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ORIGINAL RESEARCH ARTICLE

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Time from referral to ovarian tissue cryopreservation in a cohort of Danish women

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Abstract

Introduction: Young women with a cancer diagnosis often have very little time to decide whether or not to commence fertility-preserving strategies before initiating potentially sterilizing cancer treatment. Minimizing the interval from opting for fertility preservation to completion of the procedure will reduce the potential risk of delaying cancer treatment. In the current study, we have evaluated the period of time from referral to ovarian tissue cryopreservation (OTC) to actual freezing of the tissue in a cohort of Danish women.

Material and methods: The study population comprised 277 consecutive patients with both malignant and nonmalignant diseases referred for OTC from four centers in the Danish network. Statistical analysis was conducted to analyze the impact of age, diagnosis, and referring center on the time from OTC-referral to OTC. A literature search for "random start" protocols for controlled ovarian stimulation (COS) for fertility preservation in cancer patients was performed.

Results: The time from OTC-referral to OTC was significantly influenced by diagnosis, age, and referring center. Women with malignant diseases other than breast cancer, such as sarcomas, pelvic cancers, and hematological cancers, experienced a significantly shorter interval to OTC (5 days) than women with breast cancer (7 days) and nonmalignant diseases including systemic, ovarian, and hereditary conditions (13-17.5 days). Women over the age of 30 years experienced a significantly longer time to OTC ($P < 0.03$), and the diagnosis determined the length of the interval ($P < 0.001$). According to the literature, fertility preservation by oocyte vitrification requires 13-14 days, as the average time for 1 round of COS was 11 days and oocyte collection can be performed 2 days later.

Conclusions: It is in the interest of both cancer patients and clinicians to perform fertility preservation as quickly and safely as possible. In a Danish setting, OTC provides a short interval of around 6 days from the patient choosing this option to completion of the procedure. This is considerably less time than what is needed to perform COS and oocyte vitrification, and therefore OTC might be considered the preferred choice of fertility preservation when urgency is needed.

Abbreviations: COS, controlled ovarian stimulation; FP, fertility preservation; IVF, in vitro fertilization; OTC, ovarian tissue cryopreservation; RC, referring center.

KEYWORDS

cancer, fertility preservation, oocyte vitrification, ovarian tissue cryopreservation, random start ovarian stimulation

1 | INTRODUCTION

In parallel with the increasing survival rates for most forms of cancer, the interest in fertility preservation (FP), especially for young women, has increased. Loss of fertility is considered one of the most significant late effects of cancer treatment and this concern is an additional stress factor for patients.[1] Making time-pressured decisions about FP while simultaneously planning urgent cancer treatment are demanding because women have to trade-off the immediate consequences of starting cancer treatment with the long-term chances of having a biological child.

Currently, several types of FP are offered to women. Some of the most prominent include cryopreservation of mature oocytes or embryos, if the woman has a partner. Due to the widespread knowledge on controlled ovarian stimulation (COS) and in vitro fertilization (IVF) these methods are currently regarded as the preferred options for postpubertal patients.[2,3] The established technique of COS secures multiple follicles growing to the preovulatory stage, enabling aspiration of mature oocytes, which are subsequently vitrified before or after fertilization. Alternatively, one ovary, or part of an ovary, can be excised through surgery after which the cortical region of the ovary, containing >90% of the follicles, is isolated and frozen. Ovarian tissue cryopreservation (OTC) is the only fertility-preserving option for prepubertal patients, and this method is often considered as the first option for FP when there is not enough time to perform COS before cancer treatment. It is now well documented that autologous transplantation of the preserved frozen/thawed tissue will revive ovarian function in the vast majority of women (ie >95%), and the births of >130 children following this treatment have been reported.[4,5]

The two fertility-preserving strategies differ profoundly in the period of time required to obtain either mature oocytes or cortical tissue. This difference has attracted little attention despite the fact that newly diagnosed women wanting FP often urgently needs gonadotoxic treatment. COS and oocyte aspiration are usually considered to take around 2 weeks, even with random-start protocols,[6,7] whereas ovarian tissue does not need any pretreatment and can be excised as soon as an operation can be scheduled.[8] Most studies on FP, irrespective of whether focus is on freezing mature oocytes/embryos or ovarian tissue, state that the procedure was performed without delaying cancer treatment.[9-11] However, it is obviously of interest to the patient to keep the time interval between referral to OTC and the actual procedure as short as possible. The aim of the present study was to determine the period of time from referral to OTC to the excision and cryopreservation of ovarian tissue in a cohort of Danish women undergoing OTC. Further, we wanted to evaluate differences in relation to diagnostic categories, age of the patient and between each of the four referring hospitals in our network. Moreover, the time interval from OTC-referral to OTC was related to the recommended time frames for diagnosis and treatment of cancer patients provided by the Danish Health Authority, and the reported duration of COS and collection of mature oocytes for FP in oncological patients.

Key message

Fertility preservation is of great importance to cancer patients. In a cohort of Danish cancer patients, time from ovarian tissue cryopreservation referral to freezing was 6 days, which is considerably less than the 14 days needed for oocyte vitrification.

2 | MATERIAL AND METHODS

2.1 | Study population

The study population included all patients referred for OTC at the Laboratory of Reproductive Biology in Copenhagen, Denmark from June 2015 to September 2018, who subsequently underwent oophorectomy.

A total of 277 consecutive patients referred for OTC from four centers (of which three are located in Denmark and one in south Sweden) were included; Aarhus University Hospital (referring center 1 [RC1]; n = 124), University Hospital of Copenhagen (RC2; n = 100), Odense University Hospital (RC4; n = 36), and Skaane University Hospital (RC3; n = 17). Time from OTC-referral to OTC was defined as the period of time, measured in days, from first contact between the referring center and Laboratory of Reproductive Biology to schedule a date for OTC, to the day of ovarian excision and cryopreservation. The laboratory was always able to accommodate the requested dates for OTC from the referring centers and did not delay the procedure.

The patient diagnoses were categorized based upon Donnez & Dolmans,[5] with five groups of malignant diseases (n = 242) and two groups of nonmalignant diseases (n = 35) (Table 1). Diagnosis at the time of cryopreservation included breast cancer (n = 118), pelvic cancers (n = 24), hematological cancers (n = 53), sarcomas (n = 24), central nervous system and other anatomically cranially placed cancers (n = 23), systemic conditions with need of gonadotoxic chemo- or radiotherapy (n = 25), and a heterogeneous group of ovarian and hereditary conditions with the risk of primary ovarian insufficiency

TABLE 1 Time from OTC-referral to OTC in relation to diagnosis

Diagnosis	Patients (n)	Days from OTC-referral to OTC	
		Mean ± SD	Median [range]
Malignant diseases			
Pelvic cancers	24	5.8 ± 5.5	5.0 [1-27]
Kidney-related	6	7.0 ± 9.9	3.5 [1-27]
Genital-related	14	5.6 ± 3.5	6.0 [1-13]
Intestine-related (- esophagus)	4	4.5 ± 3.5	4.5 [1-8]
Hematological cancers	53	6.6 ± 6.3	5.0 [1-34]
Leukemia	17	8.2 ± 6.6	7.0 [1-22]
Lymphoma	36	5.9 ± 6.1	5.0 [1-34]
Sarcomas	24	5.4 ± 3.7	4.5 [1-18]
CNS and other cranial cancers	23	9.4 ± 10.8	6.0 [1-53]
CNS cancer	21	9.7 ± 11.3	6.0 [1-53]
Esophagus cancer	1	5.0	5.0
Cancer of nasal cavity	1	7.0	7.0
Total malignant not breast cancer	124	6.7 ± 6.9	5.0 [1-53]
Breast cancers	118	9.9 ± 7.2	7.0 [1-36]
Total malignant conditions	242	8.3 ± 7.2	6.0 [1-53]
Nonmalignant diseases			
Systemic conditions	25	12.6 ± 8.6	13.0 [2-29]
Hematological conditions	11	9.9 ± 7.0	7.0 [3-24]
Sclerosis	7	16.7 ± 9.9	20.0 [4-20]
Autoimmune	7	12.7 ± 9.2	13.0 [2-29]
Ovarian and hereditary conditions (risk of POI)	10	25.2 ± 18.9	17.5 [1-57]
Ovarian torsion	1	1.0	1.0
POI	3	16.3 ± 2.5	16.0 [14-19]
Turner syndrome	2	44.0 ± 18.4	44.0 [31-57]
Syndromes/other hereditary	4	28.5 ± 20.8	22.5 [12-57]
Total nonmalignant conditions	35	16.2 ± 13.4	14.0 [1-57]
Patients in total	277	9.3 ± 8.6	6.0 [1-57]

CNS, central nervous system; OTC, ovarian tissue cryopreservation; POI, primary ovarian insufficiency.

(n = 10). Table 1 shows a detailed list of the diagnoses of the patients included in this study. The age of the study population ranged from 3 days to 41 years, and the median age for the cohort was 27 years.

Oocyte vitrification is now gaining ground as an established procedure in Denmark but has only been offered for FP in a small number of patients. Hence, there are insufficient data to perform a comparison between oocyte vitrification and OTC within our own data.

2.2 | Literature search

A systematic search on PubMed was performed for original studies evaluating "random start"-protocols for COS for FP in cancer patients. Case reports of a single or few women were excluded.

2.3 | Statistical analyses

A negative binomial regression model was used to analyze the impact of age, diagnosis, and referring center on the time from OTC-referral to OTC. *P*-values below 0.05 were considered significant. Analysis was carried out using R version 3.4.3 (https://cran.r-project.org/).

2.4 | Ethical approval

Cryopreservation of ovarian tissue for fertility preservation has been approved by the Minister of Health in Denmark and by the ethical committee of the municipalities of Copenhagen and Frederiksberg (H-2-2011-044).

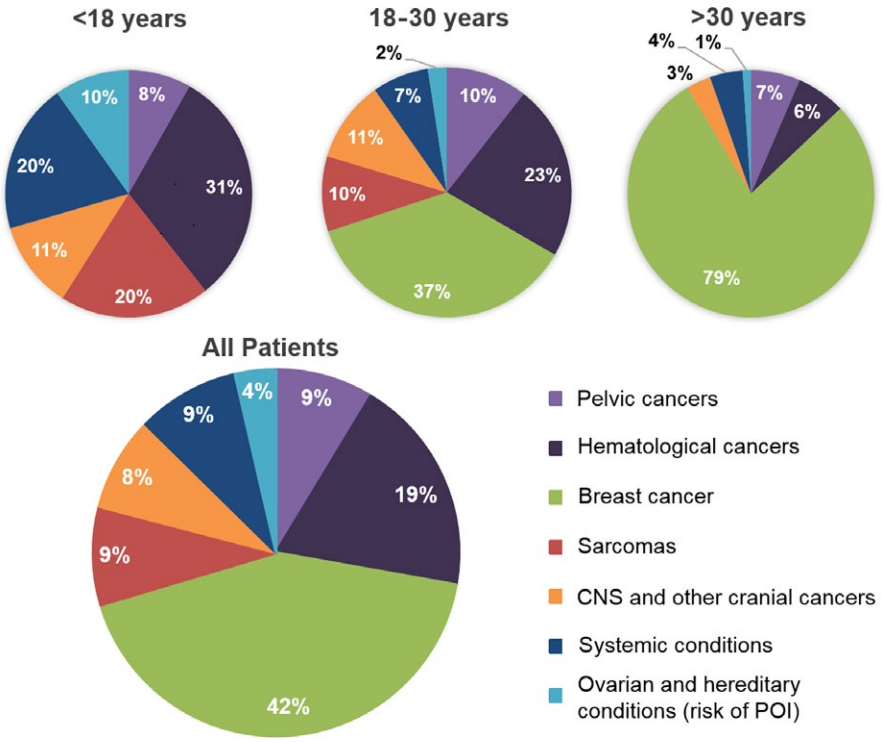

FIGURE 1 Distribution of diagnosis among the referred patients overall and according to age. Top panel depicts the distribution of diagnosis within three different age groups. Patients <18 years, n = 61. Patients between 18 and 30 years, n = 123. Patients >30 years, n = 93. Large diagram depicts the diagnosis within the whole cohort of patients (n = 277). CNS, central nervous system; POI, primary ovarian insufficiency [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Diagnosis

Figure 1 depicts the percentages of each diagnostic category within three age groups (<18, 18-30 and >30) and of the whole cohort of patients. Overall, the majority of patients referred for OTC were breast cancer patients (42%), followed by hematological cancers (19%) with the remaining 5 groups comprising <10% each. No breast cancer patients were present in the group of girls <18 years of age, but it was the most frequent diagnosis in patients >18 years. This was especially pronounced in the women over the age of 30 (79% breast cancer). Among the girls under the age of 18 hematological cancers (31%), including both Morbus Hodgkin, non-Hodgkin lymphomas and B-cell lymphomas, sarcomas (20%), and systemic conditions (20%) were the main reasons for FP.

3.2 | Days from referral to OTC to freezing of the tissue

The number of days from OTC-referral to OTC (both mean and median) are given for each of the diagnostic groups and underlying diagnoses (Table 1). Between the seven diagnostic groups, the median number of days to OTC ranged from 4.5 days (mean 5.4 days) for sarcomas to 17.5 days (mean 25.2 days) for ovarian and hereditary conditions, with an overall median time interval of 6 days (mean 9.3 days) for all diagnostic groups. Specifically, the shortest time intervals to OTC were observed in pelvic cancers, hematological cancers and sarcomas, while the longest intervals were found within the nonmalignant Turner syndrome and other hereditary disorders and syndromes. Breast cancer patients experienced a median number of days to OTC of 7 days (mean 9.9 days), ranging from 1 to 53 days.

3.3 | Diagnosis, age and referring center impact the time to OTC

The time from OTC-referral to OTC was found to be significantly influenced by age, diagnosis, and referring center with each factor independently impacting the time interval (Table 2). Women over the age of 30 experienced a significantly longer time interval to OTC than patients with an age <18 ($P < 0.03$). The diagnosis of the patient determined the length of the interval to OTC ($P < 0.001$). Patients with an ovarian and hereditary condition experienced a significant longer time interval to OTC than patients with breast cancer and other malignant conditions. Furthermore, patients with breast cancer experienced a longer time to OTC than patients with other malignant conditions. When diagnoses were grouped into 3 large categories (Table 1); "malignant conditions not breast cancer" (n = 124), breast cancer (n = 118), and nonmalignant conditions (n = 35), the median numbers of days to OTC were 5 days (mean 6.7 days), 7 days (mean 9.9 days), and 14 days (mean 16.2 days), respectively (Figure 2). Patients with malignant diseases other than breast cancer experienced a significantly shorter time interval to OTC than the remaining patients. Finally, the referring center also impacted on the number of days from OTC-referral to OTC ($P < 0.001$). RC4 provided a significantly shorter time interval to OTC when compared with RC2 and RC1, whereas RC1 provided the significantly longest interval to OTC compared with all other centers (Table 2 and Figure 3).

TABLE 2 Estimates of the number of days from OTC-referral to OTC according to age of patients, diagnosis, and referring center. Relative time was estimated using a negative binomial regression

Parameter	Days from OTC-referral to OTC	Confidence interval	*P*-value
Age (y)			
<18	1[a]		0.03
18-30	1.11[ab]	0.90-1.35	
>30	1.41[b]	1.06-1.90	
Diagnosis			
Breast cancer	1[a]		<0.001
Malignant conditions			
Pelvic cancers	0.45[b]	0.32-0.63	
Sarcomas	0.45[b]	0.32-0.64	
Hematological cancers	0.54[b]	0.42-0.69	
CNS and other cranial	0.62[bc]	0.45-0.87	
Nonmalignant conditions			
Systemic conditions	1.13[acd]	0.84-1.54	
Ovarian and hereditary conditions	2.20[d]	1.42-3.41	
Referring center			
RC1	1[a]		<0.001
RC2	0.73[b]	0.62-0.88	
RC3	0.60[bc]	0.40-0.91	
RC4	0.45[c]	0.35-0.59	

CNS, central nervous system; OTC, ovarian tissue cryopreservation; RC, referring center.
P-values <0.05 were considered significant.
[a,b,c,d]indicates significant differences between groups.

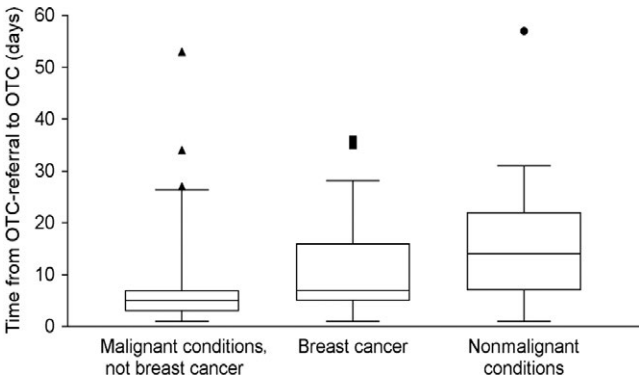

FIGURE 2 Time from OTC-referral to OTC according to the diagnosis. The different diagnoses were grouped according to Table 1 into "malignant conditions not breast cancer", "breast cancer", and "nonmalignant conditions". Patients with ovarian and hereditary conditions had a significantly longer time to OTC than patients with breast cancer and other malignant conditions. Patients with malignant disease other than breast cancer had a significantly shorter time to OTC than the remaining patients (Table 2)

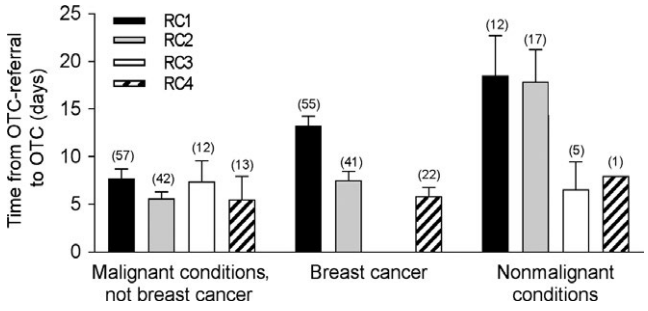

FIGURE 3 Time from OTC-referral to OTC according to diagnosis and referring center (RC). RC4 provided significantly shorter time intervals to OTC when compared with RC2 and RC1. RC1 provided the significantly longest interval compared with all other centers (Table 2)

3.4 | Duration of ovarian stimulation in random start protocols

The concept of random start COS is based on the emergence of evidence that follicular growth is not only initiated once per menstrual cycle, but rather in 2 or 3 follicular waves.[12] This allows recruitment of a follicle cohort under the influence of applied COS regardless of the timing of initiation, which is exploited for FP when there is a lack of time. Table 3 shows an overview of peer-reviewed, original articles (n = 9) reporting the duration of "random start" protocols for COS for FP in cancer patients. A total of 1150 patients were included in the 9 studies, and the average time for 1 round of COS was 11 days, irrespective of where in the menstrual cycle stimulation was initiated. In addition to this, 2 days should be added to allow for ovulation induction and subsequent oocyte collection 36 hours later. Hence, COS and oocyte pick up add around 13-14 days in total for these cancer patients.

TABLE 3 Reported duration of a "random start controlled ovarian stimulation" protocol for fertility preservation in cancer patients

Reference	Design	Patients (n)	Initiation	Duration of stimulation (mean no. of days)
Muteshi et al[7]	Retrospective cohort	127	COS	11.5 (11.2-12.0)
			rsCOS	12.2 (10.7-13.7)
Campos et al[13]	Prospective cohort	26	Follicular phase	10.6 ± 2.1
			Luteal phase	10.0 ± 0.4
Cavagna et al[14]	Cross-sectional	40	COS	10.00 ± 1.41
			Late follicular phase	9.70 ± 0.49
			Luteal phase	10.21 ± 1.23
von Wolff et al[6]	Retrospective cohort	684	COS	10.8 ± 2.4
			Late follicular phase	10.6 ± 2.7
			Luteal phase	11.5 ± 2.2
Kim et al[15]	Retrospective case/control	66	COS	10.3 (9-14)*
			rsCOS	11.4 (9-14)*
Simi et al[16]	Retrospective cohort	25	COS	10.53 ± 2.66
			Late follicular or luteal phase	9.5 ± 1.16
Rashidi et al[17]	Prospective cohort	14	COS	7.8 ± 1
			rsCOS	8.7 ± 2
Cakmak et al[18]	Retrospective cohort	128	COS	9.3 (9.0-9.5)
			Late follicular phase	10.5 (9.6-11.4)
			Luteal phase	11.5 (10.5-12.0)
von Wolff et al[19]	Prospective cohort	40	Follicular phase	10.6 ± 2.5
			Luteal phase	11.4 ± 2.6

The duration of stimulation is reported in mean (95% CI or ±SD, *in one case median [range]). Controlled ovarian stimulation (COS, early follicular phase, initiated at cycle day 2-5), random start controlled ovarian stimulation (rsCOS, initiated at any day in the cycle, late follicular phase day 6-13, luteal phase day 14-28).

4 | DISCUSSION

In this study, we reported the time from OTC-referral to the actual freezing of ovarian tissue in relation to diagnosis, age, and referring center in a cohort of Danish women undergoing FP. This period of time approximates the potential delay in cancer treatment caused by FP, that is, the time from opting for FP to completion of the procedure. The number of days from referral to OTC to freezing of the tissue within all diagnostics groups in the cohort was a median of 6 days. Overall, the shortest time intervals to OTC (4.5-5 days) were observed in patients with sarcomas, pelvic cancers, and hematological cancers, whereas the longest intervals (13-17.5 days) were present within the nonmalignant diseases including systemic, ovarian, and hereditary conditions. It was expected that the time interval from OTC-referral to OTC was longest in the nonmalignant group compared with the malignant group, but it confirms that this parameter is a crucial determinant of the speed with which OTC is executed.

Diagnosis, age, and referring center were found to significantly impact the time to OTC. The time interval from OTC-referral to OTC was found to be longer in the group of women >30 years of age; however, this may be primarily due to the large percentage of breast cancer patients in this group (79%), and not a direct age-effect. Furthermore, significant differences were found in the time to OTC between the 4 referring centers, but some of those differences were due to the lack of specific patient groups within one center. RC3 only referred young patients and did not refer any women with breast cancer for OTC. RC1 and RC2 are the two largest referral centers and represented patients with the same age and diagnosis, and in this case the difference in prolonged time to OTC was directly dependent on the referring center. These differences between centers could be due to small differences in policies regarding the indications and referral for OTC, or management of the logistics at the individual hospitals. Collectively, small differences in the time intervals to OTC exist between the four referring centers in the Danish OTC network, but current data reflect that OTC for FP is performed quickly and efficiently without causing any obvious delay in cancer treatments for the patients who need it the most.

We also found that women with malignant diseases other than breast cancer experienced a significantly shorter time to OTC (5 days) than women with breast cancer (7 days) and nonmalignant diseases (14 days). In Denmark, the Danish Health Authority provide clinically recommended and justified time frames from diagnosis of cancer to primary treatment is initiated ("Cancer pathways", Table 4).[20] In the

TABLE 4 The Danish Health Authority Cancer Pathways—clinically justified time frames

Type of cancer	Standardized duration from diagnosis to primary treatment (d)			Choice of primary treatment
	Chemotherapy	Radiation	Surgery	
Without subcategory				
Cancer in children	Individually planned			
Sarcoma	11	15	14	Predominantly surgery, but 20% (especially children and young adults) are treated with neoadjuvant chemotherapy or radiation
Breast cancer	13	13	13	Predominantly surgery with adjuvant chemotherapy, but neoadjuvant or primary chemotherapy occur
Hematological				
Acute leukemia	3	—	—	Chemotherapy is the only option
Lymphoma	3	15	—	85% receive chemotherapy
Multiple myeloma	Individually planned	—	—	70% receive chemotherapy
Pelvic				
Bowel cancer	10	14	10	Both primary surgery and neoadjuvant chemotherapy may be applied
Ovarian cancer	11	—	8	Predominantly surgery and adjuvant chemotherapy
Cervical cancer	11	15	8	50% neoadjuvant radiation or chemotherapy
Anal cancer	15	15	—	Radiation and chemotherapy concomitantly
Uterine cancer	—	—	8	Predominantly surgery and perhaps adjuvant chemotherapy
CNS and other cranial				
Head or neck cancer	11	11	7	75% radiation possibly combined with chemotherapy
Gastric and esophageal cancer	18	—	10	Surgery, often combined with neoadjuvant and adjuvant chemotherapy
Brain cancer	21	—	7	Predominantly surgery with adjuvant radiation and chemotherapy

The pathways are based on national evidence-based clinical guidelines and describe all steps of the optimal diagnosis and treatment procedures ensuring uniform, high quality across the five Danish hospital regions, including unnecessary waiting times. The success of the pathways is centrally monitored. Neoadjuvant chemotherapy: chemotherapy prior to surgery. Adjuvant chemotherapy: chemotherapy following primary surgery. Source: The Danish Health Authority—Cancer pathways and follow-up plans 2016-2018. Available at: https://www.sst.dk/da/sygdom-og-behandling/kraeft/kraeftpakker-og-opfoelgningsprogrammer.

group of hematological conditions, including leukemia and lymphomas, the choice of primary treatment in the clear majority of cases is chemotherapy with the recommendation that treatment is initiated within 3 days. The median number of days from OTC-referral to OTC for hematological conditions in the current study was 5 days (mean 6.6 days), which implies that FP would cause delay in initiation of cancer treatment in this group of patients. However, some patients with hematological conditions would need to undergo hematopoietic stem cell transplant, in which primary ovarian insufficiency rates are 70%-100% and post-treatment parenthood rates are as low as 3%-8%.[21,22] As a result, if in any way permissible in the individual case, FP would be strongly recommended in these women, and the choice of OTC would minimize the delay in cancer treatment.

In Denmark, OTC is only performed in patients with leukemia once they are in complete remission, which allows more time for FP.[23] For sarcomas, breast cancer, and pelvic cancers the recommended time frames are approximately 10-13 days, when the primary treatment is chemotherapy or neoadjuvant chemotherapy (Table 4). In these cases, the median numbers of days to OTC range between 4.5 and 7 days (mean 5.4-9.9 days), which in the majority of cases would allow time for OTC with no or a minimal delay in initiation of cancer treatment. The recommended "Cancer pathways" from the Danish Health Authority were developed to ensure that all patients receive treatment of uniform, high quality. However, the recommendations underline that every patient should be treated individually and concrete circumstances, such as complex disease or a patient's wish for extra time to consider treatment options, should be taken into account.[20] In cases where surgery is the first choice of treatment, which is the case for most brain cancers and many breast cancer patients, the time frame for the following adjuvant chemotherapy is not specified and would allow sufficient time for COS and oocyte vitrification for FP. Nonetheless, the recommended time frames for initiation of cancer treatment in most cancers highlight the urgency of treatment and the fact that these women have very little time in which to commence fertility-preserving strategies without affecting their cancer treatment.

In the current study, we found that women with malignant diseases experienced a median number of days from OTC-referral to OTC of no more than 6 days (mean 8.3 days), which is considerably less than the 13-14 days required to perform COS and oocyte vitrification. Expressed differently, 69% of breast cancer patients and 89% of the patients with the remaining malignant diseases experienced a time interval to OTC of <14 days. Even among patients without a medical indication for urgency (ie nonmalignant disease), 47% experienced a time interval to OTC <14 days in the Danish cohort. These data highlight the advantage of OTC as being a strategy with a very short time frame. This aspect is obviously of great importance concerning cancer treatment, but it may be even more important for the patient. Studies have found that one of the biggest concerns for patients with malignant diseases is the time from cancer diagnosis to the initiation of treatment, as well as the concern for FP.[24] Hence, minimizing the interval between FP-referral and FP is not merely a matter of treatment demand, but also of great value to the psychological well-being of the patients who are juggling thoughts of survival and the wish for future motherhood.

With the emergence of random start protocols for COS, many patients who previously did not have time for conventional COS before chemotherapy are now having their mature oocytes vitrified for FP. A literature review on "random start" protocols used for cancer patients showed that the duration of COS can be limited to around 11 days, which will add up to approximately 13-14 days when including ovulation induction and oocyte collection. However, in the vast majority of cancer patients, only 1 round of stimulation will be possible, and the number of oocytes retrieved has been found to be negatively correlated with age, but not with the type of cancer.[25] Although oocyte/embryo vitrification is currently used routinely for young women requiring FP,[2,3,8,26] the evidence regarding outcomes of IVF for cancer patients who have returned to use their stored oocytes, is scarce. The hitherto largest study, counting a cohort of 80 cancer patients, recently reported a cumulative live birth rate in young cancer patients (≤35 years) of only around 40%, whereas the percentage was markedly higher (around 70%) in the age-matched group of elective freezers.[26] Hence, poorer IVF outcomes achieved by cancer patients combined with a significantly lower oocyte survival rates in this group indicate that the underlying disease in cancer patients could potentially impair reproductive outcome.[26] This means that despite the advancement of random start protocols for oocyte vitrification, it is not completely straightforward. Moreover, oocyte vitrification is only now being implemented as a standard procedure in Danish fertility clinics, and cryopreservation of embryos is still considered the most established and reliable procedure in many centers. The superiority of oocyte vitrification also needs to be proven in the context of OTC, and so far, only 1 study by Diaz-Garcia et al,[8] have compared the efficacy of oocyte vitrification with that of OTC in a single-center setting. Diaz-Garcia et al[8] found a trend toward higher clinical pregnancy rates and live birth rates after oocyte vitrification compared with OTC in breast cancer patients undergoing FP. They did not find the same trend in patients with Hodgkin lymphoma or other conditions, including sarcoma, leukemia, autoimmune disease and gynecological cancers, but the number of women returning to attempt pregnancy is still low in these groups and a limiting factor to the overall conclusions in the study.[8] Moreover, Diaz-Garcia and co-workers highlight that OTC allowed for natural conception in almost half of the women and restored ovarian function in 93% of the women after 3 months.[8]

Ovarian tissue cryopreservation is currently gaining ground as a valid method to preserve and restore not only fertility, but also ovarian function in young women and girls. With OTC the concerns of the patients are met at multiple levels: by allowing a short interval between diagnosis and initiation of cancer treatment, having no concern about aggravating a hormone-sensitive cancer, and providing restoration of fertility with the chance of multiple conceptions—the natural way—and revival of circulating hormones. The latter can provide natural endogenous hormone therapy for puberty induction in childhood cancer survivors and for women who enter menopause prematurely.[27-29] In addition, the collection and in vitro maturation of immature oocytes in connection with OTC provides an additional fertility potential, which could be essential especially for patients with cancers originating in the ovary.[29] Irrespective of all the above, it should always be prioritized to treat patients as quickly and safely as possible, and in our view OTC in most instances qualifies to be the preferred option for FP, which is in accordance with the current recommendations from international societies like the American Society of Clinical Oncology and the American Society for Reproductive Medicine for women with restricted time to undergo FP.[3,30] Finally, the choice of any fertility-preserving strategy should be an individual assessment of each woman depending on the specific indication, age, gonadotoxic treatment, psychological well-being, and future wishes for motherhood or ovarian function.

5 | CONCLUSION

In conclusion, the time from opting for FP to completion of the procedure is of importance for many cancer patients, who are in need of urgent cancer treatment. Keeping the time interval for FP as short as possible will minimize any potential delay in treatment and potentially relieve the time-pressured decision-making for some patients. In this cohort study of Danish women, we found that the time from OTC-referral to freezing was considerable less than the time needed for COS and oocyte/embryo vitrification. Thus, for many women with malignant diseases, OTC would probably be the preferred choice for FP from a time-restricted perspective.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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