

Research Article

Fertility Preservation Discussion in Adult Male Cancer Patients Is Underutilized and Varies Based on Age

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Abstract *Introduction.* Oncofertility is often omitted in pretreatment discussion and planning. This study seeks to evaluate the prevalence and influencing factors of cryopreservation discussions. *Methods.* A retrospective review was performed on 3,133 male patients aged 18–60 years with a cancer diagnosis at a single institution. Data was collected for cryopreservation discussion and if cryopreservation of sperm was performed. Age, race, cancer location, primary treatment, and chemotherapy status were also recorded. *Results.* A total of 2,504 patients were included for analysis. There was documentation of counseling in 14.1% and 5.0% underwent cryopreservation. Logistic regression indicated a significant effect of age, race, site of cancer, primary treatment, and chemotherapy treatment on whether cryopreservation was discussed ($\chi^2 < 0.001$). Age and chemotherapy at any time of treatment ($P < .001$) were significantly associated with cryopreservation counseling. *Conclusion.* Our study indicates that cryopreservation is vastly under-discussed, especially in older patients and those who do not receive chemotherapy. It is important to include preservation options and counseling for all patients.

Keywords oncofertility; cryopreservation; fertility preservation

1. Introduction

Given the sequelae of cancer treatments on reproductive health, one key aspect of cancer survivorship is to focus on fertility preservation (FP) prior to initiation of treatment plans. The American Society of Clinical Oncology (ASCO) guidelines recommend that all patients with a cancer diagnosis should be counseled on the impact of their disease process and treatment on future fertility [1]. Guidelines also recommend that patients receive referrals to the appropriate reproductive and FP resources [1,2]. However, FP is often not discussed in a timely manner [3]. The reason for lack of adequate counseling and referrals for FP is unclear and likely multifactorial. A recent study of in vitro fertilization (IVF) providers showed that 20% of their cancer patients were self-referred, underscoring a lack of involvement of cancer providers in this care [4].

Studies have shown that poor prognosis, insurance status, difficulty of providing semen samples, and lack of

access to sperm banking are major barriers to adequate counseling [3,5]. Perceived infertility risk is possibly a contributor, but prospective studies regarding risk assessment are difficult to perform as they require years of follow-up and have many confounding factors. Ideally, cryopreservation is performed before initiating any treatment modality, as it is difficult to predict which patients will be able to conceive after treatment [6]. However, individualized infertility risk is difficult to predict and depends on type of cancer, treatment, and baseline fertility. Because of this, patients should be afforded a discussion regarding an overall risk, regardless of perceived risk by the treatment team. As assisted reproductive techniques have become more successful and readily available, it is important to include options and counseling for all patients.

Patients who undergo cryopreservation prior to treatment have improved fecundity compared with post-treatment counterparts [7]. It is important that all patients are able to make an informed decision whether or not to sperm bank, and at the very least, understand their risk. With the demonstration of the underutilization of FP discussion, this study aims to assess the overall frequency of FP and the factors which influence discussions between patients and physicians. We hypothesize that FP is discussed in a low percentage of patients at our institution and that there is only a small percentage of patients who follow through with cryopreservation.

2. Materials and methods

2.1. Data source

Internal review board approval was obtained for retrospective review of all male patients with a new cancer diagnosis at a single academic institution. Information was gathered on patients from the institutional tumor registry. Data was obtained from January 1st, 2012 to August 31st, 2018.

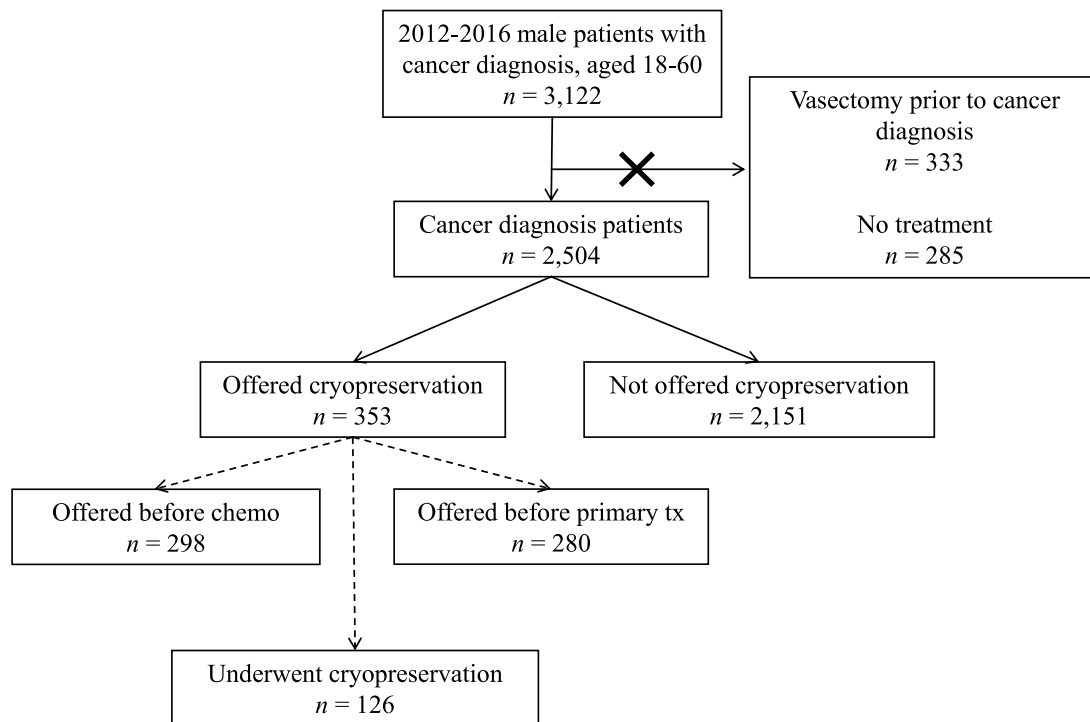


Figure 1: Flowchart of cancer patients aged 18–60 at our institution indicating their fertility discussion status and cryopreservation status.

2.2. Study population and measures

We queried our institutional cancer registry data for all male patients with a malignancy diagnosis. This database includes all patients with a new cancer diagnosis. A retrospective review was performed on 3,133 male patients aged 18–60 years with any cancer diagnosis at a single institution. Patients younger than 18 were not included as this study sought to focus on adults, which is an understudied group in regards to FP. Exclusion criteria included patients who had undergone vasectomy, sperm banking for other reasons prior to cancer diagnosis, and/or patients who received no treatment for their cancer diagnosis (Figure 1). Cryopreservation discussion was defined as documentation in the chart indicating that infertility risk was discussed, and FP options were offered. Patients who had a semen analysis in the chart were defined as having undergone preservation. Data was collected for cryopreservation discussion and if cryopreservation of sperm was performed. Age, race, cancer location, primary treatment, and chemotherapy status were also recorded. Patients were grouped from ages 18–29, 30–39, 40–49, and 50–60. The primary outcome was whether or not FP was offered. The secondary outcome was if the patient ultimately went through with cryopreservation.

2.3. Statistical analysis

Statistical analysis was performed using Stata, version 13.0 (StataCorp LLC; College Station, TX, USA). Categorical

demographic characteristics were analyzed using chi-squared testing. The use of 2-tailed *t*-test analysis assessed continuous variables. Logistic regression analysis evaluated the effect of age, race, site of cancer, primary treatment, and chemotherapy treatment on whether cryopreservation was discussed. Two-sided $P < .05$ was considered statistically significant.

3. Results

A total of 2,504 patients were included for analysis. Mean age was 49 years (SD = 10.4). There was documentation of counseling on cryopreservation in 353 patients (14.1%)—280 (79.3%) occurring before primary treatment and 298 (84.4%) before either primary or adjuvant chemotherapy. All demographic variables were significant between discussion groups except for race (Table 1).

A logistic regression indicated a significant effect of age, race, site of cancer, primary treatment, and chemotherapy treatment on whether FP was discussed ($P < .001$); see Table 2. Chemotherapy at any time of treatment (OR 6.99, 95% CI 4.45–10.99) was significantly associated with cryopreservation counseling. In patients who received chemotherapy as their primary treatment, 19.9% received counseling on FP. Testicular and prostate cancer patients were significantly more likely to be offered FP (OR 17.70, 95% CI 4.94–63.47 and OR 5.66, 95% CI 1.68–18.66, resp.). Of these individuals, 126 (35.7%) patients

Table 1: Demographic information of 2,504 patients diagnosed with cancer at our institution from 2012–2018.

	Cryopreservation discussion		P-values
	Not discussed	Discussed	
No. pts (%)	2,151 (85.9)	353 (14.1)	
Mean age	50.1	38.7	$P < .001$
No. race (%)			$P = .335$
Caucasian	1,805 (83.9)	307 (87.0)	
African American	307 (14.3)	41 (11.6)	
American Indian	7 (0.3)	2 (0.6)	
Asian	32 (1.5)	3 (0.8)	
No. primary treatment (%)			$P < .001$
Surgery	1,425 (66.2)	207 (58.6)	
Chemotherapy	394 (18.3)	98 (27.8)	
Radiotherapy	29 (1.3)	2 (0.6)	
Hormonal therapy	29 (1.3)	2 (0.6)	
Chemotherapy status (%)			$P < .001$
No. received	982 (45.7)	272 (77.1)	
No. did not receive	1,169 (54.3)	81 (22.9)	
No. site of cancer (%)			$P < .001$
Prostate cancer	241 (92.0)	21 (8.0)	
Testicular	16 (23.2)	53 (76.8)	
Renal	161 (97.6)	4 (2.5)	
Ear/nose/throat	290 (94.8)	16 (5.2)	
Stomach/esophageal	85 (91.4)	8 (8.6)	
Pancreas/liver/intestinal	395 (84.8)	71 (15.2)	
Pulmonary	150 (94.3)	9 (5.7)	
Orthopedic	16 (64.0)	9 (36.0)	
Hematology/onc	533 (82.5)	113 (17.5)	
Dermatologic	109 (95.6)	5 (4.4)	
Neurologic	155 (77.9)	44 (22.1)	
Age group			$P < .001$
18–29	86 (42.8)	115 (57.2)	
30–39	155 (68.6)	71 (31.4)	
40–49	415 (87.0)	62 (13.0)	
50–60	1,495 (93.4)	105 (6.6)	

underwent cryopreservation; see Table 3. Patients aged 30–39, 40–49, and 50–60 were significantly less likely to receive counseling when compared to patients aged 18–29 while controlling for other variables (OR 0.41, 95% CI 0.25–0.66, OR 0.12, 95% CI 0.08–0.20 and OR 0.05, 95% CI 0.04–0.09, resp., $P < .001$ for all 3 groups); see Table 4. Despite a significant difference between age groups, only 57% of 18–29 year-old patients were counseled on fertility.

Patients in all age groups underwent sperm cryopreservation, albeit at a declining rate with increasing age (Table 1). There were 126 patients (34.9%) who underwent cryopreservation after discussion, with the largest percentage in the 18–29 year-old age group (27.8%). Of all diagnoses, testicular cancer had the highest percentage of patients (53%) who cryopreserved. The only patient group without any patients proceeding to cryopreservation were those with malignancies of renal origin (Table 5).

Table 2: Logistic regression evaluating factors predictive of FP discussion.

	OR (95% CI)	P-values
Race		
Caucasian	Referent	
African American	1.02 (0.68–1.54)	.908
American Indian	1.61 (0.26–9.89)	.604
Asian	0.52 (0.14–1.93)	.329
Primary treatment		
Surgery	Referent	
Chemotherapy	1.67 (1.02–2.74)	.041
Radiotherapy	1.31 (0.82–2.11)	.261
Hormonal therapy	1.69 (0.35–8.16)	.512
Received chemotherapy		
No	Referent	
Yes	6.99 (4.45–10.99)	< .001
Site of cancer		
Urothelial	Referent	
Prostate	5.66 (1.68–18.66)	.005
Testicular	17.70 (4.94–63.47)	< .001
Renal	0.57 (0.13–2.49)	.455
Ear/nose/throat	0.65 (0.19–2.19)	.485
Esophageal	1.20 (0.27–5.35)	.807
Gastric	0.88 (0.20–3.92)	.869
Small bowel	1.69 (0.34–8.48)	.519
Colorectal	1.45 (0.47–4.47)	.518
Hepatobiliary	0.87 (0.24–3.18)	.835
Pancreatic	2.52 (0.79–8.07)	.12
Lung	0.57 (0.15–2.19)	.416
Cardiothoracic	0.63 (0.08–4.64)	.648
Bone	2.28 (0.47–11.16)	.308
Hematologic	1.64 (0.52–5.17)	.401
Skin	0.95 (0.22–4.09)	.942
Neurologic	2.49 (0.80–7.75)	.113
Soft tissue	1.55 (0.43–5.56)	.5
Eye	1.19 (0.16–9.05)	.865
Endocrine	0.97 (0.25–3.69)	.96
Age group		
18–29	Referent	
30–39	0.41 (0.25–0.66)	< .001
40–49	0.12 (0.08–0.20)	< .001
50–60	0.06 (0.04–0.09)	< .001

Table 3: Cryopreservation outcomes depending on FP discussion status.

FP discussed (%)	Patient cryopreserved	
	No	Yes
No	2,148 (99.8)	3 (0.2)
Yes	230 (65.1)	123 (34.9)

Table 4: Cryopreservation outcomes depending on the patient's age factor.

Age	Patient cryopreserved	
	No	Yes
18–29	125 (62.2)	76 (27.8)
30–39	194 (85.8)	32 (14.2)
40–49	467 (97.9)	10 (2.1)
50–60	1,592 (99.5)	8 (0.5)

Table 5: Cryopreservation percentages by cancer.

Site of cancer	Cryopreserved (%)	
	No	Yes
Prostate cancer	259 (98.9)	3 (1.1)
Testicular	32 (46.4)	37 (53.6)
Renal	165 (100)	0 (0)
Ear/nose/throat	301 (99.7)	1 (0.3)
Stomach/esophageal	92 (98.9)	1 (1.1)
Pancreas/liver/intestinal	458 (98.3)	8 (1.7)
Pulmonary	155 (97.5)	4 (2.5)
Orthopedic	19 (76.0)	6 (24.0)
Hematology/onc	595 (92.1)	51 (7.9)
Dermatologic	112 (98.2)	2 (1.8)
Neurologic	259 (98.9)	3 (1.1)

4. Discussion

Since the inclusion of FP in the ACSO guidelines in 2006, there has been an increase in its universal recognition by clinicians. However, widespread utilization in the adult population appears to be lacking and its frequency remains undefined [1]. To the authors' knowledge, our study provides the largest reviewed cohort for FP which assesses confounding factors. Not surprisingly, only 14.1% of patients had documentation that they were offered FP during a visit before any treatment. Analysis revealed that young populations are most likely to be offered FP, however, even in the youngest population (ages 18–29), only 57% had a documented discussion of FP. This suggests a barrier between providers and patients that warrants further evaluation. Of patients who were counseled, 35% ultimately cryopreserved, showing that men with new cancer diagnoses are interested in future fertility, but that there is room for improvement in getting patients who are counseled to sperm bank. Younger patients were significantly more likely to undergo sperm banking, but a small subset of patients in the oldest age group still cryopreserved. There were no discernible similarities between these older patients to explain why some did or did not bank. This indicates that all age groups are interested in future fertility and at-risk patients are not receiving adequate counseling. This supports the guideline recommendation that all patients of childbearing age should be counseled on and offered cryopreservation. However, it is interesting to note that cancer of renal origin was the only diagnosis group in which patients did not cryopreserve. This calls into question whether all patients need the same level of counseling and implicates that a better risk assessment system will improve patient screening and discussion. It is clear that age plays a role, however patients could have a worse prognosis, or have other personal reasons to not bank.

Testicular cancer and prostate cancer were associated with significantly increased rates of documented counseling on FP. This is likely attributable to urologists being more

knowledgeable regarding patient infertility and thus more likely to offer FP, as they are the main providers in patients with these diseases. Surgical intervention of prostate cancer involves division of the vas deferens, yielding the patient sterile, and thus the risk is more concrete, which may lead to a higher rate of discussion. Malignancies of hematologic origins including lymphoma and leukemia were not individually predictive of providers discussing FP. Lymphoma and leukemia are common malignancies in young men and these patients are at higher risk of infertility [8]. It is unclear why discussion was rarer in this population while it underscores an opportunity for improvement. Chemotherapy, when compared to surgical treatment, was more commonly associated with fertility counseling; however only 19.9% of patients were offered FP. Chemotherapy is a known risk factor for infertility after treatment, specifically with alkylating agents [9]. Radiation has been shown to have significant implications on semen parameters and fertility but was not shown to have increased FP discussion in our cohort [10]. Overall, this data demonstrates the lack of fertility discussions in all male cancer patients, especially those with known high risk treatment modalities.

FP appears to be a pediatric focused issue in the literature—there are few studies assessing provider discussion with patients regarding FP in the adult population. A 2002 study utilizing a questionnaire for pediatric oncologists revealed that 91% thought sperm banking to be important but less than half of providers had this discussion and referred patients to specialists [11]. Despite this, there is supporting evidence that cancer patients have a high interest in future fertility. Stein et al. found that regret regarding fertility was the most common theme in discussion groups of young male cancer survivors [12]. Our study builds on this data, further indicating that FP is not routinely discussed. The reason for poor adherence to the guidelines is unclear. Fertility resources and sperm preservation techniques are well established and easily accessible, furthering the importance of providing adequate counseling [13,14,15]. Schover et al. reported that only 57% of cancer survivors under the age of 35 could recall being informed about the possibility of infertility after their treatment [16]. The psychological burden of fertility in cancer patients is also well studied and reported [11,16,17]. A high percentage of patients who bank sperm would recommend it to others with the same disease [18,19]. Our study suggests there are significant barriers to fertility discussion. Increased FP awareness as well as collaboration between specialties may provide further improvement in FP in the adult population. FP awareness includes knowledge about the impact of cost, prognosis, lab availability, and financial support systems. Sperm banking and annual storage costs are often not readily available and may deter patients from preservation.

Providers may assume that patients with poor prognosis either cannot produce a sample or that the discussion is not important. Based on our findings, urologic diagnoses have a higher rate of discussion—therefore provider knowledge and access to FP resources may be a barrier that can be overcome.

As this was a retrospective review, there are inherent limitations of this study. As a single center series, there is a likelihood that local practice patterns could greatly influence these results and that generalizability to other centers, both academic and community-based, may be limited. This study relies on the electronic medical record and physician charting and there is likely a subset of patients who were offered cryopreservation, but it was not documented. However, this emphasizes the importance of documentation which is listed in the ASCO guidelines. It should be noted that there is a template that is available at our institution in oncology consultation notes, but it was rarely seen during chart review. Our institution also lacked a collaborative consortium or fertility coordinator (although one has been hired recently), which has been shown at other institutions to improve rates of FP [5]. Radiation was not subdivided into targeted area, which may influence the results, as certain radiation treatments are higher risk than others. Likewise, cumulative dose of alkylating agents (if received) was not assessed. The lack of insurance and socioeconomic data is likely an unaccounted-for confounding factor. This would be of interest for further assessment as this may add another important area of improvement.

Our study highlights a gap between providers and patients regarding FP. As discussed previously, this is likely due to barriers of both provider and patient education. Our data can help highlight *at risk* patients and clinical care sites which may warrant more attention, such as hematologic malignancies or younger patients. The focus should be both on system-wide changes as well as risk assessment tools. There are studies showing improvement in discussion rates with implications of formalized FP programs. However, the overall rates were still only 43% [5]. This study showed that even when patients were offered cryopreservation, they followed through only 34.9% of the time. There is room for improvement by identifying modifiable barriers and implementing changes. Our study also suggests that improvement in risk assessment may better direct resources, as cancer of certain organ systems may not need as in-depth counseling. The ASCO guidelines do not address risk levels for patients, merely that all patients at risk for infertility should receive counseling. Our study indicates that there may be subsets of patients that may need more intensive counseling. For example, no patients with a renal cancer diagnosis cryopreserved. Patients with renal masses are often older and the treatment is purely surgical. An older patient with a renal mass does not necessarily need the same

FP discussion as a younger patient with a testicular mass. A better risk assessment tool and modification of the ASCO guidelines to reflect this difference may improve adequate counseling.

5. Conclusion

The impact of cancer treatment on fertility presents a significant psychological burden which can be reduced in patients with whom FP is discussed and in those who bank sperm [12,18]. The results of the large cohort of men with cancer diagnoses assessed in this study reveal a low percentage of patients receiving fertility counseling at our institution. Younger patients, those with testicular or prostate cancer and those undergoing chemotherapy had increased rates of a FP discussion; and those with other high-risk malignancies and treatments were significantly less likely to receive this counseling. As men in all age groups cryopreserved, it is important to offer FP to all men with fertility potential with a new cancer diagnosis. Even when patients were offered FP, there was a demonstrable gap between discussion and cryopreservation. Further efforts to improve overall FP and cryopreservation are needed.

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

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