Reproductive and sexual health care in oncology: current practice and challenges

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Chapter 12

Sexual and fertility-related adverse effects of medicinal treatment for cancer; a national evaluation among medical oncologists

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INTRODUCTION

Advances in diagnostic techniques and therapies have improved the survival rates of patients with different cancer types. As a result, the focus in healthcare has expanded from survival to long-term quality of life. Therefore, specialists' knowledge about the effects of therapy on fertility and sexual functioning is essential [1–3]. With 11,7000 cancer cases in the Netherlands in 2019, over 7000 of all invasive cancers are diagnosed in adults of reproductive ages [4]. Therefore, for cancer patients, but especially for patients of reproductive age, attention must be paid to sexual functioning and fertility before, during and after cancer treatment.

Sexual dysfunction is a common problem among men and women facing cancer and cancer treatments. Prevalence of sexual dysfunction depends on the type of cancer and treatment, ranging from 28 to 70% [5–10]. Multiple variables may contribute to sexual dysfunction, including hair loss, psychological impact, body image, fatigue, surgery and hormonal changes with consequences such as dry mucous membranes. In men, the most common sexual complaints associated with chemotherapy are decreased desire and erectile dysfunction. For example, platinumbased chemotherapy can lead to nerve damage, resulting in erectile dysfunction and anejaculation [11–13]. Loss of sexual desire and vaginal dryness are most commonly seen in women [11, 12]. One study performed by Baumgart et al. found dyspareunia in 57% of women with breast cancer using aromatase inhibitors. In 31% of women using tamoxifen, compared to 9–21% of age-matched controls [14].

Gonadal dysfunction caused by chemotherapy is a risk factor for decreased fertility in men and women [15]. The effects of chemotherapy on fertility depend on several factors like age, sex and chemotherapeutic regime. In women, treatment with chemotherapy may cause amenorrhea, premature ovarian failure and early menopause [11, 16]. In men, treatment with cytotoxic chemotherapy is associated with signifcant gonadal damage and impaired spermatogenesis. Germinal epithelial damage can result in temporary or permanent oligo- or azoospermia. Alkylating agents and platinum compounds are likely to cause infertility due to gonadotoxic effects [17, 18]. For men and women undergoing cytotoxic chemotherapy, several options for preserving fertility exist [18, 19]. These fertility preservation (FP) methods are often experienced as being invasive and distressing. Hence patients may experience psychological complaints such as depression and anxiety. Contrastingly, when persons are deprived of their chance of FP when their fertility is at risk of being impacted, this may cause even more grief and psychological issues [20]. Fertility counselling and pursuing fertility preservation is known to be associated with less regret and greater quality of life [21].

Despite the generally known impact of potential toxic cancer drugs on fertility and sexual function, it is still expected that patients do not receive fertility or sexual counselling by healthcare providers [22–24]. The percentage of patients who reported being uninformed about potential infertility due to cancer treatments varies from 0 to 85% [25, 26]. In previous studies, physicians have indicated various reasons for the lack of discussing fertility and sexual

problems [27–29]. Clinicians described unfamiliarity with fertility preservation, lack of confidence in abilities, lack of agreement with guidelines and fertility preservation and uncertainty about outcome expectancy as barriers to discuss [27]. In the Netherlands, most oncologists see oncofertility or sexual counselling as their responsibility, but it is discussed often or always by only 68.3% according to selfreported practice [30]. Only a minority of Dutch oncologists (18.5%) discussed sexual function regularly [31]. Other surveys mentioned a lack of knowledge regarding the adverse effects of cancer drugs and possible ways to prevent or treat them [28, 29]. However, no studies specifcally describe which knowledge is available among oncologists.

The primary aim of this study was to explore medical oncologists' knowledge of the adverse effects of commonly used cancer drugs regarding their effect on fertility and sexual function. Additionally, the relationship between this knowledge and characteristics such as years of experience and frequency of prescription drugs was evaluated. Knowledge of oncologists with breast cancer, gynaecological and urological malignancies as areas of expertise has been separately evaluated, as many patients sufering from breast cancer or testicular cancer are in reproductive age [4, 32, 33]. Furthermore, we aimed to examine if being involved with cancer of the (internal) genital tract is a factor for improved knowledge of sexual and fertility-related adverse effects.

METHODS

Study design and cohort identification

A questionnaire was used for collecting data in a cross-sectional postal survey. The sample consisted of all 433 members of the Dutch Society for Medical Oncology (NVMO) with several areas of expertise. The inclusion criteria were being a practising medical oncologist in the Netherlands. All members were requested to provide information concerning specifc tumour expertise, employment setting, education level, years of oncology experience, type of hospital, age and gender.

Instrument design and development

The questionnaire was developed by the authors. Cancer drugs and their possible sexual or reproductive related adverse effects were identifed by checking all oncology guidelines, the Summary of Product Characteristics (SmPC) and Netherlands Pharmacovigilance Centre Lareb, in collaboration with a professor of Medical Oncology (SO) and a pharmacist/PhD-student in sexual adverse drug reactions (RG). The SmPC is a mandatory document in Europe for the registration of drugs, with drug information generally based on registration trials and is used by pharmacists and medical specialists. Lareb is the national pharmacovigilance centre that registers possible new adverse reactions of drugs. Information about most and least frequently used oncology drugs in the Netherlands was obtained via the GIPdatabank [34], a database

with Dutch health insurance data on the use of reimbursed drugs over 5 years. The content of the questionnaire was evaluated by four oncologists in an anonymous pilot study and modifed using their feedback. The fnal version comprised a demographic sheet and a list of common cancer drugs with their possible infuence on sexual function and future reproductive ability. Demographic data included professional background, experience in oncology practice, gender and age. Participants were provided with a list of cancer drugs and asked to indicate, using multiplechoice options, which cancer drugs may adversely affect sexual function and fertility. They were explicitly asked not to look up these potential effects in reference documents. Oncologists were able to mark the option 'I don't know' if they were unsure about possible sexual and fertility-related adverse effects of a specifc drug. Furthermore, Likert-scale items measured practices, attitudes, the content of sexual and fertility counselling content, responsibility, need for education, and barriers regarding discussing sexual function and fertility issues. Our survey data concerning the discussion of sexuality and fertility issues were processed separately [30, 31].

Survey administration

The questionnaires were sent to all medical oncologists who were a member of the NVMO in January 2013. Reminders were sent to non-responders in July, 2013 and January, 2014. In addition, an information letter concerning the study and a post-paid return envelope were added, as well as an optout possibility. Data were collected anonymously in order to limit self-reporting bias.

Analysis

Data analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA). Demographic information and answers to the part of the survey that concerned medication were analysed using descriptive statistics. For all results, a distinction was made between answers regarding fertility and answers regarding sexual function. Adverse drug reactions were considered legitimate if reported in the SmPC text of the drug. Adverse effects on fertility and sexual function reported at Lareb were also included in the evaluation of the results. Observed differences between demographic information and specifc answers were identifed using the Pearson's Chi-Square test or Fisher's Exact Test (2-sided). P-values <0.05 were considered statistically signifcant. For further analysis, subgroups with oncologists who marked 'breast cancer', 'nephrology/urology' or 'gynaecology' as area of expertise were analysed separately. In addition, the group was divided into two almost equally sized groups according to experience: 10 years or less and more than 10 years of work experience. Answers for the five most prescribed oncolytics according to the GIP databank [34] were added up and divided into two groups: 'not once filled in that this medication has any negative effect' and 'filled in one or more times that this medication has a negative effect'. The same was done for the five least prescribed oncolytics.

Ethical considerations

In the Netherlands, research that does not involve patients or interventions is not subject to approval from ethical boards. As the study did not concern any information recorded by the investigator so that subjects could be identifed and as it did not compromise the study participants' integrity, no formal ethical approval was needed for this study.

RESULTS

The survey was distributed among 433 oncologists, of which 209 returned the survey (48.3%). Notifcation of refusal was received from 48 oncologists. Reasons mentioned for not participating included lack of time, no interest, too many questions and too many surveys. Of the 209 returned surveys, 9 were returned to sender because practicing abroad, 26 oncologists were retired, and 6 were members of the society but not medical oncologists. These 41 did not meet the inclusion criteria, which decreased the eligible participants to 392. Of the returned questionnaires, 120 questionnaires had been almost fully completed. 15 of 120 questionnaires were excluded because important answers were missing. Another 5 questionnaires had a partly completed 'medication' section, but were used for analysis. Thus, 105 surveys of 392 practicing oncologists (26.8%) were analysed.

Demographics

The mean age of the respondents was 45.1 years (range 30–64), 54.3% were female and 44.8% male. Most of the participating oncologists had breast cancer as area of interest (75.1%), other frequently mentioned areas of interest included colorectal, gynaecology and nephrology-urology, as depicted in Table 1.

Table 1. Demographic characteristics

Demographic characteristics of participating oncologists (n=105)	**n (%)**
Age (years)	
Mean 45,1 years (range 30-64)	
Age 30-40	44 (41.9%)
Age 40-50	26 (24.8%)
Age 50-60	24 (22.9%)
Age >60	10 (9.5%)
Unknown	1 (1.0%)

Table 1. Demographic characteristics (*continued*)

Demographic characteristics of participating oncologists (n=105)	n (%)
Gender	
Male	47 (44.8%)
Female	57 (54.3%)
Unknown	1 (1.0%)
Oncology experience (years)	
1-2	18 (17.1%)
3-5	26 (24.8%)
6-10	12 (11.4%)
11-15	17 (16.2%)
>15	30 (28.6%)
Unknown	2 (1.9%)
Function	
Oncologist	66 (62.9%)
Haematologist	9 (8.6%)
Resident oncologist	18 (17.1%)
Resident haematologist	12 (11.4%)
Hospital type	
University hospital	35 (33.3%)
District general teaching hospital	25 (23.8%)
District general hospital	39 (37.1%)
Categorical cancer hospital	3 (2.9%)
University hospital and district general hospital	2 (1.9%)
Area of interest [a]	
Breast	79 (75.2%)
Colorectal	70 (66.7%)
Palliative care	52 (49.5%)
Gynaecology	46 (43.8%)
Nephrology and urology	48 (45.7%)
Haematology	28 (26.7%)
Lymphoma	27 (25.7%)
Head and neck	14 (13.3%)
Neuroendocrine	14 (13.3%)
Skin	8 (7.6%)
Sarcomas	8 (7.6%)
Lung	3 (2.9%)
Other	16 (15.2%)

[a] Most oncologists reported multiple areas of expertise

Knowledge of fertility- and sexuality-related adverse effects of cancer drugs/therapy

Table 2 shows which drugs that are used in cancer therapy, were mentioned to have a negative effect on fertility, ovulation, spermatogenesis and sexual function according to 100–105 medical oncologists. Drugs of which 50% or more of oncologists marked 'I don't know' whether these drugs negatively affect fertility, ovulation, spermatogenesis or sexual function, were chlormethine (n=73, 72.3%), aminogluthemide (n=65, 63.1%), interleukin-2 (n=62, 62.0%), cyproterone (n=55, 55.0%) and busulfan (n=51, 50.0%).

Drugs that were most often believed to negatively affect fertility were cisplatin (n=81, 80.2%), epirubicin (n=78, 78.0%), cyclophosphamide (n=80, 77.7%), doxorubicin (n=76, 76.0%) and anthracycline (n=78, 75.0%). For sexual adverse effects, most mentioned drugs were tamoxifen (n=67, 65.7%), GnRH-agonists (n=64, 63.4%), autologous stem cell transplantation (n=59, 57.8%), cisplatin (n=58, 57.4%) and epirubicin (n=57, 57.0%). Drugs that were believed not to harm fertility were herceptin (n=69, 67.6%), bisphosphonates (n=63, 60.6%), imatinib (n=55, 54.5%), rituximab (n=51, 50.0%) and 5-fuoruracil (n=47, 44.8%). For sexual function herceptin (n=66, 64.7%), bisphosphonates (n=61, 58.7%), imatinib (n=51, 50.5%), methotrexate (n=50, 49.0%), rituximab (n=50, 49.0%) and 5-fuoruracil (n=45, 42.9%) were noted not to be of harm.

Differences between knowledge of oncologists with or without breast cancer, nephrology/urology or gynaecology as areas of expertise

Table 3 provides an overview of cancer drugs that can be prescribed as mono- or combination therapy in breast cancer. Total respondents varied between 98 and 103. About fertility and sexual function, answers of oncologists with breast cancer as an area of expertise were compared with oncologists without breast cancer as an area of expertise. No signifcant difference in answering was found between these groups with regard to fertility or sexual function. Concerning sexual function, in SmPC texts, sexual adverse drug reactions were registered for GnRH-agonists, megestrol, methotrexate and tamoxifen only. Among oncologists with breast cancer as area of expertise, 48 (63.2%) thought that GnRH-agonists could negatively affect sexual function and 28 (36.8%) believed it would not. Among oncologists without breast cancer as area of expertise, these percentages were 69.6% (n=16) and 30.4% (n=7), respectively. Megestrol was believed to negatively affect sexual function by 52.0% (n = 39) of oncologists with breast cancer as an area of expertise, as by 69.6% (n=16) of oncologists who had not. Among oncologists with breast cancer as area of expertise 27 (35.5%) thought that methotrexate could negatively affect sexual function and 49 (64.5%) believed it would not. Percentages within the group of oncologists without breast cancer as area of expertise were 29.2% (n=7) and 70.8% (n=17) respectively.

TABLE 2 CANCER DRUGS/THERAPY AND THEIR BELIEVED EFFECT ON FERTILITY, OVULATION, SPERMATOGENESIS AND SEXUAL FUNCTION

	Number of respondents*	Negative effect on fertility (% yes ; % no)	Negative effect on ovulation (% yes ; % no)	Negative effect on spermatogenesis (% yes ; % no)	Negative effect on sexual functioning (% yes ; % no)	I don't know
5 FluorUracil	105	36 (34.3%) ; 47 (44.8%%)	31 (29.5%) ; 52 (49.5%)	41 (39.0%) ; 42 (40.0%)	38 (36.2%) ; 45 (42.9%)	22 (21.0%)
Aminoglutethimide	103	15 (14.6%) ; 23 (22.3%)	14 (13.6%) ; 24 (23.3%)	5 (4.9%) ;33 (32.0%)	17 (16.5%) ; 21 (20.4%)	65 (63.1%)
Anthracycline	104	78 (75.0%) ; 20 (19.2%)	74 (71.2%) ; 24 (23.1%)	73 (70.2%) ; 25 (24.0%)	55 (52.9%) ; 43 (41.3%)	6 (5.8%)
Autologous stem cell transplantation	102	65 (63.7%) ; 13 (12.7%)	60 (58.8%) ; 18 (17.6%)	60 (58.0%) ; 18 (17.6%)	59 (57.8%) ; 19 (18.6%)	24 (23.5%)
Bisphosphonates	104	1 (1.0%) ; 63 (60.6%)	0 (0.0%) ; 64 (61.5%)	0 (0.0%) ; 64 (61.5%)	3 (2.9%) ; 61 (58.7%)	40 (38.5%)
Busulfan	102	38 (37.3%) ; 13 (12.7%)	32 (31.4%) ; 19 (18.6%)	37 (36.3%); 14 (13.7%)	19 (18.6%) ; 32 (31.4%)	51 (50.0%)
Chlorambucil	101	35 (34.7%) ; 19 (18.8%)	30 (29.7%) ; 24 (23.8%)	36 (35.6%) ; 18 (17.8%)	18 (17.8%) ; 36 (35.6%)	47 (46.5%)
Chlormethine	101	18 (17.8%) ; 10 (9.9%)	16 (15.8%) ; 12 (11.9%)	15 (14.9%) ; 13 (12.9%)	9 (8.9%) ; 19 (18.8%)	73 (72.3%)
Cisplatin	101	81 (80.2%) ; 10 (9.9%)	70 (69.3%) ; 21 (20.8%)	70 (69.3%) ; 21 (20.8%)	58 (57.4%) ; 33 (32.7%)	10 (9.9%)
Cyclophosphamide	103	80 (77.7%) ; 12 (11.7%)	71 (68.9%) ; 21 (20.4%)	73 (70.9%) ; 19 (18.4%)	52 (50.5%) ; 40 (38.8%)	11 (10.7%)
Cyproteron	100	22 (22.0%) ; 23 (23.0%)	15 (15.0%) ; 30 (30.0%)	21 (21.0%) ; 24 (24.0%)	30 (30.0%) ; 15 (15.0%)	55 (55.0%)
Doxorubicin	100	76 (76.0%) ; 16 (16.0%)	70 (70.0%) ; 22 (22.0%)	68 (68.0%) ; 24 (24.0%)	56 (56.0%) ; 36 (36.0%)	8 (8.0%)
Epirubicin	100	78 (78.0%) ; 13 (13.0%)	70 (70.0%) ; 21 (21.0%)	67 (67.0%) ; 24 (24.0%)	57 (57.0%) ; 34 (34.0%)	9 (9.0%)
Etoposide	101	66 (65.3%) ; 14 (13.9%)	52 (51.5%) ; 28 (27.7%)	54 (53.5%) ; 26 (25.7%)	44 (43.6%) ; 36 (35.6%)	21 (20.8%)
GnRH-agonists	101	53 (52.5%) ; 32 (31.7%)	63 (62.4%) ; 22 (21.8%)	41 (40.6%) ; 44 (43.6%)	64 (63.4%) ; 21 (20.8%)	16 (15.8%)
Herceptin (trastuzumab)	102	4 (3.9%) ; 69 (67.6%)	1 (1.0%) ; 72 (70.6%)	0 (0.0%) ; 73 (71.6%)	7 (6.9%) ; 66 (64.7%)	29 (28.4%)
Ifosfamide	101	71 (70.3%) ; 13 (12.9%)	60 (59.4%) ; 24 (23.8%)	62 (61.4%) ; 22 (21.8%)	51 (50.5%) ; 33 (32.7%)	17 (16.8%)
Interferon-a	103	12 (11.7%) ; 43 (41.7%)	6 (5.8%); 49 (47.6%)	7 (6.8%) ; 48 (46.6%)	27 (26.2%) ; 28 (27.2%)	48 (46.6%)
Interleukine-2 (Aldesleukine)	100	7 (7.0%) ; 31 (31.0%)	4 (4.0%) ; 34 (34.0%)	5 (5.0%) ; 33 (33.0%)	16 (16.0%) ; 22 (22.0%)	62 (62.0%)
Imatinib	101	6 (5.9%) ; 55 (54.5%)	1 (1.0%) ; 60 (59.4%)	2 (2.0%) ; 59 (58.4%)	10 (9.9%); 51 (50.5%)	40 (39.6%)
Irinotecan	102	55 (53.9%) ; 25 (24.5%)	49 (48.0%) ; 31 (30.4%)	52 (51.0%) ; 28 (27.5%)	44 (43.1%) ; 36 (35.3%)	22 (21.6%)
Lomustine	100	35 (35.0%) ; 20 (20.0%)	32 (32.0%) ; 23 (23.0%)	32 (32.0%) ; 23 (23.0%)	20 (20.0%) ; 35 (35.0%)	45 (45.0%)
Megestrol	100	41 (41.0%) ; 40 (40.0%)	44 (44.0%) ; 37 (37.0%)	21 (21.0%) ; 60 (60.0%)	54 (54.0%) ;27 (27.0%)	19 (19.0%)

TABLE 2 CANCER DRUGS/THERAPY AND THEIR BELIEVED EFFECT ON FERTILITY, OVULATION, SPERMATOGENESIS AND SEXUAL FUNCTION (*continued*)

	Number of respondents*	Negative effect on fertility (% yes ; % no)	Negative effect on ovulation (% yes ; % no)	Negative effect on spermatogenesis (% yes ; % no)	Negative effect on sexual functioning (% yes ; % no)	I don't know
Melphalan	100	54 (54.0%) ; 12 (12.0%)	42 (42.0%) ; 24 (24.0%)	49 (49.0%) ; 17 (17.0%)	27 (27.0%) ; 39 (39.0%)	34 (34.0%)
Methotrexate	102	53 (52.0%) ; 30 (29.4%)	46 (45.1%) ; 37 (36.3%)	49 (48.0%) ; 34 (33.3%)	33 (32.4%) ; 50 (49.0%)	19 (18.6%)
Platinum analogues	102	71 (69.6%) ; 17 (16.7%)	64 (62.7%) ; 24 (23.5%)	66 (64.7%) ; 22 (21.6%)	52 (51.0%) ; 36 (35.3%)	14 (13.7%)
Procarbazine	100	36 (36.0%) ; 18 (18.0%)	30 (30.0%) ; 24 (24.0%)	31 (31.0%) ;23 (23.0%)	20 (20.0%) ; 34 (34.0%)	46 (46.0%)
Rituximab	102	3 (2.9%) ; 51 (50.0%)	1 (1.0%) ; 53 (52.0%)	1 (1.0%) ; 53 (52.0%)	4 (3.9%) ; 50 (49.0%)	48 (47.1%)
Tamoxifen	102	48 (47.1%) ; 44 (43.1%)	52 (51.0%) ; 40 (39.2%)	21 (20.6%) ; 71 (69.6%)	67 (65.7%) ; 25 (24.5%)	10 (9.8%)
Taxanes	102	71 (69.6%) ; 20 (19.6%)	62 (60.8%) ; 29 (28.4%)	69 (67.6%) ; 22 (21.6%)	51 (50.0%) ; 40 (39.2%)	11 (10.8%)
Vinblastine	100	43 (43.0%) ; 24 (24.0%)	33 (33.0%) ; 34 (34.0%)	43 (43.0%) ; 24 (24.0%)	30 (30.0%) ; 37 (37.0%)	33 (33.0%)
Vincristine	102	44 (43.1%) ; 28 (27.5%)	34 (33.3%) ; 38 (37.3%)	44 (43.1%) ; 28 (27.5%)	32 (31.4%) ; 40 (39.2%)	30 (29.4%)

*nOT ALL RESPONDENTS ANSWERED EACH QUESTION

Differences between knowledge of oncologists with or without breast cancer, nephrology/urology or gynaecology as area of expertise

TABLE 3 OVERVIEW OF ANSWERS OF ONCOLOGISTS WITH- AND WITHOUT BREAST CANCER AS AREA OF EXPERTISE REGARDING MEDICATION INDICATED IN BREAST CANCER THERAPY

	SmPC registered adverse effects (F=fertility, S=sexual function)	Total respondents* (breast cancer vs no breast cancer)	Oncologists with breast cancer as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	Oncologists who do not have breast cancer as an area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	*P-value*
5-FluorUracil	**F:** *Spermatogenesis or ovulation disorder*	103 (79 vs 24)	28 (35.4%) ; 51 (64.6%)	8 (33.3%) ; 16 (66.7%)	*0.849*
	S: *No data is available on sexual function*[a]		33 (41.8%) ; 46 (58.2%)	5 (20.8%) ; 19 (79.2%)	*0.063*
Cyclophosphamide	**F:** *Attenuation of spermatogenesis, ovulation disorder, amenorrhea, azoospermia, aspermia, oligospermia, oligomenorrhea*	101 (77 vs 24)	62 (80.5%) ; 15 (19.5%)	18 (75%) ; 6 (25%)	*0.561*
	S: *No data is available on sexual function*		42 (54.5%) ; 35 (45.5%)	11 (45.8%) ; 13 (54.2%)	*0.456*
Doxorubicin	***F:** Risk of amenorrhea, oligospermia or azoospermia and risk of irreversible infertility*	98 (75 vs 23)	56 (74,7%) ; 19 (25.3%)	19 (82,6%) ; 4 (17.4%)	*0.432*
	***S:** No data is available on sexual function*		45 (60.0%) ; 30 (40.0%)	11 (47.8%) ; 12 (52.2%)	*0.302*
Epirubicin	***F:** In women: amenorrhea or premature menopause In men: damaged spermatozoa or irreversible infertility*	98 (75 vs 23)	57 (76.0%) ; 18 (24.0%)	20 (87.0%) ; 3 (13.0%)	*0.386*
	***S:** No data is available on sexual function*		46 (61.3%) ; 29 (38.7%)	11 (47.8%) ; 12 (52.2%)	*0.251*
GnRH-agonists	**F:** *No data is available on fertility*	99 (76 vs 23)	41 (53.9%) ; 35 (46.1%)	11 (47.8%) ; 12 (52.2%)	*0.606*
	S: *Erectile dysfunction, vulvovaginal dryness, breast enlargement, loss of libido, gynecomastia, sore breasts*		48 (63.2%) ; 28 (36.8%)	16 (69.6%) ; 7 (30.4%)	*0.573*
Herceptin (trastuzumab)	**F:** *No data is available on fertility*	100 (77 vs 23)	3 (3.9%) ; 74 (96.1%)	1 (4.3%) ; 22 (95.7%)	*1.000*
	S: *No data is available on sexual function*		6 (7.8%) ; 71 (92.2%)	1 (4.3%) ; 22 (95.7%)	*1.000*
Megestrol	***F:** Possible negative effect on fertility.*	98 (75 vs 23)	34 (45.3%) ; 41 (54.7%)	7 (30.4%) ; 16 (69.6%)	*0.205*
	***S:** Sore breasts, erectile dysfunction, loss of libido*		39 (52.0%) ; 36 (48.0%)	16 (69.6%) ; 7 (30.4%)	*0.138*

TABLE 3 OVERVIEW OF ANSWERS OF ONCOLOGISTS WITH- AND WITHOUT BREAST CANCER AS AREA OF EXPERTISE REGARDING MEDICATION INDICATED IN BREAST CANCER THERAPY (*continued*)

	SmPC registered adverse effects (F=fertility, S=sexual function)	Total respondents* (breast cancer vs no breast cancer)	Oncologists with breast cancer as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	Oncologists who do not have breast cancer as an area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	*P-value*
Melphalan	**F:** *In women, amenorrhea. In men azoospermia and risk of (ir)reversible infertility*	98 (75 vs 23)	41 (54.7%) ; 34 (45.3%)	14 (60.9%) ; 9 (39.1%)	*0.600*
	S: *No data is available on sexual function*		24 (32.0%) ; 51 (68.0%)	4 (17.4%) ; 19 (82.6%)	*0.175*
Methotrexate	**F:** *Defective oogenesis or spermatogenesis, infertility*	100 (76 vs 24)	43 (56.5%) ; 33 (43.4%)	11 (45.8%) ; 13 (54.2%)	*0.357*
	S: *Inflammation or ulceration of vagina, gynecomastia, loss of libido, impotence*		27 (35.5%) ; 49 (64.5%)	7 (29.2%) ; 17 (70.8%)	*0.566*
Tamoxifen	**F:** *Amenorrhea*	100 (76 vs 24)	36 (47.4%) ; 40 (52.6%)	11 (45.8%) ; 13 (54.2%)	*0.895*
	S: *Irritation of genitalia externa*[c]		52 (68.4%) ; 24 (31.6%)	16 (66.7%) ; 8 (33.3%)	*0.872*
Taxanes (paclitaxel, cabazitaxel, docetaxel)	**F:** *Impaired fertility in animal studies*	100 (76 vs 24)	53 (68.7%) ; 23 (30.3%)	17 (70.8%) ; 7 (29.2%)	*0.919*
	S: *No data is available on sexual function*		40 (52.6%) ; 36 (47.4%)	12 (50.0%) ; 12 (50.0%)	*0.822*
Vinblastine	**F:** *Impaired fertility, aspermia*	98 (75 vs 23)	31 (41.3%) ; 44 (58.7%)	13 (56.5%) ; 10 (43.5%)	*0.200*
	S: *No data is available on sexual function*		26 (34.7%) ; 49 (65.3%)	5 (21.7%) ; 18 (78.3%)	*0.243*
Vincristine	**F:** *Infertility, azoospermia, amenorrhea*	100 (76 vs 24)	31 (40.8%) ; 45 (59.2%)	13 (54.2%) ; 11 (45.8%)	*0.250*
	S: *No data is available on sexual function*		27 (35.5%) ; 49 (64.5%)	7 (29.2%) ; 17 (70.8%)	*0.566*

Two respondents who completed the medication part, didn't choose their areas of interest, so they were excluded from this analysis

[a] ***According to Lareb, the following adverse effects were reported for 5-fluoroUracil: impotence(1x), vaginal / vulvar erosion(2x), vulvovaginal burning sensation(1x)***

[b] ***According to Lareb, the following adverse effect was reported for tamoxifen: absence of menstruation (1x)***

[c] ***According to Lareb, the following adverse effects were reported for tamoxifen: vulvar problems (3x), vaginal dryness (1x), vulvovaginal inflammation (1x) and pruritus (2x), itch (1x), dyspareunia (1x), impotence (1x) etc.***

Tamoxifen was believed to negatively affect sexual function by oncologists with breast cancer as an area of expertise, as by oncologists who had not (68% and 67%). The same applied for fertility (47% and 46%). Cancer-specifc drugs which are indicated for advanced or non-advanced forms of testicular cancer according to the SmPC texts are listed in Table 4. The total number of respondents varied between 98 and 99 oncologists. Concerning fertility and sexual function, answers of oncologists with 'nephrology/urology' as area of expertise were compared with oncologists who do not have 'nephrology/urology' as an area of expertise. Estimations of which cancer drugs negatively affect fertility or not were similar between these two groups. No signifcant difference in answering was seen concerning fertility, but a signifcant difference was seen in answering with regard to sexual function. Oncologists with 'nephrology/urology' as area of expertise estimated more often that these drugs negatively affect sexual function, in comparison to oncologists who did not have 'nephrology/ urology' as area of expertise (Cisplatin 68.9% vs 48.1%, Etoposide 57.8% vs 35.2%, Ifosfamide 66.7% vs 38.9%, Vinblastine 50.0% vs 16.7%). Table 5 provides an overview of cancer drugs that can be prescribed as mono- or combination therapy in ovarian cancer. The total number of respondents varied between 98 and 101. A signifcant difference in answering was only seen for melphalan concerning sexual function. Melphalan was believed to negatively affect sexual function by 17 (39.5%) oncologists with gynaecology as area of expertise, compared to 11 (20.0%) oncologists who had not (p=0.034). For all other drugs, no signifcant difference in answering was seen with regard to fertility and sexual function.

Years of experience

Findings regarding differences in answers related to years of oncology experience are listed in Table 6. Most oncologists (n=46, 88.5%) with 10 years or less of work experience estimated that at least one of the five most prescribed drugs could negatively affect fertility. This number was similar for oncologists with more than 10 years of work experience: 86.7% (n=39). With respect to sexual function, 28.8%(n =15) of oncologists with 10 years or less of work experience believed none of the five most prescribed medications can negatively affect sexual function in comparison to 37.8% (n=17) of oncologists with more than 10 years of work experience. No signifcant difference was found between these groups when looking at the five most prescribed oncolytics (fertility p=0.789, sexual function p=0.351) and the five least prescribed oncolytics (fertility p=0.986, sexual function p=0.461).

TABLE 4 OVERVIEW OF ANSWERS OF ONCOLOGISTS WITH- AND WITHOUT NEPHROLOGY/UROLOGY AS AREA OF EXPERTISE REGARDING MEDICATION INDICATED IN TESTICULAR CANCER THERAPY

	SmPC registered adverse effects (F=fertility, S=sexual function)	Total respondents* (nephro/uro vs no nephro/uro)	Oncologists with nephro/uro as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	Oncologists who do not have nephro/uro as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	*P-value*
Cisplatin	**F:** *Risk of irreversible infertility. Abnormal spermatogenesis*	99 (45 vs 54)	37(82.2%) ; 8 (17.8%)	43 (78.6%) ; 11(20.4%)	*0.744*
	S: *No data is available on sexual function*		31 (68.9%) ; 14 (31.1%)	26 (48.1%) ; 28 (51.9%)	*0.038*
Etoposide	**F:** *Possibly decreased fertility*	99 (45 vs 54)	30 (66.7%) ; 15 (33.3%)	36 (66.7%) ; 18 (33.3%)	*1.000*
	S: *No data is available on sexual function*		26 (57.8%) ; 19 (42.2%)	19 (35.2%) ; 35 (64.8%)	*0.025*
Ifosfamide	**F:** *Abnormal spermatogenesis, azoospermia, oligospermia, decreased levels of female sex hormones, amenorrhea*	99 (45 vs 54)	32 (71.1%) ; 13 (28.9%)	39 (72.2%) ; 15 (27.8%)	*0.903*
	S: *Sexual function and libido are usually not affected*		30 (66.7%) ; 15 (33.3%)	21 (38.9%) ; 33 (61.1%)	*0.006*
Vinblastine	**F:** *Decreased fertility, irreversible infertility, aspermia*	98 (44 vs 54)	24 (54.5) ; 20 (45.5%)	20 (37.0%) ; 34 (63.0%)	*0.083*
	S: *No data is available on sexual function*		22 (50.0%) ; 22 (50.0%)	9 (16.7%) ; 45 (83.3%)	*0.000*

** **Two respondents who completed the medication part, didn't choose their areas of interest and were thus excluded from this analysis***

TABLE 5 OVERVIEW OF ANSWERS OF ONCOLOGISTS WITH- AND WITHOUT GYNAECOLOGY AS AREA OF EXPERTISE REGARDING MEDICATION INDICATED IN OVARIAN CANCER

	SmPC registered adverse effects (F=fertility, S=sexual function)	Total respondents* (gyn vs no gyn)	Oncologists with gynaecology as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	Oncologists who do not have gynaecology as area of interest. Negative effect on fertility or sexual function Yes (%) ; No (%)	*P*
Cisplatin	**F:** *Risk of irreversible infertility. Abnormal spermatogenesis*	99 (44 vs 55)	37(84.1%) ; 7 (15.9%)	43 (78.2%) ; 12(21.8%)	*0.458*
	S: *No data is available on sexual function*		27 (61.4%) ; 17 (38.6%)	30 (54.5%) ; 25 (45,5%)	*0.495*
Cyclophosphamide	**F:** *Abnormal spermatogenesis, azoospermia, aspermia, oligospermia, ovulation disorder, amenorrhea, oligomenorrhea*	101 (45 vs 56)	36 (80.0%) ; 9 (20.0%)	44 (78.6%) ; 12 (21.4%)	*0.860*
	S: *No data is available on sexual function*		26 (57.8%) ; 19 (42.2%)	27 (48.2%) ; 29 (51.8%)	*0.339*
Doxorubicin	***F:** Risk of oligospermia or azoospermia and risk of irreversible infertility*	98 (43 vs 55)	31 (72.1%) ; 12 (27.9%)	44 (80.0%) ; 11 (20.0%)	*0.359*
	***S:** No data is available on sexual function*		28 (65.1%) ; 15 (34.9%)	28 (50.9%) ; 27 (49.1%)	*0.158*
Etoposide	**F:** *Possibly decreased fertility*	99 (44 vs 55)	29 (65.9%) ; 15 (34.1%)	37 (67.3%) ; 18 (32.7%)	*0.886*
	S: *No data is available on sexual function*		23 (52.3%) ; 21 (47.7%)	22 (40.0%) ; 33 (60.0%)	*0.223*
Ifosfamide	**F:** *Abnormal spermatogenesis, azoospermia, oligospermia, amenorrhea*	99 (44 vs 54)	29 (65.9) ; 15 (34.1%)	42 (76,4%) ; 13 (23.6%)	*0.251*
	S: *Sexual function and libido are usually not affected*		25 (56.8%) ; 19 (43.2%)	26 (47.3%) ; 29 (52.7%)	*0.345*
Melphalan	**F:** *In women amenorrhea. In men azoospermia and risk of (ir)reversible infertility*	98 (43 vs 55)	26 (60.5%) ; 17 (39.5%)	29 (52.7%) ; 26 (47.3%)	*0.444*
	S: *No data is available on sexual function*		17 (39.5%) ; 26 (60.5%)	11 (20.0%) ; 44 (80.0%)	*0.034*

** **Two respondents who completed the medication part, didn't choose their areas of interest and were thus excluded from this analysis***

TABLE 6 OVERVIEW OF ANSWERS OF ONCOLOGISTS WITH ≤ 10 YEARS OR > 10 YEARS OF EXPERIENCE REGARDING THE 5 MOST AND THE 5 LEAST PRESCRIBED ONCOLYTICS*

	Total respondents	**Oncologists with ≤ 10 years of experience who not once filled in medication harms fertility**	**Oncologists with ≤ 10 years of experience who filled in one or more times that these medication has a negative effect on fertility**	**Oncologists with > 10 years of experience who not once filled in medication has a negative effect on fertility**	**Oncologists with > 10 years of experience who filled in one or more times that these medication has a negative effect on fertility**	***P-value***
5 most prescribed oncolytics *(cyclophosphamide, taxanes, rituximab, cisplatin, Herceptin)*	97	6 (11.5%)	46 (88.5%)	6 (13.3%)	39 (86.7%)	*0.789*
5 least prescribed oncolytics *(chlormethine, procarbazine, busulfan, doxorubicin, vinblastine)*	96	8 (15.7%)	43 (84.3%)	7 (15.6%)	38 (84.4%)	*0.986*
	Total respondents	**Oncologists with ≤ 10 years of experience who not once filled in medication has a negative effect on sexual function**	**Oncologists with ≤ 10 years of experience who filled in one or more times that these medication has a negative effect on sexual function**	**Oncologists with > 10 years of experience who not once filled in medication has a negative effect on sexual function**	**Oncologists with > 10 years of experience who filled in one or more times that these medication has a negative effect on sexual function**	***P-value***
5 most prescribed oncolytics *(cyclophosphamide, taxanes, rituximab, cisplatin, herceptin)*	97	15 (28.8%)	37 (71.2%)	17 (37.8%)	28 (62.2%)	*0.351*
5 least prescribed oncolytics *(chlormethine, procarbazine, busulfan, doxorubicin, vinblastine)*	96	20 (39.2%)	31 (60.8%)	21 (46.7%)	24 (53.3%)	*0.461*

*Based on numbers from the GIPdatabank (34)

DISCUSSION

This study was aimed to gain insight into the knowledge of Dutch oncologists in sexual and fertility-diminishing adverse effects of cancer drugs. According to our understanding, this study was the first to evaluate this knowledge. Results of this study revealed that oncologists have different beliefs about these effects. The lack of knowledge about adverse effects is consistent with results from other surveys. This gap in knowledge may be the reason that adverse effects of cancer drugs leading to infertility or sexual dysfunction are not often discussed in clinical practice [22–24, 27–29, 31].

According to our results, awareness among oncologists could be further improved concerning possible fertility-related adverse effects of cancer drugs, as many oncologists misestimated this or filled in they were unsure about adverse effects. For example, most oncologists estimated correctly that drugs like cisplatin (80.2%), cyclophosphamide (77.7%) or doxorubicin (76.0%) may negatively affect fertility. However, percentages were lower when looking at drugs such as chlorambucil (34.7%), busulfan (37.3%), procarbazine (36.0%) and vinblastine (43.0%). More remarkable was that 33–51% of oncologists indicated they did not know anything about the effects on fertility of these drugs, even though both SmPC texts and literature state that all of these agents may negatively affect fertility [16, 35]. Given that a signifcant number of oncologists made incorrect estimates or indicated they were unaware, this may also have consequences for discussing FP options and referral to fertility specialists. Another part of our nationwide survey was used to identify practice behaviour and attitudes of medical oncologists regarding fertility preservation [30]. Dutch oncologists considered discussing fertility as their responsibility, but in practice discussing fertility is infuenced by a number of barriers such as prognosis and type of hospital. Half of the respondents declared to possess sufficient knowledge regarding fertility preservation (n=57, 47.5%). However, only 68.3% of oncologists indicated discussing the subject often or always [30]. Findings by Covelli et al., who performed a qualitative study to evaluate clinicians' barriers to discussing infertility and fertility preservation, suggest insufficient education and collaboration between fertility specialists and oncologists [27].

For each drug, at least one oncologist believed sexual complaints were associated with the drug treatment. In general, oncologists' opinions differed per drug: For some drugs, only 2.9% (bisphosphonates) and 3.9% (rituximab) of oncologists believed there could be potential sexual adverse effects. For other drugs, 63.4% (GnRH agonists) and 65.7% (tamoxifen) of oncologists believed sexual adverse effects were possible. It will remain unclear whether oncologists just picked available options or if their answers were based on their knowledge and experience in the clinic. Indeed, in literature and SmPC texts, GnRH agonists and tamoxifen are reported to increase the risk for sexual dysfunction [9, 14]. For example, the SmPC text of triptorelin, a gonadotropin agonist, estimated that 30–40% of men and more than 10% of women would be affected by sexual complaints [36, 37]. Sexual activity (including kissing, caring and self-masturbation) had changed for more than 70% of men and women after cancer

treatment [12]. From the literature, it is known that high dose chemotherapy can induce loss of desire for sex and trouble feeling aroused for men and women.

Moreover, neurotoxic chemotherapy (e.g. platinum compounds) can also induce erectile dysfunction in men and chemotherapy, in general, can cause abrupt, premature ovarian failure, leading to genitourinary atrophy, dryness, and pain in men women [9, 13]. However, most profoundly for drugs that can be considered chemotherapy, these effects are not often mentioned in SmPC texts. These omissions in the SmPC, maybe the explanation for a relatively low amount of oncologists being aware of possible sexual adverse effects of chemotherapy.

Another part of our survey also evaluated the discussion of sexual function, showing that the risk of sexuality-related adverse effects is barely discussed during informed consent conversations between Dutch oncologists and their patients [31]. Over 84% of participants stated having little or no knowledge of possible sexual adverse effects, 36% of oncologists considered lack of knowledge as a reason for avoiding discussion about sexual function. Regardless of their knowledge, over 72% of participants would like to acquire more training in counselling about sexual function [31].

In the current study, oncologists with breast cancer as an area of expertise had the same beliefs about the possible negative effects of cancer drugs on fertility and sexual function as oncologists without breast cancer as area of expertise. Interestingly, over 31% of the oncologists believe tamoxifen has no adverse effect on sexual function, while both SmPC texts and literature state the opposite [14, 38, 39]. According to different studies, tamoxifen users can experience reduced sexual interest (32–44%), dyspareunia, vaginal dryness and/or insufficient lubrication (30–40%) and orgasmic dysfunction (42%) [14, 38, 39].

Oncologists with 'nephrology/urology' as area of expertise marked signifcantly more often that cancer medication prescribed for testis malignancies may negatively affect sexual function (50–68.9%) in comparison to oncologists with other areas of expertise (16.7–48.1%). With no other explanation available, we hypothesise that oncologists with 'nephrology/urology' as area of expertise are more aware of sexuality because of involvement of the external male genitalia in testicular cancer and the relatively young age of affected men. For drugs, they often prescribe, no information is available in the SmPC texts on sexual function. However, articles are available in literature describing negative effects on sexual function from treatments such as cisplatin, etoposide, ifosfamide and vinblastine [13, 40]. A decrease in sexual activity (34%), loss of desire (25%) and ejaculation disorder (28%) was reported among patients treated for testicular cancer with chemotherapy [41]. With regard to oncologists with gynaecology as an area of expertise, we also hypothesised that they should be more aware of sexual and fertility-related adverse effects because of the involvement of the genital tract in ovarian cancer. However, with a single exception, no signifcant differences were seen in answering compared to the oncologists without gynaecology as an area of expertise.

Finally, when evaluating the results regarding the work experience of oncologists, one fnding stands out in particular. For both the five most- and least prescribed oncolytic drugs,

oncologists seemed to be more aware of fertility than sexual function. Varied reasons could explain the difference between fertility and sexuality knowledge. In the SmPC, the official drug information leafet, fewer sexual adverse drug reactions are registered than are known from the literature. In registration trials, patient self-reporting methods are often used to collect information on 'non-critical adverse drug reactions, which can lead to underreporting and underregistration of sexual adverse effects. Bonierbale et al. illustrated this difference reporting sexual adverse drug reactions in a study among 4557 depressive patients when evaluating spontaneous reports on sexual adverse drug reactions (35%) and when physicians specificallyasked for sexual adverse drug reactions (69%) [42]. Another potential reason is that healthcare professionals might assume that sexual function is not essential when patients are facing life-threatening diseases such as cancer. Almost 45% of oncologists indicated they do not discuss sexual function if they believe the patient is too ill [31].

Another interesting fnding is that no signifcant difference is seen between years of work experience and the estimated possible negative effect of oncolytic on fertility and sexual function. A study conducted among oncologists by Adams et al. found no signifcant differences in knowledge of FP by seniority or years in service [43]. Furthermore, no signifcant difference is seen between oncologists' clinical experience and a 'confidence in knowledge' score in regards to fertility issues, shown in a study performed by Louwe et al. [44]. Altogether, these results indicate that years in service do not seem to influence knowledge of fertility-related subjects, demonstrating there is room for education among oncologists from all levels of experience.

Our study should be interpreted with acknowledgement of its limitations. First of all, a non-validated postal survey was used for this study. This possibly led to selection bias, as oncologists who were more interested in subjects of fertility and sexuality were possibly more willing to participate. Also, one could assume that oncologists with at least some knowledge of adverse effects participated. The results may not directly reflect the clinical reality and may even be worse. Participants were asked not to look up adverse effects of cancer drugs evaluated in our survey as stated in the questionnaire. However, it will remain unknown whether oncologists have indicated what they thought or whether information has been searched for. Since the questions contained multiple choice answers, oncologists may have guessed correct answers. As the survey was executed in 2014, results may not apply to the current situation. Additional knowledge may have been obtained in the past few years, with growing public attention for the subjects fertility and sexual function. However, not much has been added to the literature and reference documents regarding specifc sexual and fertility-related adverse effects. Therefore, the authors believe that this omission is probably negligible.

Based on the results of this survey, it can be concluded that the knowledge of oncologists is lagging what is known in literature and SmPC texts about fertility and sexuality-related adverse effects and needs to be optimised to some extent. Overall, findings from this study, supported by findings from the additional two studies based on our nationwide survey [30, 31] suggest that more awareness is needed about sexual and fertility-related adverse effects

of cancer treatments. Strategies for creating more awareness among oncologists have to be investigated and regular routines in practice that can provide patients with adequate information and counseling. Informing patients about possible adverse effects can contribute to the quality of life of cancer patients and survivors. This study also highlights the need for more broadly available extensive information regarding sexual and fertility-related adverse effects of commonly prescribed cancer drugs. Additionally, more attention should be paid to this topic in medical school or during residency and practicing as an oncologist.

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