental material; n.a. – not administered; *numbers corresponding to one patient indicated without range; **p = 0.007 (Median Test); ***treosulfan was not included in CED computation; ****2 x OEPA 1 x COPP 2 x ABVD 2 x JEB

Abbreviations: ABVD — doxorubicin 25 mg/m^2 on days 1 and 15, bleomycin 10,000 units/m^2 on days 1 and 15, vinblastine 6 mg/m^2 on days 1 and 15, dacarbazine 375 mg/m^2 on days 1 and 15; BCD — bleomycin 15 mg/m^2 daily, cyclophosphamide 600 mg/m^2 daily, dactinomycin 600 ug/m^2 daily for two days; BuCyEto — preparative regimen (cumulative dose) busulfan 16 mg/m^2, cyclophosphamide 120 mg/kg, etoposide 40 mg/kg; CED — cyclophosphamide equivalent dose; COPP — cyclophosphamide 650 mg/m^2 on days 1 and 8, vincristine 1.4 mg/m^2 on days 1 and 8, procarbazine 100 mg/m^2 on days 1–14, prednisone 40 mg/m^2 on days 1–14; CPT-SIOP-2009 — Intercontinental Multidisciplinary Registry and Treatment Optimization Study for Patients With Choroid Plexus Tumors – carboplatin 350 mg/m^2 on cycles 2, 4 and 6: on days 2 and 3, cyclophosphamide 1000 mg/m^2 on cycles 1, 3 and 5: on days 2 and 3, etoposide 100 mg/m^2 on cycles 1, 2, 4, 5and 6: on days 1–5, vincristine 1.5 mg/m^2 on cycles 1–6: on day 5; CyTreo — preparative regimen (cumulative dose) cyclophosphamide 120 mg/kg, treosulfan 36000 mg/m^2; Cx — chemotherapy; IE plus VAdriaC for Ewing's Sarcoma — vincristine 2mg/m^2 on day 1 only, doxorubicin 45 mg/m^2/day x 2 days, doxorubicin 35 mg/m^2/day x 2 days, cyclophosphamide 900 mg/m^2/day x 5 days, etoposide 100 mg/m^2 /day x 5 days, ifosfamide 1800 mg/m^2 /day x 5 days, total dose of doxorubicin 550 mg/m^2; JEB — carboplatin 600 mg/m^2 on day 1, etoposide 120 mg/m^2 on days 1–3, bleomycin 15 mg/m^2 on days 2, 9 and 12; OEPA — prednisone 60 mg/m^2 on days 1–15, vincristine 1.5 mg/m^2 on days 1, 8 and 15, doxorubicin 40 mg/m^2 on days 1 and 15, etoposide 125 mg/m^2 on days 1–5

Table 3. Responses provided by the male survivors (n = 17)

Variable	n (%)
Feel sexual desire Feel low sexual desire	16 (94.1) 1 (5.9)
Able to get an erection Unable to get an erection	17 (100) 0 (0)
Able to ejaculate Unable to ejaculate	17 (100) 0 (0)
Able to insert penis into vagina Unable to insert penis into vagina	15 (88.2) 2 (11.8)
Have a partner No partner	10 (58.8) 7 (41.2)
Sexual activities per week, median (min-max)	3 (0–10)
Libido*, median (min-max)	9 (3–10)
Do not use contraception Use contraception Barrier contraceptives *Coitus interruptus* Contraception used by partner	4 (23.5) 13 (76.5) 10 (76.9) 1 (7.7) 2 (15.4)
Trying to conceive at the moment, Not trying to conceive at the moment	3 (17.7) 14 (82.4)
Time trying to conceive (months), median (min-max)	1 (1–12)
Have biological children Do not have biological children	4 (23.5) 13 (76.5)
Time to conceiving (months), median (min-max)	2 (1–16)
Partner has children Did not know if the partner has children Partner does not have children	1 (5.9) 6 (35.3) 10 (58.8)
Azoospermic in semen analysis Did not undergo semen analysis	2 (11.8) 15 (88.2)
Received chemotherapy during adulthood Received radiotherapy during adulthood Take medication constantly	2 (11.8) 1 (5.9) 2 (11.8)
Close** relatives had fertility problems Close** relatives did not have fertility problems	1 (5.9) 16 (94.1)

*scored from 1 to 10; **defined as grandfather, father, brother, cousin

Table 4. Responses provided by the female survivors (n = 17)

Variables	n (%)
Normal puberty Delayed puberty	15 (88.2) 2 (11.8)
Age of menarche, median (min-max)	14 (12–17)
Regular menstrual cycle Irregular menstrual cycle	12 (70.6) 5 (29.4)
Have a partner Divorced No partner	10 (58.8) 2 (11.8) 5 (29.4)
Sexual activities per week, median (min-max)	1 (0–9)
Libido*, median (min-max)	5 (0–10)
Do not use contraception Use contraception Barrier contraceptives Hormonal contraceptives *Coitus interruptus* All types of contraceptives No answer	8 (47.1) 7 (41.2) 3 (42.9) 2 (28.6) 1 (14.3) 1 (14.3) 2 (11.8)
Have biological children Do not have biological children	7 (41.2) 10 (58.8)
Time to conceive (months), median (min-max)	3 (1–8)
Partner has children Partner does not have children The partner has never had another partner Has never have sexual relation	2 (11.8) 10 (58.8) 3 (17.6) 2 (11.8)
Experienced some fertility concerns No fertility problems	2 (11.8) 15 (88.3)
Had gynecological problems Did not have gynecological problems	3 (17.6) 14 (82.4)
Have been treated for infertility Treated with hormonal replacement therapy Close** relatives had fertility problems	0 0 0
Received chemotherapy during adulthood Received radiotherapy during adulthood Take medication constantly	2 (11.8) 1 (5.9) 4 (23.6)

*scored from 1 to 10; **defined as sister, mother, grandmother

not intend to conceive and did not have biological children (67.5%) at the time of the evaluation. The median time of conception after cessation of contraceptives in four males (23.5%) who had offspring was two months (range 1–16). Three males had one child each, one survivor had two healthy children. Two respondents (11.8%) underwent semen analysis, both were found to be azoospermic. Both were married or had a partner, one survivor was trying to conceive. One of the azoospermic males was treated for Ewing's sarcoma, diagnosed at 15 years of age (CED 35964 mg/m^2), another one – for Hodgkin's lymphoma, diagnosed at 12 years of age (CED 4571 mg/m^2). Another patient reported concerns potentially affecting reproductive health was chemo- and radiotherapy received beyond 18 years of age, one suffered from parotitis during childhood and one male reported impaired fertility as a family problem.

Perception of the reproductive health in females

The responses of female survivors are summarized in Table 4. Two (11.8%) out of 17 females reported delayed puberty. Median age of menarche was 14 (12–17) years — slightly delayed as compare to healthy Lithuanian population (13.5 years) [15]. Twelve (70.6%) participants had regular menstrual cycles, whereas 5 (29.4%) reported irregular bleeding. More than half of respondents (58.8%) were married or had a partner. Females reported median 1 (0–9) sexual activity per week, and 5 (0–10) points of libido on average. Seven (41.2%) survivors succeeded to conceive with a median time of conception was three [1–8] months after cessation of contraception. Eight (47.1%) females did not use any methods to avoid conception while the other half used different contraceptives (Tab. 4). The pregnancies terminated in seven full term pregnancies and three

miscarriages. Only two (11.8%) females reported fertility problems. However, gynecological concerns such as pelvic adhesion, polycystic ovarian syndrome, uterine leiomyomas /fybroids were more frequent. One participant suffered/ from a sexually transmitted disease, another one underwent surgeries of the uterus or ovaries. None of the participants were treated for infertility or sought for assisted reproduction, hormonal replacement therapy (HRT) or had family history of infertility. Two (11.8%) females reported having received chemotherapy or radiotherapy beyond the age of 18. Four respondents took daily medicines: Two (11.8%) were taking L-Thyroxine (both of them had children), one — *beta blockers*, the fourth one was on immunoglobulin replacement therapy due to a secondary immune deficiency following HSCT.

DISCUSSION

The current study is the first attempt to address the quality of reproductive health in Lithuanian childhood cancer survivors. The crosscut survey aimed at capturing impairments of reproductive health in a specific cohort of childhood cancer survivors known to have long-term late effects related to cancer treatment.

The most relevant limitation of our study is a low number of survivors who reported their experiences. The obtained results derived only from 34 out of 346 (9.8%) addressed survivors who fulfilled the questionnaires. More than half of the consignees (190, 54.9%) received the questionnaire but did not wish to participate in the survey. This fact raises a concern of feasibility to address such a delicate issue as reproductive and sexual health in childhood cancer survivors many years after treatment — the median follow-up of the respondents was 14 years. One could speculate that those who did have sexual or fertility worries were reluctant to disclose them or opted for the 'right to be forgotten' [16]. The stigma of cancer is still prevalent and many survivors prefer to avoid sharing their disease- or treatment-related experiences and its consequences. Some parents of very young children protected them from knowing that they were treated for cancer (personal experience), and presumably did not inform them about the mailed invitation. Other studies reported a variable response rate to the questionnaires regarding the reproductive function in childhood cancer survivors – the percentage of responders varied from 29.3% to 78.6% [13, 17–21]. A low response rate may suggest a response bias and limited ability to generalize the results. On the other hand, many survivors pointed out insufficient information on the impact of cancer treatment on fertility and its preservation options [6, 21–23]. Raising awareness of potential fertility harm after completion of therapy would facilitate the assessment of reproductive health in the future.

Of note, one third (34.7%) of our survivors did not receive the mail due to demographic changes in the country – the emigration rate in Lithuania was the third highest in the European Union in 2017 [24], young emigrants (20–34 years) comprising the largest group [25]. A high number of citizens who left their home country reflected a global trend of extreme mobility of young people. Thus, a pan-European system of surveillance of pediatric cancer survivors such as Survivorship Passport [26] would enable to provide an appropriate and timely care to this vulnerable population across Europe. The implementation of this digital tool translated to several European languages would facilitate access to the information on treatment and recommendations of care independently of the living place, at least in Europe.

The second limitation of the study was a retrospective way to retrieve data on treatment. In contrast to the cancer type distribution in all survivors eligible for the study (n = 346) who were treated mostly for leukemia [n = 165 (47.7%), Supp. 2] in the responders' cohort lymphoma was the predominant diagnosis [n = 15 (44.1%), Table 1]. The documentation analysis was limited to the study participants' records. As a consequence, the treatment applied was quite heterogenous, especially in the solid tumor group. Thus, only a descriptive data review could be carried out. Nevertheless, even in such a small and heterogenous group we could demonstrate much higher exposure to gonadotoxic drugs expressed as a significantly higher median CED in solid tumors as compared to leukemia and lymphoma ($p = 0.014$) as well as more complex treatment. Although there is no data comparing median CEDs across different types of childhood cancer, some studies have shown that solid tumors, particularly sarcomas, are treated with a high-dose alkylating agent therapy, which is related to males' infertility in the adulthood as well as treatment for Hodgkin lymphoma can cause infertility in males [17].

In our survey, the perception of sexual dysfunction among childhood cancer survivors was similar to that observed among healthy population: in males the rate of low sexual desire or difficulties in penetration did not exceed 11.2% that is comparable to the rate observed in young healthy Lithuanian males [27]. The results differ from data reported by other groups showing high prevalence of sexual dysfunction in childhood cancer survivors [28, 29]. The inconsistency is most probably attributable to a non-response bias as discussed above. There are no data on exact prevalence of infertility among healthy Lithuanian population. Datta et al., reported an infertility rate of 12.5% among healthy women and 10.1% among men in Britain [30]. According to World Health Organization, global infertility prevalence rates are difficult to determine, however, approximately one in every four couples in developing countries had been found to be affected by

infertility [31]. Specifically, adult cancer survivors encounter reproductive health worries as well – womens' pregnancy rates are quite low [32]. It seems that the adverse effect of systemic treatment was strongly related with a patient's age [33], therefore childhood cancer survivors are exposed at increased risk of infertility. Males are in a higher risk for hypogonadism and sexual dysfunction [34]. Both male and female survivors lacked knowledge about infertility and underestimated the risk of infertility [35]. In our study only few males had biological children and attempted to conceive probably due to the young age of the respondents (median current age was 25 years). However, in this small cohort study, two males were azoospermic, both were treated with high cumulative doses of gonadotoxic drugs, CED ≥ 4000 mg/m^2, which is known to be related to impaired spermatogenesis [17].

The percentage of men having low semen quality in male childhood cancer survivors (11.8%) are in parallel with semen quality of young men from the general population in Baltic countries (11–15% of them have low semen quality) [36]. Our study replicated the data published by other study groups who found that infertility was most prevalent among male survivors treated for sarcomas and Hodgkin lymphoma. In addition, the risk of permanent sterility was especially high when the cumulative dose of cyclophosphamide was greater than 7.5 g/m^2 [17, 37]. This finding raises a concern that the number of azoospermic survivors could be higher if semen analysis was offered as a routine follow-up investigation and points out on the relatively easy preservation of fertility in male adolescents.

Only a few of female participants reported delayed puberty, fertility-related or gynecological problems. None of the respondents was treated for infertility or used HRT, with 29.4% reported an irregular menstrual cycle. Few studies investigated the age of menarche of childhood cancer survivors. Some findings suggested that childhood cancer treatment including cranial radiation in girls resulted in a significantly earlier menarche [38]. Other stated that cranial irradiation appeared to have a minimal impact on the onset of puberty [39]. However, survivors of the central nervous system tumors appeared to be at significant risk of both early and late menarche associated with radiotherapy [40]. Our study did not include a comparison group, it would be insightful to compare reproductive health of survivors with their healthy siblings as it was done in some other studies [14, 41]. Data from other studies showed that female survivors are at a future risk of premature menopause (before 40 years) [42–44], they also had an increased risk of clinical infertility (> 1 year of attempts at conception without success) compared to siblings [41]. Our current study did not include a hormonal analysis that could have given a better estimation of the prevalence of sexual dysfunction. Other similar studies found that cancer survivors had significantly lower anti-Müllerian hormone and higher follicle-stimulating hormone levels [19, 45–48].

In addition, psychosexual and social problems of childhood cancer survivors could be taken into account as they were reported in other studies, such as lower rates of marriage and parenthood, delayed sexual intercourse, and concerns regarding the reproductive function [49, 50]. As the study included the survivors treated more than a decade ago, none of them was appropriately informed about the impact of the treatment on reproductive health. The availability of fertility preservation techniques was quite limited at that time. Due to the dramatic changes occurred in current practice, prospective counseling on fertility preservation must be offered to all patients and their families.

CONCLUSIONS

To summarize, we found a low prevalence of sexual dysfunction, fertility related or puberty disorders in childhood cancer survivors, however, considering a low response rate, the results should be interpreted with caution. Potential azoospermia after high CED in male patients should imply mandatory fertility preservation before treatment whenever possible. This study is the first attempt to address the quality of reproductive health in Lithuanian childhood cancer survivors that unraveled important concerns to be improved in clinical practice. Implementation and equal access to fertility preservation techniques (e. g. cryopreservation of semen and ovarian tissue) should be prioritized to minimize adverse effect of infertility after cancer therapy. An appropriate counseling of all cancer patients and families on potential adverse effect of the treatment on reproductive health would facilitate a highly warranted prospective research in a larger scale in the future.

Acknowledgments

Not applicable.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

ESR wrote the manuscript, ZB and ZG designed female questionnaire, RA and GV designed male questionnaire, ESR, MJ and RV collected and retrieved the data, ESR, KZ and JR analyzed the data, JR conceptualized and supervised the study. All authors contributed to the study conception, bioethical approval, critically revised the manuscript, agreed and approved the final version for submission.

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Development of a questionnaire to evaluate female fertility care in pediatric oncology, a TREL initiative

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Abstract

Background: Currently the five-year survival of childhood cancer is up to 80% due to improved treatment modalities. However, the majority of childhood cancer survivors develop late effects including infertility. Survivors describe infertility as an important and life-altering late effect. Fertility preservation options are becoming available to pre- and postpubertal patients diagnosed with childhood cancer and fertility care is now an important aspect in cancer treatment. The use of fertility preservation options depends on the quality of counseling on this important and delicate issue. The aim of this manuscript is to present a questionnaire to determine the impact of fertility counseling in patients suffering from childhood cancer, to improve fertility care and evaluate what patients and their parents or guardians consider good fertility care.

Methods: Within the framework of the EU-Horizon 2020 TREL project, a fertility care evaluation questionnaire used in the Netherlands was made applicable for international multi-center use. The questionnaire to be used at least also in Lithuania, incorporates patients' views on fertility care to further improve the quality of fertility care and counseling. Results evaluate fertility care and will be used to improve current fertility care in a national specialized pediatric oncology center in the Netherlands and a pediatric oncology center in Lithuania.

Conclusion: An oncofertility-care-evaluation questionnaire has been developed for pediatric oncology patients and their families specifically. Results of this questionnaire may contribute to enhancement of fertility care in pediatric oncology in wider settings and thus improve quality of life of childhood cancer patients and survivors.

Keywords: Fertility care, Late effects, Pediatric cancer, Questionnaire, Reproductive health

Introduction

Currently the five-year survival rate of childhood cancer is up to 80% in most European countries due to improved treatment regimens [1, 2]. However, these treatments may result in multiple long term adverse health effects such as infertility [3–7]. Impaired fertility, infertility and early menopause are highly ranked on the list of relevant side effects affecting quality-of-life in cancer survivors [8, 9]. Long-term survival after treatment for childhood cancer is associated with increased risk of impaired quality-of-life and higher prevalence of psychosocial problems often related to infertility issues [8, 9]. Fertility is thus recognized as a critical component of quality of life in young cancer survivors. Therefore, international and national guidelines recommend discussing fertility

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preservation (FP) before initiation of any therapy [10–14]. However, studies have shown that the majority of childhood cancer survivors (CCSs) report they had not received relevant information about reproductive health, do not know their fertility status and perceive the reproductive counseling during and after the gonadotoxic treatment as insufficient [15, 16]. Parents and patients prefer to be informed on fertility risks and preservation possibilities soon after the diagnosis, as early discussion could lead to improved quality of life, improved coping with the cancer diagnosis, cancer treatment and possible infertility, and improved social well-being, irrespective of the risk or possibilities for preservation [17–26]. Fertility counseling has revealed a beneficial impact on the quality of life after cancer treatment, regardless of the decision to preserve fertility or not [19, 23].

Adequate fertility counseling for girls with cancer comprises of individualized future fertility risk assessment and communication as well as provision of strategies to preserve gonadal material in order to maintain maximal fertility potential. This has been integrated in the Dutch amendment of the Edinburgh criteria "Standard of Cancer Care for fertility preservation" [27–29]. New fertility preservation options have become available in the past years and the importance of timely triage on gonadal damage risk, subsequent provision of information and counseling has been recognized by both patients, parents and healthcare providers [30]. Currently, oocyte cryopreservation is available for a small subset of pubertal patients who can postpone their treatment at least 2 weeks for oocyte harvest. For the majority of girls receiving high risk therapy the only available option is ovarian tissue cryopreservation. Some patients receiving radiotherapy to the pelvis can opt for a transposition of the ovaries. The American Society of Clinical Oncology has published three clinical practice guidelines with evidence-based recommendations for fertility preservation for patients with childhood cancer [8, 11, 31]. A study of compliance with these recommendations reported, however, that none of the patients above the age of 13 had been counseled for fertility preservation [32, 33]. Recently published guidelines by the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) advise that all patients should be informed on their potential risk of gonadal damage and should be offered counseling on fertility preservation options [34–36].

However, it is unknown how patients experience the fertility care and to date no validated questionnaires exist to evaluate this in a pediatric cancer setting. We intent to improve oncofertility care and evaluate what patients consider adequate fertility care including the impact of receiving information regarding reproductive health and fertility counseling towards fertility preservation in childhood cancer patients. Both onco-fertility care and fertility preservation methods for girls are considered standard of care since publication of the ASRM statement and IGHG guidelines [30, 36, 37]. Contrastingly, pre-pubertal male fertility preservation techniques are still considered experimental [35]. Therefore, this manuscript focusses on female fertility care. This will be evaluated using an oncofertility-care-evaluation questionnaire, initially developed at the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands. The Twinning in Research and Education to Improve Survival in Childhood Solid Tumours in Lithuania (TREL) is an EU-Horizon 2020 funded project that aims to improve different aspects of childhood cancer care (including survivorship care). This is done through an extensive collaboration between Vilnius University Hospital Santaros Klinikos (VULSK, Lithuania) and research intensive project partners. Implementation of Work package 6 (WP6) of the TREL project will allow to extend the oncofertility quality assessment to Lithuania. Thus, an oncofertility-care-evaluation questionnaire, which is currently used in the Netherlands was adapted for international multicenter use and in particular in Lithuania in order to improve fertility care in two pediatric oncology centers as part of the **P**reserving ov**AR**ian function through cryopr**E**servation and informing gir**L**s with cancer about infertility due to gonadotoxic treatment (PAREL) study and the TREL initiative. The aim of this manuscript is to present an oncofertility-care-evaluation questionnaire. The questionnaire aims to determine the impact of receiving information and fertility counseling in childhood cancer patients and their parents/guardians and evaluate what they consider good fertility care. This insight may be used to improve fertility care.

Methods

Design of the questionnaire

The questionnaire for evaluation of fertility care for girls, currently used in the Netherlands, is based on multiple validated questionnaires concerning decision regret, reproduction concern and the evaluation of fertility care in an adult setting. Relevant sections of these questionnaires were combined in the new questionnaire. Additionally, some questions were amended to fit the pediatric oncology setting and some new questions were developed. The questions from the Decision regret scale by Brehaut et al. [38] and the decisional conflict scale by O'Connor [39] were used to evaluate regret patients have concerning challenges they face in decision-making. The Dutch Reproductive Concern Scale (RCS-NL (*Voortplanting Bezorgdheid schaal*)) by Garvelink et al. [40] was used for questions regarding the patients' concerns about

infertility. We based questions concerning experiences with the fertility care on the patient-centeredness questionnaire-infertility (PCQ-infertility), which has been developed for subfertile couples [41].

The questionnaire is divided in 5 sections. The first section includes general questions to evaluate how worried patients and parents were about fertility at the time of diagnosis, whether they could recall having a conversation about fertility, and whether they proactively asked for this information. The second section contains questions concerning the first conversation regarding fertility with the nurse practitioner or the pediatric oncologist and focusses on timing and clarity of the information. The third section contains questions regarding the counseling with respect to timing and content, the knowledge on the personal risk of gonadal damage, as well as risks and benefits of the fertility preservation options. Questions regarding emotions of the patients and parents and feelings of control are also included. The fourth section contains questions regarding perceived knowledge on infertility following the information and emotions concerning the information. The last section consists of 4 open questions regarding improvement of fertility care.

The initial questionnaire was developed at the Princess Máxima Center and contains 41 items. It is given to all girls who received counseling by a fertility-gynecologist and participate in the PAREL study. The PAREL study has been approved by the Medical Ethics Committee Utrecht (METC nr. NL72115.041.19). To make it applicable for multicenter use within the TREL framework, and in particular in Lithuania, the questions were translated from Dutch to English and afterwards from English to Lithuanian (Supplemental texts 1–3). To validate the Lithuanian translation the reverse translation from Lithuanian to English was performed. No significant discrepancies between the wordings occurred. The Lithuanian version was reviewed by two pediatric oncologists, a gynecologist, two patients and parents, who were all native speaker Lithuanian and all spoke and understood English. Lastly, the Lithuanian version was compared to the Dutch version with help of the English translation by a native Dutch-speaking author.

Given the existing differences in patient numbers and the current fertility counseling system, the questionnaire was adapted to the Lithuanian situation to assess the situation of fertility counseling at VULSK within the framework of collaboration with the TREL initiative. This questionnaire contained 43 items. A separate Lithuanian questionnaire for girls who did not receive counseling by a fertility-gynecologist was created and contained 31 items. The adjustments from the Dutch to the Lithuanian version are summarized in Supplemental Table 1. The separate Lithuanian questionnaire for girls who did not receive counseling is summarized in Supplemental Table 2. The questionnaire regarding the quality of fertility counseling is currently used for all families after oncofertility counseling in the Princess Máxima Center in the Netherlands as part of the PAREL study [30]. The adapted version will be used in Lithuania for all parents and children ≥14 years old who are currently undergoing treatment or in remission for less than 5 years and who are regularly followed up at the VULSK.

Use of the questionnaire in two pediatric cancer centers

Princess Máxima Center (The Netherlands) Since May 2018 all pediatric cancer care has been centralized in one national pediatric cancer center, the Princess Máxima Center. Around 600 children are newly diagnosed with pediatric cancer in the Netherlands every year. A 5-step oncofertility care plan is implemented since 2019 [30]. These 5 steps are 1) identification of all newly diagnosed patients, 2) triage of patients for fertility risk, 3) information provision, 4) offering counseling to a selected subgroup and 5) offer fertility preservation techniques to those at high risk of infertility, as previously described [30]. Patients are triaged on their risk of gonadal damage at the moment of diagnosis and subsequently informed by their pediatric oncologist or a dedicated oncofertility nurse practitioner. We use the developed triage table to estimate the cyclophosphamide equivalent dose (CED) score and radiation to the gonads [30]. Patients are classified as low, intermediate or high risk of infertility. The CED scores are classified as low (≤4000 mg/m^2), intermediate (4000–6000 mg/m^2) or high risk (≥6000 mg/m^2) of gonadal damage [36]. However, also age at diagnosis and expected radiation to the ovaries are taken into account to estimate a personalized risk for every patient. The subset of high and intermediate risk patients is actively encouraged to go to the fertility specialist for counseling, but also low risk patients can be referred for counseling upon request. Those who are referred for counseling are given the questionnaire three to 6 months after the counseling.

Center for Pediatric Oncology and Hematology at Vilnius University Hospital Santaros Klinikos (VULSK) (Lithuania) The TREL consortium is formed by VULSK and 8 leading research institutions each covering different areas of the project activities according to their expertise in pediatric oncology. TREL will be delivered in 7 work packages (WP) addressing training in tumour specific laboratory research and clinical trials, cross-cutting education on genome-wide sequencing and treatment innovations, enhancing skills in observational studies on the quality of survivorship including fertility preservation

and research methodology as well as project and innovation management. TREL is a European twinning effort that aims to strengthen research networking and education in Lithuania with the ultimate goal to improve survival and quality of life of children with solid tumours (brain tumours, neuroblastoma and renal tumours). The development of the questionnaire is part of WP6 of the TREL collaboration. WP6 specifically focusses on the quality of survivorship and late effects research.

In Lithuania the questionnaire will be implemented at the Center for Pediatric Oncology and Hematology (CPOH) at VULSK, which is the biggest pediatric oncology and hematology center in Lithuania and the Baltic region. VULSK covers two thirds of pediatric cancer patients in Lithuania. Children aged from 1 month to 18 years are treated at the VULSK, every year 50–60 new patients with childhood cancer are diagnosed and treated. Approximately 50 patients and 20 survivors are currently in treatment or in remission for less than 5 years and are regularly followed up at the VULSK. At the moment, fertility counseling at VULSK is rather sporadic, gonadal tissue preservation is available after a consultation with qualified fertility specialists, but there is no developed fertility care system in place. In Lithuania the preservation of reproductive tissue is embedded in the national legislation and can be offered only to children over 14 years old. A triage system similar to the one used in the Princess Máxima Center is being developed to stratify patients according to their risk for infertility/gonadal damage [30]. Patients will be informed by the pediatric oncologist and referred to a gynecologist or urologist. VULSK aims to hand out the questionnaires three to 6 months after counseling or diagnosis. All patients will be classified as low, intermediate or high risk at the moment of diagnosis. Taking into account lower total number of patients in VULSK, the questionnaire for girls will be handed out to boys too. No changes are needed since the questions are not female specific. A developed table for boys to estimate the infertility risk by calculating CED score will be used [35].

Discussion

The increasing number of CCSs is a reason why research is increasingly focusing on their well-being. They are at risk for infertility, which affects quality of life. As reported in a previous study on reproductive health of Lithuanian CCSs [42], many of them point out that they receive insufficient information about the impact of cancer treatment on fertility and possible preservation options. Discussing the risk for infertility with pediatric cancer patients and their parents/guardians before the gonadotoxic treatment is crucial. This paper describes the adaptation of a fertility care evaluation questionnaire for children with cancer, currently used in the Netherlands for multicenter use applicability. This is part of the collaborative effort of two TREL partners with the aim to enhance fertility care in pediatric oncology settings with a wider perspective.

It is well known that patients and parents do not remember all of the given information in stressful situations. Some studies even suggest that only 20% of the given verbal information is retained [43, 44]. In order to improve fertility counseling of childhood cancer patients, an evaluation of the current quality of fertility care will be performed using a questionnaire. To adjust the content of the information to the patient's needs, we need to know what they consider to be important. However, no suitable questionnaire for this population existed. Therefore, we developed the current questionnaire and have implemented it in two countries. Even though, published reports suggest that patients and parents prefer this information at the time of diagnosis, for some tumour types this is not feasible [17–26]. The best timing of giving information is different for every patient e.g. in most renal tumour patients the risk of infertility can only be determined after nephrectomy, which is 4–6 weeks after diagnosis and treatment with chemotherapy in the SIOP RTSG protocol [30, 45]. Also most children with acute lymphoblastic leukemia are assigned to a treatment arm after the first 4 weeks of induction chemotherapy [30]. Therefore, a patient-tailored decision, based on international evidence and expert-based guidelines can be made to determine the timing of discussing gonadal damage (Supplemental Table S3) [30, 34–36].

Since fertility care is structured differently in the Netherlands and Lithuania, the Lithuanian questionnaire was adjusted to the local situation, e.g. a nurse practitioner is not available in the Lithuanian health system. Also the patient population will be slightly different, since a proportion of VULSK patients who receive a questionnaire may not have received oncofertility counseling by experts. In comparison, all patients receiving the questionnaire in the Netherlands have received fertility counseling from fertility experts. Bearing in mind the different cultural backgrounds, different legislations and different system of fertility counseling of childhood cancer patients in two different countries, it could be expected that the answers to the same questions may vary. This may reveal cultural differences that may influence future fertility care strategies.

Conclusion

Oncofertility counseling is an important part of pediatric cancer care, yet no questionnaire to evaluate this existed for the pediatric population. The developed questionnaire to evaluate oncofertility care in two countries may provide insight in the views of patients and their family on offered fertility care and on improvements that could be made. Results of this questionnaire may contribute to enhanced oncofertility settings in pediatric oncology departments in a wider range of cultural and geographic settings, thereby improving quality of life of childhood cancer patients and survivors.

Abbreviations

CCSs: Childhood cancer survivors; CED: Cyclophosphamide equivalent dose; CPOH: Center for Pediatric Oncology and Hematology; FP: Fertility preservation; IGHG: International Late Effects of Childhood Cancer Guideline Harmonization Group; PAREL: Preserving ovARian function through cryoprEservation and informing girLs with cancer about infertility due to gonadotoxic treatment; PCQ-infertility: Patient-centeredness questionnaire-infertility; RCS-NL: Dutch Reproductive Concern Scale; TREL: Twinning in Research and Education to Improve Survival in Childhood Solid Tumours in Lithuania; VULSK: Vilnius University Hospital Santaros Klinikos; WP6: Work package 6.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-09450-2.

Additional file 1.

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Authors' contributions

MEMvdP, ES-R, JR and MMvdH-E designed the study and wrote the manuscript. MEMvdP and MMvdH-E designed the Dutch questionnaire and translated it to English. ES-R and JR translated the questionnaire into Lithuanian. ZB, GV and AMEB made suggestions to improve the manuscript. All co-authors reviewed the final article for intellectual content. In all, this document represents a fully collaborative work. The author(s) read and approved the final manuscript.

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Availability of data and materials

All questionnaires generated during this study are included in this published article [and its supplementary information files]. For further questions, the corresponding author can be contacted.

Declarations

Ethics approval and consent to participate

The PAREL study has been approved by the Medical Ethics committee Utrecht (METC nr. NL72115.041.19). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent is obtained from all participants asked to complete the questionnaire in the PAREL study.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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Implementation and Evaluation of Preimplantation Genetic Testing at Vilnius University Hospital Santaros Klinikos

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Abstract. ***Background and Objectives:*** The most effective treatment of infertility is in vitro fertilization (IVF). IVF with Preimplantation Genetic Testing (PGT) allows to identify embryos with a genetic abnormality associated with a specific medical disorder and to select the most optimal embryos for the transfer. PGT is divided into structural rearrangement testing (PGT-SR), monogenetic disorder testing (PGT-M), and aneuploidy testing (PGT-A). This study mostly analyzes PGT-SR, also describes a few cases of PGT-M. The aim of this study was to implement PGT procedure at Vilnius University Hospital Santaros Klinikos (VUHSK) Santaros Fertility Centre (SFC) and to perform retrospective analysis of PGT procedures after the implementation.

Materials and Methods: A single-center retrospective analysis was carried out. The study population included infertile couples who underwent PGT at SFC, VUHSK from January 01st, 2017 to December 31st, 2020. Ion PGM platform (Life Technologies, USA) and Ion ReproSeq PGS View Kit (Life Technologies, USA) were used for the whole genome amplification. Results were assessed using descriptive statistics.

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Results: PGT was successfully implemented in VUHSK in 2017. During the analyzed time period, thirty-four PGT procedures were performed for 26 couples. Two procedures were performed in 2017, 7 procedures – in 2018, 13 – in 2019, and 12 – in 2020. In comparison with all IVF procedures, 2.5% procedures were IVF with PGT, a highest percentage was in 2020 (3.8% of all procedures). The main indication for PGT was balanced chromosomal rearrangements (in 85.3% cases). In all 34 cases 515 oocytes were aspirated in total, 309 oocytes were fertilized, oocytes fertilization rate exceeded 60%. A normal diploid karyotype was found in 46 (16.8%) biopsied embryos. Out of all PGT procedures, 9 (26.5%) resulted in a clinical pregnancy. Six (66.7%) pregnancies were confirmed in 2019, and 3 (33.3%) – in 2020. Three (33.3%) pregnancies resulted in spontaneous abortion, 6 (66.7%) – in delivery.

Conclusions: The implementation of PGT in VUHSK was successful. The most common indication for PGT was a reciprocal translocation. Oocytes fertilization rate exceeded 60%, a normal karyotype was found less than in one-fifth of biopsied embryos. A highest clinical pregnancy rate was achieved in 2019 when almost half of women conceived, which is probably related to the experience gained by the multidisciplinary team. This is the first study analyzing IVF with PGT in Lithuania, however, the results should be interpreted with caution due to a low number of total procedures performed.

Keywords: assisted reproductive technology, fertility, in vitro fertilization, preimplantation genetic testing

Preimplantacinio genetinio tyrimo įdiegimas ir vertinimas Vilniaus universiteto ligoninėje Santaros klinikose

Santrauka. ***Įvadas:*** Efektyviausias nevaisingumo gydymo būdas – pagalbinio apvaisinimo (PA) procedūra. PA su preimplantaciniu genetiniu tyrimu (PGT) leidžia identifikuoti genetiškai pakitusius embrionus ir atrinkti tinkamiausius embrionus įkelti į gimdą. Šio tyrimo tikslas – įdiegti PGT į klinikinę praktiką Vilniaus universiteto ligoninės Santaros klinikų (VULSK) Santaros vaisingumo centre (SVC) ir atlikti PGT procedūrų retrospektyvinę analizę po įdiegimo.

Metodika: Atlikta retrospektyvinė analizė, į tyrimą įtrauktos VULSK nuo 2017 m. sausio 1 d. iki 2020 m. gruodžio 31 d. gydytos nevaisingos poros, kurioms taikytas PGT. Ion PGM platforma (Life Technologies, USA) ir Ion ReproSeq PGS View Kit (Life Technologies, USA) buvo naudota atlikti viso genomo sekvenavimą. Rezultatai įvertinti aprašomosios statistikos metodais.

Rezultatai: PGT įdiegtas į klinikinę praktiką VULSK SFC 2017 metais. Buvo atliktos 34 PGT procedūros 26 poroms. Dvi procedūros atliktos 2017 m., 7 procedūros – 2018 m., 13 procedūrų – 2019 m., 12 – 2020 m. PGT sudarė 2,5 % visų PA procedūrų, didžiausias procentas, palyginti su visomis PA procedūromis, pasiektas 2020 metais (3,8 %). Dažniausia indikacija atlikti PGT – subalansuotas chromosomų persitvarkymas (85,3 % atvejų). Kiaušialąsčių apsivaisinimo dažnis siekė 60 %. Normalus diploidinis kariotipas rastas 16,8 % embrionų, kuriems atlikta biopsija. Iš visų PGT procedūrų 9 (26,5 %) procedūros baigėsi klinikiniu nėštumu. Šeši (66,7 %) nėštumai patvirtinti 2019 m., 3 (33,3 %) – 2020 metais. Trys (33,3 %) nėštumai baigėsi savaiminiu persileidimu, 6 (66,7 %) – gimdymu.

Išvados: PGT sėkmingai įdiegtas į klinikinę praktiką VULSK. Dažniausia indikacija atlikti PGT – subalansuotas chromosomų persitvarkymas – reciprokinė translokacija. Kiaušialąsčių apsivaisinimo dažnis siekė 60 %, normalus diploidinis kariotipas nustatytas mažiau nei pektadaliui embrionų. Didžiausias klinikinių nėštumų dažnis pasiektas 2019 metais, tada beveik pusė moterų pastojo. Du trečdaliai nėštumų baigėsi gimdymu. Šiame tyrime, pirmajame Lietuvoje, apžvelgiamos PA procedūros su PGT, tačiau tyrimo rezultatai turėtų būti interpretuojami atsargiai, atsižvelgiant į mažą atliktų procedūrų skaičių.

Raktažodžiai: pagalbinis apvaisinimas; preimplantacinė genetinė diagnostika; vaisingumas

Introduction

Infertility is one of major health concerns nowadays and has been recognized as a public health issue by the World Health Organization (WHO) (1,2). Infertility is a disease characterized by a failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse (3). It affects

about 8–15% of all reproductive age couples (4,5). The most effective treatment of infertility is in vitro fertilization (IVF) which success rate is on average 25–35% and depends on the age of the couple, type and duration of infertility and other factors (6). IVF together with Preimplantation Genetic Testing (PGT) is performed to select the best embryos and to increase the pregnancy rate, to reduce the abortion rate, the multiple birth rate, the malformation rate and the rate of pointless treatments with artificial reproductive technology (ART) (7). PGT is a genetic testing procedure which allows to identify embryos with a genetic abnormality associated with a specific medical disorder known to affect one or both parents and to select the most optimal embryos for the transfer (8). PGT is divided into structural rearrangement testing (PGT-SR), monogenetic disorder testing (PGT-M), and aneuploidy testing (PGT-A) (9–11). This study mostly analyzes PGT-SR which is performed if one or both partners have chromosomal rearrangements and a high risk of passing genetic disorders to the offspring. PGT-SR decreases the risk of early pregnancy loss due to chromosome abnormalities and gives a chance to deliver a child without unbalanced structural chromosome rearrangement (12,13). In addition, this study describes a few cases of PGT-M in which both parents were carriers of pathogenic variants of autosomal recessive monogenic diseases.

The **aim of this study** was to implement PGT procedure at Vilnius University Hospital Santaros Klinikos (VUHSK) Santaros Fertility Centre (SFC) and to perform retrospective analysis of PGT procedures after the implementation. To evaluate the effectiveness of the PGT implementation, the goals of the retrospective analysis were set as: assessment of the most common indications for PGT; assessment of oocytes fertilization rate and results of genetical testing of embryos; assessment of the frequency of PGT in comparison with IVF/ICSI without PGT; and assessment of the outcomes of IVF with PGT measured by a clinical pregnancy rate.

Materials and Methods

The study population

A single-center retrospective analysis was carried out. The study was approved by the Vilnius Regional Committee of Biomedical Research (Approval No.2021/3-1327-804). The study population included infertile couples counseled by the multidisciplinary team and treated at SFC, VUHSK from January 01st, 2017 to December 31st, 2020. All couples that underwent PGT during this timeframe were enrolled to the study. Couples were identified at the institutional electronic database, demographic and treatment-related data were retrieved and anonymized. Data included age, type and duration of infertility or recurrent pregnancy loss, previous obstetric-gynecological history, and previous infertility treatment. The embryological data of PGT procedure for each couple included the number of oocytes retrieved, fertilization rate, the quantity and quality of embryos after intracytoplasmic sperm injection (ICSI), the number of embryos and blastomeres biopsied and transferred, indications and outcomes of PGT procedures.

Embryos cultivation and biopsy

For PGT analyses all *embryos creation* was performed using common assisted reproduction techniques, all protocols and procedures were approved by VUHSK. Oocytes were aspirated using Cook double lumen puncture set (Cook, Australia) during the ultrasound controlled ovarian puncture for all women, directly transferred into FertiCult IVF medium (FertiPro, Belgium) and incubated until the processing in 5.5% CO2 and 37°C incubator (Astec, Japan). Two hours after aspiration, the oocytes were denuded using 135 micrometers Denuding pipette (Gynetics, Belgium) and 10% Hialuronidase (FertiPro, Belgium). Two hours after denudation ICSI procedure was performed, sperm cells were injected using RI Integra TM 3 micromanipulator (Research Instruments, UK), 35° Injection and 35°

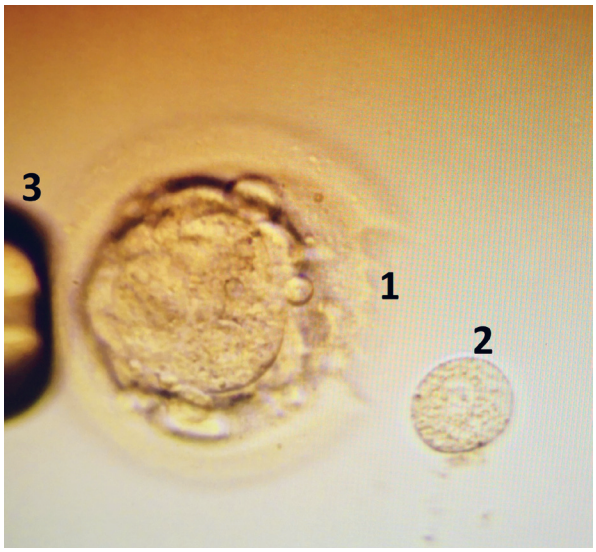

Figure 1. Laser assisted 4th day embryo (morula) biopsy. 1 – laser ablation of *zona pellucida*, 2 – biopsed single blastomere, 3 – holding pipette.

Holding micropipettes (Reproline, Germany) under an inverted Nikon Eclipse Ti microscope (Nikon, Japan). After ICSI procedure all embryos were cultivated in 50 microliters drops in the one step SAGE medium (Origio, Denmark) under the mineral oil (Irvine Scientific, USA). All embryos were revised 24, 48, and 72 hours after ICSI. According to the development speed of embryos, on day 3–4, the single embryo blastomere biopsy was performed using 1480 nm / 400 mW solid state diode laser with a pulse length range 0.005–2.0 ms / 5–2000 µs (RI Saturn 5^{TM}, Research Instruments, UK) and RI Integra TM 3 micromanipulator (Research Instruments, UK) (Figure 1). Single use 50 micrometers Biopsy pipettes (Reproline, Germany) for the single blastomere biopsy were used.

All *embryo biopsies* were performed by the same embryologist. RI Viewer program (Research Instruments, UK) was used to select the best blastomere, to ablate the *zona pellucida* of the embryo and to cut the single blastomere which was quickly aspirated by the biopsy pipettes and directly transferred into the 0.2 ml microtubes with PBS/PVA (Life Technologies, USA). After the biopsy of embryos all samples were immediately transported on ice to the VUHSK Centre for Medical Genetics (CMG) for a further genetical analysis.

Single blastomere genetical analysis

Chromosomal rearrangement (PGT-SR) testing of DNA from blastomere or trophectoderm biopsy was performed using the next-generation sequencing (NGS) technology according to the recommendations of the manufacture of reagents. Ion PGM platform (Life Technologies, USA) and Ion ReproSeq PGS View Kit (Life Technologies, USA) were used for the whole genome amplification, amplified DNA fragmentation and sequencing at low coverage (0.01×). Primary data analysis was performed using Torrent Suite™ Software on the Torrent server (Life Technologies, USA) and the analysis of chromosomal copy number alterations was performed using Ion Reporter™ software (Life Technologies, USA) in Thermo Fisher Cloud. This test was designed for the detection of chromosomal aneuploidy and large unbalanced rearrangements, thus ≥4.5 Mb-sized small known deletions and duplications could be specifically tested using advanced analysis workflow. Deletions and/or duplications ≥48 Mb in size were detected using a standard analysis workflow. The balanced chromosome rearrangements, uniparental disomy, some triploidies and point mutations were not detected during PGT-SR testing.

Testing for monogenic diseases (PGT-M for pathogenic variants in *POMK* and *SMN1* genes) was performed additionally using PGD-SEQ™ POMK Panel and Reagent Kit (Journey Genomics S.L.,

Spain) and PGD-SEQ™ SMN1 Panel and Reagent Kit (Journey Genomics S.L., Spain). This test allowed to combine PGT-M and PGT-SR analysis. During the first step starting from biopsied blastomeres, the whole genome was amplified using reagents provided in Ion ReproSeq PGS View Kit (Life Technologies, USA). Part of the first amplification product was used for the second region-specific amplification (PGT-M). Using appropriate PGD-SEQ™ Panel and Reagent Kit, the specific pathogenic variants and more than 130 potentially informative selected nearby polymorphisms were amplified. The PGT-M and PGT-SR libraries were sequenced using Ion ReproSeq PGS View Kit (Life Technologies, USA). The analysis of monogenic diseases was performed using PGD-SEQ software that allowed to detect carrying the disease-causing mutations embryos.

The following criteria were used for data quality evaluation: Median of the Absolute values of all Pairwise Differences (MAPD) metric value <0.3, a number of fragments (reads) mapped to the reference genome (hg19) per sample ≥50.000 (a recommended value is 100.000–300.000), the higher confidence and precision values (≥1) indicating a change in the number of copies, and reflecting correctly detected number of copies.

The results of analysis were reported as following: no DNA identified (not transferable) – no amplified DNA library after the whole genome amplification step, thus samples were not further tested; not interpreted (not transferable) – data quality did not meet quality criteria, no clear conclusion could be given; pathology (not transferable) – aneuploidy or copy number variants identified by PGT-SR testing, monogenic disease causing genotype and / or aneuploidy or copy number variants identified by PGT-M (plus PGT-SR) testing; normal (transferable) – no disease causing chromosomal aneuploidies, structural rearrangements and / or monogenic disorders were identified.

Embryo transfer and pregnancy confirmation

After performing PGT-SR or PGT-M, on day 5 of fresh cycle, from 1 to 3 genetically normal embryos (without chromosomal abnormalities or monogenic disease) were transferred to the uterus by Cook Access Nano embryo transfer catheter (Cook, USA). If no transferable embryos were identified by PGT analysis, the possibility to transfer not tested (no DNA identified) or not interpreted but the best morphological quality embryos were discussed with the couple explaining the risk. All embryos were transferred in fresh cycle without embryo freezing. According to the Lithuanian Law for Assisted Reproduction, the maximum number of embryos which could be transferred to the uterus during one assisted reproduction cycle is three. During the time of this study more than one embryo was transferred only for women older than 30 years of age and if the morphological embryo quality was poor.

Serum human chorionic gonadotropin-β was measured 14 days after oocyte retrieval and a clinical pregnancy was confirmed by transvaginal ultrasound at 5–6 weeks. If a clinical pregnancy was achieved, a prenatal genetic testing of pregnant women was highly recommended in all cases.

Statistical analysis

Analysis was performed and characteristics were assessed using descriptive statistics. SPSS ver. 17 (IBM Corp., Armonk, NY) was used for all quantitative analyses.

Results

Couples characteristics

During the period from January 01st, 2017 to December 31st, 2020, 34 PGT procedures were performed for 26 couples. In the majority (24, 70.6%) of cases, couples were undergoing PGT for the first time, in 9 (26.4%) cases – for 2nd time. One couple underwent PGT 3 times (2 out of 3 pro-

cedures were performed at SFC). In total 34 PGT procedures were performed, each procedure was analyzed as a single case.

The age of participants of the study on time the procedure was performed was on average 34 years and ranged from 28 to 42, age did not differ between males and females. The duration of subfertility varied. Time trying to conceive was 4 years on average, however, minimum duration of infertility was 2 years and maximum – 17 years. Ten (38.5%) couples (14 (41.2%) cases) already had biological children, one of them was diagnosed with type 1 spinal muscular atrophy, another one – with 21 chromosome trisomy. One male had a daughter diagnosed with a chromosomal abnormality from a previous marriage. The BMI of females was 24.6 kg/m^2 on average. Almost one third of women (32.4%) was overweight, 4 (11.4%) were obese.

Genetic counseling of the couples

Before IVF treatment all couples were counseled by the multidisciplinary team regarding genetical testing. A variety of chromosomal abnormalities identified to PGT patients is listed in Table 1. The most common indication for PGT was structural chromosomal rearrangements in 29 (85.3%) cases. Structural rearrangements included 6 (20.7%) Robertsonian translocations, 22 (75.9%) reciprocal translocations, and one (3.4%) chromosome inversion. Other indications were sex chromosome abnormality (2 cases, 5.9%), monogenic disease carriers (2 cases, 5.9%), and a high spontaneous chromosomal mutation risk in 1 (2.9%) case. As for monogenic disease carriers, in one case female and male were heterozygous carriers of *POMK* gene pathogenic variant c.136C>T, p.(Arg46Ter), in second case – female and male were heterozygous carriers of *SMN1* gene 7-8 exons deletion. In one case identified as a high spontaneous chromosomal mutation risk, a female patient already had a child with trisomy 21, she also had two miscarriages and a termination of pregnancy due to trisomy 18.

Oocytes fertilization, embryos development and genetical testing

In all 34 cases 515 oocytes were aspirated in total, on average 15 (from 1 to 33) oocytes per case. After ICSI was performed, 309 oocytes were fertilized, on average 9 (from 1 to 20) per case. Fertilization rate exceeded 60%. Good quality embryos (274, 88.7% of all fertilized) were biopsied and sent for DNA amplification.

Table 1. Variety of chromosomal abnormalities identified to PGT patients.

	Structural chromosomal rearrangements	PGT, n
Robertsonian translocation		6
1	45,XY,der(13;14)(q10;q10)	4
2	45,XX,der(13;14)(q10;q10)	1
3	45,XY,der(14;21)(q10;q10)	1
Reciprocal translocation		22
1	46,XY,t(9;12)(q32;q22)	2
2	46,XY,t(8;13)(p23.3;q14.1)	2
3	46,XY, t(3;8)(q25;p23)	1
4	46,XX,t(15;19)(q24;q13.3)	2
5	46,XX,t(13;18)(q12.3;q21.3)	2
6	46,XY,t(1;15)(p36.2;q15)	2
7	46,XX,t(4;8)(q13;q11.23)	1
8	46,XX,t(X;3)(p22.1;q21)	2
9	46,XY,t(10;15)(q24;q26.1)	2
10	46,XX,t(5;6)(p12;q14)	1
11	46,XX,t(6;14)(q14;q32.2)	1
12	46,XX,t(8;9)(q22.1;q13)	1
13	46,XY,t(7;13)(p13;q22)	1
14	46,XX,t(2;6)(p23;q21)	1
15	46,XX,t(13;14)(q14.2;q11.2)	1
Inversion		1
46,XY,inv(1)(q21q42)		1
Sex chromosome abnormality		2
45,X[4]/46,XY[30]		1
45,X[27]/47,XYY[16]/46,XY[7]		1

In more than half of cases (18, 52.9%) biopsies were performed on day 3 embryos, in 16 (47.1%) cases – on day 4 embryos. Out of all biopsied embryos, further developed 190 (69.3%), on average 6. Genetic analysis showed that normal diploid karyotype was found only in 46 (16.8%) biopsied embryos, 112 (40.9%) embryos had chromosomal aneuploidies, 65 (23.7%) embryos were not interpreted due to chaotic genomic imbalances, for 51 (18.6%) embryos no DNA was identified after the whole genome amplification step. In more than third (13, 38.2%) PGT procedures none of embryos had normal diploid karyotype. In 25 (73.5%) cases blastocysts on 5th day of development were transferred to uterus. In 4 (11.8%) cases no embryos were developing after biopsy, therefore, the transfer was not performed. During the majority of procedures (15, 44.1%) one embryo was transferred, in 8 (23.5%) cases – two embryos, and in 2 (5.9%) cases – 3 embryos. In four cases genetically uninterpreted but the best morphological quality embryos were transferred, the risk was explained to the couples and the signed permission for this type of transfer was received. One female conceived after transferring an uninterpreted embryo, a healthy girl (karyotype 46,XX) was born.

The outcomes of PGT

The first PGT at SFC was performed in September 2017. To compare with all IVF procedures performed at SFC, only 2 procedures were performed in 2017 (0.9% out of 216 procedures), 7 – in 2018 (1.9% of 375 procedures), 13 – in 2019 (3.0% of 435 procedures), and 12 – in 2020 (3.8% of 320 procedures) (Figure 2).

In 2017 and 2018 none of the procedures resulted in a clinical pregnancy. Almost half (6, 46.2%) procedures performed in 2019 resulted in a clinical pregnancy, and in 2020 – 3 (25%). Out of all PGT procedures, 9 (26.5%) times embryos were not transferred to uterus, 15 (44.1%) procedures were unsuccessful, 1 (2.9%) time biochemical pregnancy was diagnosed, 9 (26.5%) procedures resulted in a clinical pregnancy. Six (66.7%) clinical pregnancies were confirmed in 2019, 3 (33.3%) – in 2020. Out of 9 clinical pregnancies, 3 (33.3%) pregnancies resulted in a spontaneous abortion, 6 (66.7%) pregnancies – in delivery. Four newborns were delivered in 2019 (in one case twins), and 3 newborns – in 2020.

Discussion

PGT was successfully implemented in VUHSK in 2017. During the time period from 2017 to 2020, 34 PGT procedures were performed. During the same time period 1346 IVF/ICSI procedures were performed in total: 216 in 2017, 375 in 2018, 435 in 2019, and 320 in 2020. Thirty-four PGT cases make only 2.5% of all IVF procedures.

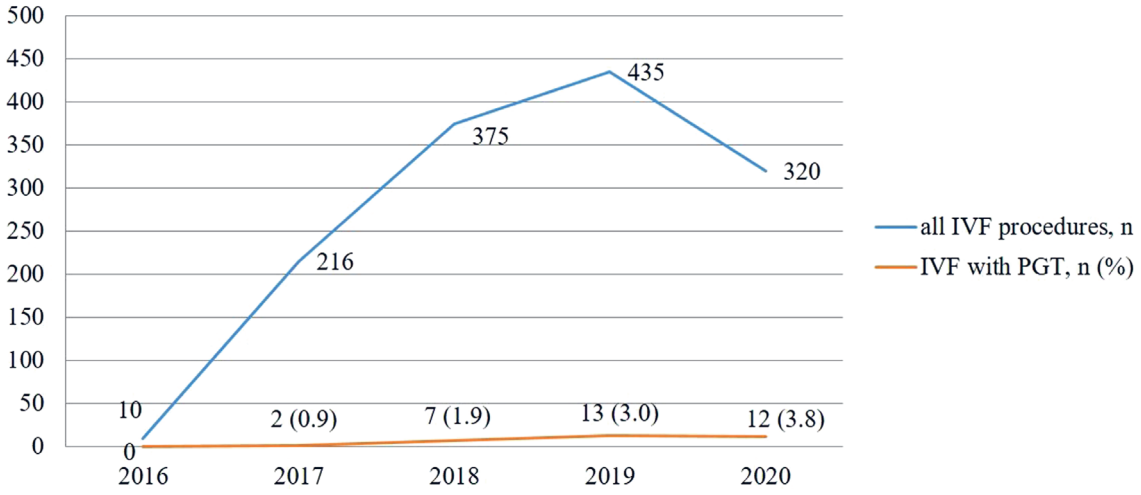

Figure 2. A comparison of total number of IVF procedures with IVF with PGT.

The most common indication for PGT-SR in our study was a structured chromosomal rearrangement – reciprocal translocation, in 22 (64.7%) of cases. It is a typical finding as reciprocal translocations together with Robertsonian translocations and inversions are the most common chromosomal structural abnormalities (13). The genetic testing in this study was performed by NGS, it allowed to identify and screen for embryos with reduced viability such as mosaic embryos and those with partial aneuploidies or triploidy. Other studies revealed that NGS improves pregnancy outcomes versus array comparative genomic hybridization (14), there was a tendency towards a higher live birth rate for NGS testing in comparison with fluorescence in-situ hybridization and microarray comparative genomic hybridization (15).

As it was mentioned, all embryos were transferred in fresh cycles in our study. Although we could not find data comparing outcomes between fresh and frozen cycles when PGT-SR or PGT-M was applied, it is known that time to a clinical pregnancy is likely to be shorter using fresh embryo transfer during conventional IVF/ICSI than in a 'freeze all' strategy (16). More than one or double embryo transfer (DET) demonstrates a superior pregnancy and live birth rate, however, it is associated with a significantly higher risk of multiple gestations and increased risk for maternal and neonatal morbidity (17,18). As it was noticed, a maximum number of embryos allowed by Law in Lithuania to transfer during one cycle is three. In order to achieve the best pregnancy rate after IVF/ICSI, more than 1 embryo is usually transferred in Lithuanian clinics for assisted reproduction. In our study more than one embryo was transferred in more than half of cases, however, these cases included women older than 30 years of age and poor morphological quality embryos. Three embryos were transferred in two cases only – in one case a procedure was unsuccessful, in another case it resulted in a twin delivery.

In our study the outcomes of PGT were evaluated by a clinical pregnancy rate only. However, due to a small number of cases included in the analysis, the another important quality criteria – live birth rate – was not evaluated (15,19,20). Other evaluation method of PGT outcomes is ongoing pregnancy rate at 20 weeks' gestation per embryo transfer (21). According to the retrospective analysis performed we could state that the best outcomes of PGT measured by a clinical pregnancy rate were achieved in 2019 when almost half (46.2%) of procedures resulted in clinical pregnancies. Regardless of the low number of cases the increased clinical pregnancy rate is probably related to the team of embryologist and medical geneticists gaining more experience – medical geneticists from VUHSK CMG successfully participated in the GenQA external quality assessment for PGT for chromosomal rearrangements. According to other studies, the clinical pregnancy rate after PGT varies from 25% to 59% and depends on many factors such as a type of chromosomal rearrangement, a type and method of PGT used, age and other characteristics of partners and the experience of the team (13,15,19,25,26). Outcomes of the procedures performed at SFC in 2019 was similar to the results obtained at other centers. However, in 2020 the quality rate dropped down. It is important to notice that from March to May of 2020 SFC was closed due to the lockdown as a consequence of COVID-19 pandemic. It is likely this contributed to a decrease in a total number of IVF/ICSI procedures thus an increase in a percentage of IVF/ICSI with PGT in comparison with total IVF procedures (Figure 2).

The Law for the Assisted Reproduction was enforced by the Lithuanian Parliament on 01/01/2017, therefore, studies investigating assisted reproductive technology (ART) in Lithuania were very limited. The first public University Hospital ART center in Lithuania, SFC at VUHSK was established in 2016 and the first PGT at SFC was performed in September 2017. The first successful live birth after PGT in Lithuania was achieved in 2019 (27). According to the Law, PGT could have been applied only after a multidisciplinary genetic counselling for couples with a high risk for passing genetic disorders to their offspring. Routine genetic testing of all *in vitro* created embryos is prohibited by the Law, explaining a low percentage of PGT procedures compared with all IVF procedures. Some

other centers perform PGT for all IVF/ICSI patients as a routine genetic testing. Although limited evidence suggests that PGT-A could be beneficial in the ≥38 years old population (22), and PGT-A use is associated with improved live birth rates in couples with recurrent pregnancy loss undergoing frozen embryo transfer (FET) (23), a value of PGT as an universal genetic screening for all IVF patients has yet to be determined and remains controversial (20,24). However, routine genetic testing would have contributed to a higher number of PGT procedures in our study and probably to a higher percentage of clinical pregnancies and live births, as well as more experience gained by the multidisciplinary team.

On account of a low total number of procedures only a descriptive data analysis was carried out since the results of statistical tests could be misleading in our study. A low number of procedures and live births could be recognized as a major limitation of the study, however, PGT procedure was successfully implemented, and this is the first time when data regarding PGT in Lithuania was analyzed, therefore, a ground for a further research was prepared. The comparison group in future studies could include patients who underwent IVF/ICSI without PGT and outcomes of procedures could be compared as it was done in other studies (19,22). Results of this study will provide an insight to a further clinical practice at SFC and will contribute to a better outcomes of ART procedures in Lithuania.

Conclusions

To summarize, PGT was successfully implemented in VUHSK after the adoption of Lithuanian Law for the Assisted Reproduction. During the evaluation period the most common indication for PGT-SR was a balanced chromosomal rearrangement – reciprocal translocation. Oocytes fertilization rate exceeded 60%, however, a normal diploid karyotype was found less than in one-fifth of biopsied embryos. Out of all IVF/ICSI procedures, PGT contained only 2.5% which is related to the prohibition of routine genetic testing of embryos by Law in Lithuania. Out of all PGT procedures more than a quarter resulted in a clinical pregnancy. The clinical pregnancy rate was highest in 2019 when almost half of women conceived. Increased clinical pregnancy rate could be related to the experience gained by the multidisciplinary team. This is the first study analyzing and systematizing PGT procedures in Lithuania. Nevertheless, the results should be interpreted with caution due to a low number of total procedures performed.

Author Contributions

Conceptualization, Z.G; methodology, Z.G., D.R.; software, E.S. Z.G.; validation, Z.G. and D.R.; formal analysis, E.S.; investigation, E.S.; resources, A.A., R.G., D.R. A.U.; data curation, A.A. D.R.; writing – original draft preparation, E.S.; writing – review and editing, Z.G.; D.R., E.D., K.G., visualization, Z.G.; supervision, Z.G., D.R.; project administration, A.A. and D.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Vilnius Regional Committee of Biomedical Research (Protocol Code PA-EFEKT-2021, Approval No.2021/3-1327-804).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflict of interest.

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CASE REPORT
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Case Report: Specific ABL-Inhibitor Imatinib Is an Effective Targeted Agent as the First Line Therapy to Treat B-Cell Acute Lymphoblastic Leukemia With a Cryptic *NUP214*::*ABL1* Gene Fusion

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Acute lymphoblastic leukemia (ALL) with recurrent genetic lesions, affecting a series of kinase genes, is associated with unfavorable prognosis, however, it could benefit from treatment with tyrosine kinase inhibitors (TKI). *NUP214*::*ABL1* fusion is detected in 6% of T-cell acute lymphoblastic leukemia (T-ALL), and is very rare in B-ALL. We present a case of adolescent with B-ALL and a cryptic *NUP214*::*ABL1* fusion which was initially missed during diagnostic screening and was detected by additional RNA sequencing. Treatment with specific ABL-inhibitor Imatinib was added later in therapy with a good effect. Initial treatment according to conventional chemotherapy was complicated by severe side effects. At the end of Consolidation, the patient was stratified to a high risk group with allogeneic hematopoietic stem cell transplantation because of insufficient response to therapy. At that time, targeted RNA sequencing detected *NUP214*::*ABL1* gene fusion which was previously missed due to a small microduplication in the 9q34 chromosome region. Gene variant analysis revealed no TKI-resistant *ABL1* mutations; therefore, treatment with Imatinib was added to target the *NUP214*::*ABL1* fusion protein. A negative minimal residual disease was achieved, and treatment was downgraded to intermediate risk protocol. Combining routine genetic assays with next-generation sequencing methods could prevent from missing atypical gene alterations. Identification of rare targetable genetic subtypes is of importance in order to introduce targeted therapy as early as possible that may improve survival and reduce toxicity.

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Abbreviations: ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; FISH, fluorescence *in situ* hybridization; HR+HSCT, high risk block chemotherapy with hematopoietic stem cell transplantation; ICU, intensive care unit; IR-High, intermediate-high risk group; MRD, minimal residual disease; NGS, next-generation sequencing; PEG-Asp, pegylated-asparaginase; RT-PCR, reverse transcription polymerase chain reaction; SNP-A, single nucleotide polymorphism array; TKI, tyrosine kinase inhibitor; TP1, time point 1: end of Induction, day 29; TP2, time point 2: end of Consolidation 1, day 71; VHR, very high risk chemotherapy.

Treatment with ABL1 inhibitor imatinib mesylate revealed as a highly effective targeted therapy against the leukemia driving protein kinase.

Keywords: case report, targeted therapy, tyrosine kinase inhibitors, acute lymphoblastic leukemia, imatinib, BCR-ABL1-like

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with certain cytogenetic aberrations being long-recognized to be anticipated an unfavourable prognosis. A new *BCR-ABL*-like subgroup of tyrosine-kinase driven ALL has been associated with a poor response to chemotherapy, a high relapse risk, and unfavorable long-term outcomes (1). In the 2016 updated World Health Organization classification of myeloid neoplasms and acute leukemia, *BCR-ABL1*-like B-ALL was added as a new provisional entity (2). Its gene expression profile is similar to *BCR*::*ABL1*, however, is lacking *BCR*::*ABL1* fusion (3). The presence of Nucleoporin 214-ABL Proto-Oncogene 1 (*NUP214*::*ABL1*) gene fusion is detected in 6% of T-ALL, whereas it is rare in B-ALL (4). A series of genes that activate tyrosine kinase and cytokine receptor signaling are affected in *BCR-ABL1*-like ALL, suggesting the potential interest of targeted treatment with tyrosine kinase inhibitors (TKI) (5). However, the therapeutic effect of TKI for the *NUP214*::*ABL1*-positive patients is disputable as clinical experience is limited (6–11). Standard worldwide screening methods for known *ABL1* gene fusions include fluorescence *in situ* hybridization (FISH) analysis and reverse transcription polymerase chain reaction (RT-PCR) (12). Nevertheless, these screening techniques detect a limited number of alterations as *BCR-ABL1*-like ALL is known for its highly heterogeneous background (13).

We present a case of pediatric B-ALL with a cryptic *NUP214*::*ABL1* gene fusion which was initially missed during diagnostic screening due to unusual genetic alteration and was identified by the targeted next-generation sequencing (NGS) only. Treatment with a first-generation TKI (imatinib) was added to the chemotherapy with a good effect.

CASE DESCRIPTION

A 15 year-old boy with no previous significant medical history was admitted to our pediatric department in July 2020 for high fever, petechial and hemorrhagic rash, and vomiting. The blood count showed hemoglobin 51 g/L, platelet count 34 × 10^9/L, and hyperleukocytosis 464.5 10^9/L. Immunophenotyping confirmed the expression of B-lymphoid markers CD45, CD19, CD10, CD20, CD81, CD22, cCD22, CD24, and cCD79a. Routine genomic screening by a single nucleotide polymorphism array (SNP-A) detected normal male karyotype 46,XY without larger aberrations in size ≥5 Mb. FISH and RT-PCR did not detect any of the following recurrent rearrangements: *BCR*::*ABL1*, *KMT2A*, *EPOR*, *ABL1*, *ABL2*, *RUNX1* (*CSF1R*), *PDGFRB*, *E2A* (*TCF3*), *JAK2*, *ETV6*::*RUNX1*, or *CRLF2*. Cerebrospinal fluid showed three WBC/μl and ~5.8% of aberrant phenotype B-lymphoid cells, with no leukemic blasts in cytospin. B-ALL, CNS1 was diagnosed.

Treatment was conducted according to ALLTogether protocol Induction B with dexamethasone, vincristine, daunorubicin, pegylated-asparaginase (PEG-Asp), and intrathecal methotrexate. At the end of induction, at time point 1 (TP1), minimal residual disease (MRD) in bone marrow showed residual cells of 0.79% by flow cytometry (FC) and 0.03% by IG/TCR

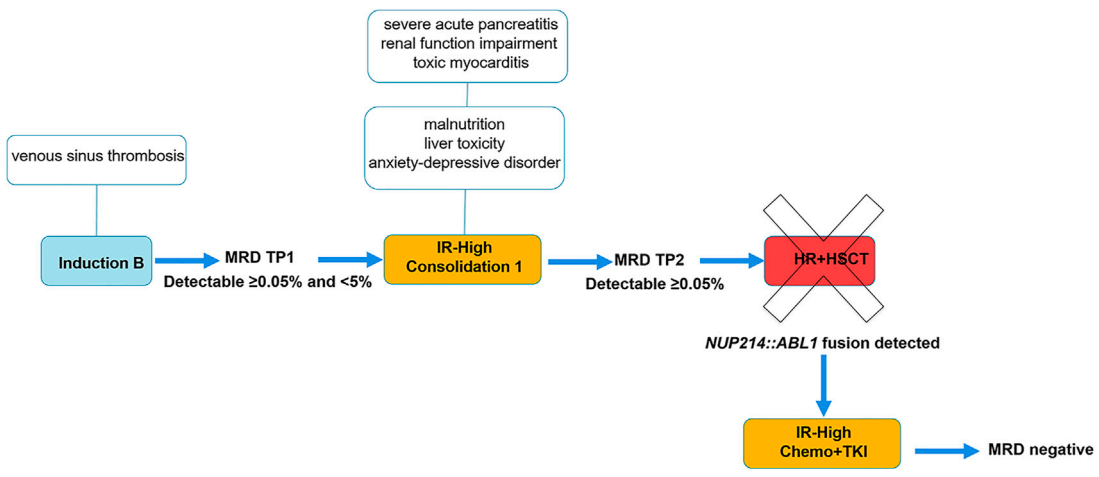

FIGURE 1 | Treatment flowchart and timeline of symptoms. Abbreviations: HR+HSCT, high risk block chemotherapy with hematopoietic stem cell transplantation; IR-High, intermediate-high risk group; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor; TP1, time point 1: end of Induction, day 29; TP2, time point 2: end of Consolidation 1, day 71.

TABLE 1 | Cases of B-ALL with a cryptic *NUP214*::*ABL1* fusion.

Case	Age/ gender	Karyotype and/or key lesions	WBC, $\times 10^9$/ L	Treatment phase when *NUP214*:: *ABL1* detected	Method used for detection	Response to induction treatment	TKI use	Outcome	References
1	26/F	47,XX,inv(9)(p13q34),+10(11)	N/A	End of induction	RNA-seq	Corticosteroid resistance	Dasatinib added to the second Induction cycle and as a single agent started at +35 d. Post allo-HSCT for 23 months, continued at the time of manuscript	CR1	(10)
2	14/M	IKZF1 p.Ser402fs mutation; PAX5deletion;CDKN2A/ CDKN2B deletion	220.7	N/A	RNA-seq; confirmed by RT-PCR	N/A	N/A	N/A	(20)
3	16/M	46, XY IKZF1(IK6) and p.Ala79fs mutation	135.6	N/A	RNA-seq; confirmed by RT-PCR	N/A	N/A	N/A	(20)
4	15/F	46,XX	260.0	Disease progression after 1st relapse	High resolution SNP array; confirmed by RT-PCR	Corticosteroid resistance and Induction failure	Dasatinib in combination with chemotherapy at disease progression	CR2 after introduction of dasatinib, however, lethal outcome because of disease progression	(18)
5	13/F	46,XX, t(2;16)(q11.2;q11.2)	480.0	Post allo-HSCT	Targeted RNA; confirmed by RT-PCR	Poor -> allo-HSCT	None	CR1	(19)

allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR1, first complete remission; CR2, second complete remission; N/A, not applicable; RT-PCR, reverse transcription polymerase chain reaction; SNP, single nucleotide polymorphism.

quantitative PCR, respectively. Discrepancy in the lab results was interpreted as a subclone of leukemic cells that was not captured by PCR, and the patient was stratified to intermediate-high risk (IR-H) due to a slow response to the therapy as per protocol (**Figure 1**). Consolidation with dexamethasone, vincristine, 6-mercaptopurine, cyclophosphamide, cytarabine, PEG-Asp, and intrathecal methotrexate was given according to IR-H protocol. Bone marrow evaluation on day 71, time point 2 (TP2) still showed positive MRD: ~0.18% and 0.07% by FC and IG/TCR quantitative PCR respectively. The patient was stratified into High-Risk (HR) group with allogeneic hematopoietic stem cell transplantation (allo-HSCT) (**Figure 1**).

Chemotherapy was complicated by multiple side effects. The patient was treated at the intensive care unit twice because of repeated tonic-clonic seizures caused by venous sinus thrombosis in Induction phase and because of severe acute pancreatitis in Consolidation 1. Acute pancreatitis was complicated by multiple organ dysfunction including renal function impairment and toxic myocarditis. Furthermore, the patient suffered from malnutrition, liver toxicity and mixed anxiety-depressive disorder. On day 71 (TP2), targeted RNA sequencing was performed on patient's RNA sample using TruSight Pan-Cancer sequencing kit as described earlier (14). Sequencing data analysis revealed t(9;9)(q34;q34)/*NUP214*::*ABL1* gene fusion. Exon 33 of the *NUP214* gene and exon 3 of the *ABL1* gene were fused. RT-PCR method was used to confirm *NUP214*:: *ABL1* fusion transcript. Gene variant analysis showed no TKI-resistant *ABL1* mutations; therefore, treatment with a first-generation TKI imatinib mesylate was added to the conventional chemotherapy. Complete remission (CR) was achieved within a month, and treatment was downgraded to intermediate-risk protocol (**Figure 1**). At the time of writing the manuscript, the patient is in the first CR 24 months from diagnosis.

The present report was conducted in accordance with the guidelines of the Declaration of Helsinki. Institutional ethical review board permission for a case report was obtained and a written informed consent was received from the patient and his parents.

DISCUSSION

Cryptic *NUP214*::*ABL1* fusion is a rare genetic entity carrying kinase activating alterations and making the patients candidates for TKI treatment. Although *ABL1* gene rearrangements are most commonly detected in B-ALL, *NUP214*::*ABL1* fusion transcript is mainly described in T-ALL patients (7–9,11,15), whereas in

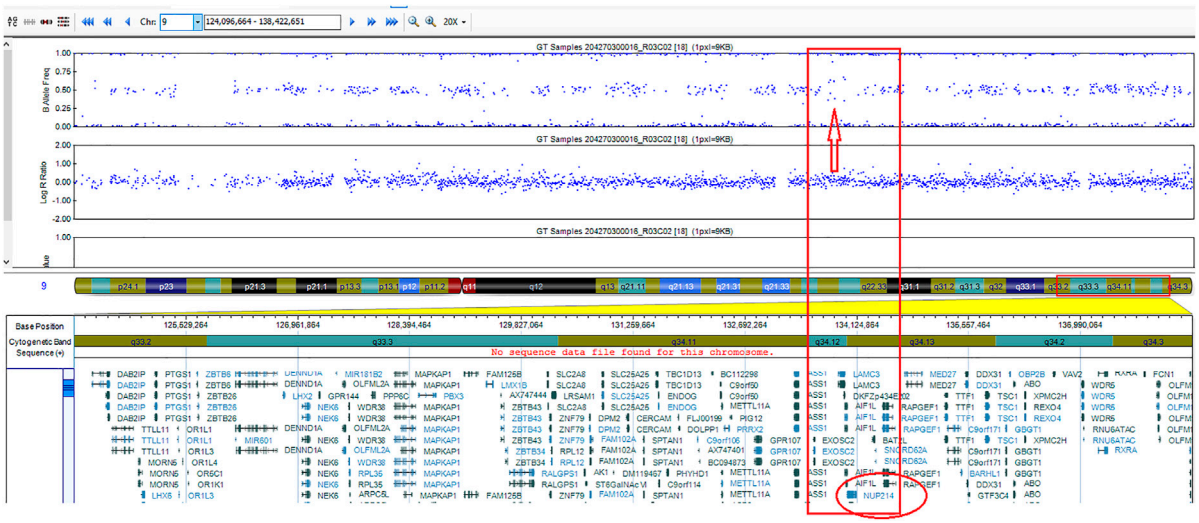

FIGURE 2 | SNP-A karyotyping analysis: 9q34 amplification delimited by *NUP214* and *ABL1* genes.

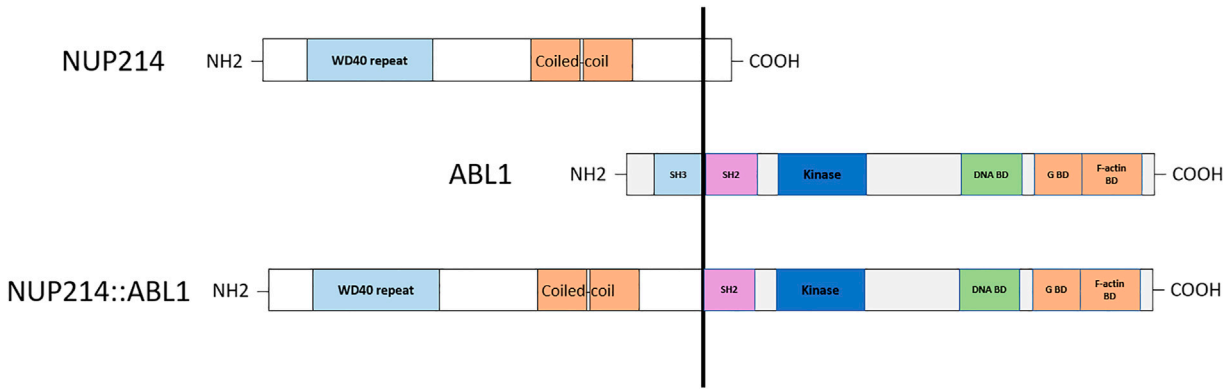

FIGURE 3 | Schematic representation of the chimeric NUP214::ABL1 protein.

B-ALL its expression is described in individual cases only. In T-ALL, chimeric NUP214::ABL1 protein showed to be sensitive to TKI in preclinical and clinical studies (11), whereas in B-ALL the role of TKI still needs to be established. In pediatric population, approximately 10%–15% of B-ALL cases reveal a *BCR*::*ABL1*-like profile representing a biologically and clinically challenging group (3). ABL class tyrosine kinase fusion genes are expected to be clonal leukemia drivers and usually respond well to ABL class inhibitors imatinib or dasatinib. Imatinib is generally regarded as the safest of the TKIs, with no long-term irreversible side effects. Although many authors recommend second or third-generation TKIs to override the frequent ATP-binding site mutations (16,17), in our case imatinib showed a very good effect, as there was no evidence of *ABL1* mutations.

To the best of our knowledge, only five B-ALL cases with *NUP214*::*ABL1* fusion caused by intrachromosomal microduplication had been published so far, data are summarized in **Table 1**. The patients reported were teenagers or young adults, all being >13 years old at the time of diagnosis. Four patients, for whom data was available, had high hyperleukocytosis (WBC >100 × 10^9/L) at presentation, similarly to our case. In all reported cases, the patients had a poor initial response to therapy and were stratified to very high risk (VHR) chemotherapy (case #4) or allogeneic hematopoietic stem cell transplantation (allo-HSCT) (cases #1 and #5). Two patients received treatment with TKI after allo-HSCT and achieved negative MRD, however, subsequent disease progression in case #4 resulted in lethal outcome. One patient (#5) underwent successful allo-HSCT without additional TKI use.

Unlike in previously reported cases, we initiated treatment with a first-generation TKI imatinib mesylate with high efficacy. Two cases (cases #1 and #4) reported a second-generation TKI dasatinib, and a choice of TKI was not specified in the cases #2 and #3. Mechanisms of resistance to imatinib are known to be related to the mutations of ATP-binding site in *BCR*::*ABL1* positive ALL, therefore, dasatinib, nilotinib or ponatinib are

preferred as first line therapy (16,17). In our case, gene variant analysis revealed no TKI resistant *ABL1* mutations, which could explain a good effect of Imatinib which was added to the first line of conventional chemotherapy. This subsequently allowed to downgrade the treatment to IR-H risk thus evading allo-HSCT and potentially life-threatening further toxicity.

Detection of cryptic *ABL1* gene rearrangements by conventional genetic analysis can be a challenge (20, 19). Among the reported cases, *NUP214*::*ABL1* fusion was identified early in treatment, after the first cycle of induction, in one B-ALL case only, using NGS techniques (10). In two cases, the fusion was initially missed by routine diagnostic methods and detected later by SNP-A or targeted RNA sequencing (20, 19) (**Table 1**). In our case, the *ABL1* gene break was initially missed by FISH array (*ABL1* Break Apart Probe) due to a small 445 Kb microduplication in the 9q34 chromosome region and was detected later by performing targeted RNA sequencing. SNP-A karyotyping missed microduplication which was smaller than 5 Mb in size (**Figure 2**). *NUP214* and *ABL1* genes are located at the edges of the 9q34 region, therefore, FISH cannot successfully detect *NUP214*::*ABL1* gene fusion due to technical limitations (**Figure 3**). This particular cryptic fusion mechanism was described in detail by Tsujimoto et al. (20). In our previous retrospective population-based *BCR*::*ABL1*-negative B-other ALL cohort study, we did not detect any ABL-class fusions in pediatric Lithuanian patients (14), making this case to be the only *NUP214*::*ABL1* gene fusion case in Lithuanian childhood B-ALL emphasizing very rare incidence of this aberration. Some authors suggest that all patients with B-ALL should undergo NGS analysis in parallel with conventional genetic screening (13). In our case, adding TKI to the first line treatment enabled us to downgrade the treatment risk group for the patient. However, earlier NGS results detecting targetable genomic alteration would have been beneficial by allowing initiation of targeted therapy and possibly preventing severe drug-induced side effects.

CONCLUSION

Identification of rare targetable genetic subtypes is of importance in order to introduce individualized targeted therapy as early as possible to improve survival and reduce toxicity. Combining TKI with chemotherapy for *ABL1* rearranged B-ALL should be considered for the first-line treatment. B-ALL in adolescent patients without detected recurrent cytogenetic or molecular abnormalities (B-others) should be immediately analyzed further by NGS methods to prevent from missing atypical gene alterations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Vilnius University Hospital Santaros Klinikos. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ES-R designed the study, collected, analyzed and interpreted the data and wrote the manuscript; GV designed and supervised the study, interpreted the data and critically reviewed the manuscript; RN and VD designed the study, performed genetic analysis, interpreted the data and critically reviewed the manuscript; SS designed the study, collected and interpreted the data and critically reviewed the manuscript. All authors agreed and approved the final version of manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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