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The Impact of Fertility Preservation on Treatment Delay and Progression-Free Survival in Women with Lymphoma: A Single-centre Experience

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Lymphoma affects many young women of childbearing age. The American Society of Clinical Oncology recommends early discussion of the reproductive risks of treatment, and referral to fertility preservation (FP) specialists when appropriate (Loren*, et al* 2013). Women referred for FP undergo a several-step process including ovarian stimulation, oocyte retrieval, and oocyte or embryo storage (De Vos *et al* 2014). Barriers to FP include poor access to reproductive specialists and concerns for treatment delay (Quinn*, et al* 2015, Quinn*, et al* 2009). The real-world treatment delay and outcomes among female lymphoma patients attempting FP with modern techniques have not been reported previously.

At our institution, practitioners are required to address fertility in all newly diagnosed cancer patients through the use of automated prompts in the electronic medical record. We have a dedicated in-house fertility preservation patient navigator (FPPN) to educate patients and expedite referrals to the reproductive specialists. We performed a retrospective chart review of lymphoma patients that contacted any fertility specialist prior to treatment at Northwestern University from 1 May 2006 until 31 August 2015. Patients who underwent FP were compared to women that contacted a FPPN but did not undergo preservation. The Northwestern University institutional review board approved the use of the clinical database for this project.

Our primary objective was to assess differences in time to treatment (TTT) associated with FP. In newly diagnosed patients, TTT was defined as the time from the initial haematology consultation until the initiation of therapy. In patients with relapsed disease, TTT was defined as the time from the date of biopsy or haematology consultation until treatment initiation. Our

secondary objective was to assess progression-free survival (PFS), which was defined as time from date of treatment until progression or death. The Wilcoxon rank sum test was used to compare age, TTT and follow-up time between groups. Fisher's exact test was used to compare stage, planned treatment setting, and Eastern Cooperative Oncology Group performance score (ECOG PS). Kaplan-Meier curves with the log rank test were used to compare PFS between the two groups, using a two-tailed significance level of 0.05.

A total of 128 patients were identified from a fertility patient log, including 40 who underwent FP. Thirty-three of 40 patients undergoing FP and 50 of 93 patients who chose not to undergo FP were available for analysis. Reasons for exclusion included patients seen by reproductive endocrinology only and no haematologist consulted at Northwestern, lack of chemotherapy treatment records, or no treatment received following fertility contact. Pertinent baseline characteristics are outlined in Table I. Comparing the two groups, there was a significant difference in age (p=0.01), but not in stage (p=0.05), planned treatment setting (p=0.99) or ECOG PS (p=0.99). Median follow-up was 39.3 (1.5 – 103.4) months, and did not differ between controls and those undergoing FP (p=0.16).

Median TTT among FP patients was 28 days overall (range: 18-76) versus 15.5 days (range: 0-74) for controls (p< 0.001; Figure 1A). Factors other than FP led to treatment delays prior to and after FP. The median time to first contact with a fertility specialist was 0 days (range -15 to +11) from haematology consultation, with several patients having contact prior to their haematology visit. The median time from oocyte retrieval until treatment initiation was 5 days (range 0-21). Seven patients had greater than 8 days from oocyte collection to treatment. The reasons were variable: 3 had delays in diagnostic work-up; 1 deferred for a trip out of town; 2 were treated subsequently at an outside institution; and 1 had follicular lymphoma with no urgency to treat. The median number of days to complete stimulation protocol was 11 (range: 5-14). A median of 14 oocytes (range: 0-37) were retrieved per patient. In 2 women, no oocytes could be successfully retrieved. Five women achieved pregnancy following FP compared to 6 controls. Of these, 3 were spontaneous and 2 required reproductive assistance, one from frozen embryos and one from frozen oocytes. Of 3 women returning to use their frozen gametes, 2

were successful and 1 was unsuccessful. Ovarian stimulation did not result in any known complications.

In total, 15 patients relapsed after contacting a fertility specialist, including 7 patients in the control group and 8 in the FP arm. Patients who subsequently relapsed in both arms had high-risk features prior to fertility. There was no difference in 1-year and 5-year PFS between FP patients compared to controls (FP: 1-year PFS=81.6%, 5-year PFS = 71.4%; Controls: 1-year PFS =93.8%, 5-year PFS= 83.7%, p=0.17; Figure 1B).

Our study has some limitations, including those associated with a retrospective analysis. Only patients who contacted a fertility specialist were included and therefore our analysis is subject to selection bias. Our population was heterogeneous with a wide range of lymphoma subtypes, stages and treatments received. Additionally, the relatively small number of patients available for analysis limited our ability to match patients based on age, disease or prognosis, and thus there were some baseline differences between groups. However, our uniform method of referral is a major strength of our study. To our knowledge, our institution is one of the few major universities with a FPPN to centralize the collection of data on women undergoing FP, and provides a bridge between the fields of reproductive endocrinology and malignant haematology. Overall, this analysis provides important information regarding the expected delays and outcomes associated with FP. Our study demonstrates that if referral is prompt, FP contributes minimal delay to treatment and is not associated with adverse outcomes. Furthermore, it underscores the importance of access to specialists in FP and the role of the fertility navigator.

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Author Contributions:

Drs. Allen and Winter had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Winter, Allen, Pavone, Moravek.

Acquisition, analysis, or interpretation of data: Allen, Pavone, Smith, Rafael Confino, Winter.

Drafting of the manuscript: Winter, Allen.

Critical revision of the manuscript for important intellectual content: Allen, Winter, Pavone, Smith, Gordon, Kazer, Lawson.

Statistical analysis: Rademaker.

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Administrative, technical, or material support: Confino, Smith.

Study supervision: Winter, Pavone.

Conflict of Interest Disclosures:

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Table I. Patient Characteristics

PATIENT CHARACTERISTICS	**Patients undergoing Fertility Preservation n (%)***			**Controls n (%)***		
Median Age (Range), years	26 (20-35)			29 (17-45)		
Disease	**All**	**HL**	**NHL**	**All**	**HL**	**NHL**
Number of patients	33 (100)	21 (67)	12 (33)	50 (100)	31 (62)	19 (38)
Planned Treatment Setting						
Frontline	25 (76)	14 (67)	11 (92)	37 (74)	24 (77)	13 (68)
R/R	8 (24)	7 (33)	1 (8)	13 (26)	7 (23)	6 (32)
Treatment						
ABVD	12 (36)	12 (57)	---	23 (46)	23 (74)	---
R-CHOP-like †	8 (24)	---	8 (64)	6 (12)	---	6 (32)
escBEACOPP	2 (6)	2 (10)	---	1 (2)	1 (3)	---
DA-EPOCH-R	2 (6)	---	2 (18)	4 (8)	---	4 (21)
R-Hyper-CVAD	1 (3)	---	1 (9)	4 (8)	---	4 (21)
HDCT + SCT	7 (21)	7 (33)	---	10 (20)	7 (23)	3 (16)

Other‡	1 (3)		1 (9)	2 (4)		2 (11)
Ann Arbor Stage§						
I/II	28 (85)	17 (81)	11 (92)	32 (64)	23 (74)	9 (47)
III/IV	5 (15)	4 (19)	1 (8)	17 (34)	8 (26)	9 (47)
Bulky (>10cm)	9 (27)	6 (29)	3 (25)	10 (20)	4 (13)	6 (32)
ECOG PS¥						
0	24 (73)	17 (81)	7 (58)	38 (76)	22 (71)	16 (84)
≥ 1	5 (12)	2 (10)	3 (25)	9 (18)	6 (19)	3 (16)
LDH > ULN	9 (27)	4 (19)	5 (42)	17 (34)	7 (23)	10 (53)
ESR ≥ 50	9 (27)	9 (43)	---	11 (22)	11 (35)	---
B symptoms	10 (30)	8 (38)	2 (17)	19 (38)	13 (42)	6 (32)

HL: Hodgkin lymphoma; NHL: non-hodgkin lymphoma; R/R: relapsed/refractory; ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine; R-CHOP: rituximab, cyclophosphamide, Adriamycin, vincristine, prednisone; escBEACOPP: escalated bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; DA-EPOCH-R: dose adjusted etoposide prednisone, vincristine, cycophosphamide, Adriamycin, rituximab; R-HyperCVAD: Course A- cyclophosphamide, vincristine, Adriamycin, dexamethasone, cytarabine, mesna, methotrexate; Course B- methotrexate, leucovorin, cytarabine; HDCT + SCT: high dose chemotherapy plus stem cell transplant; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; ESR: erythrocyte sedimentation rate.

* % Percent of specified histology

† R-CHOP, BR (bendamustine rituximab), R-CVP (rituximab, cyclophosphamide, vincristine, prednisone)

‡ Involved field radiotherapy, radio-immunotherapy, romidepsin

§ One patient with NHL seen at relapse, initial staging information not available.

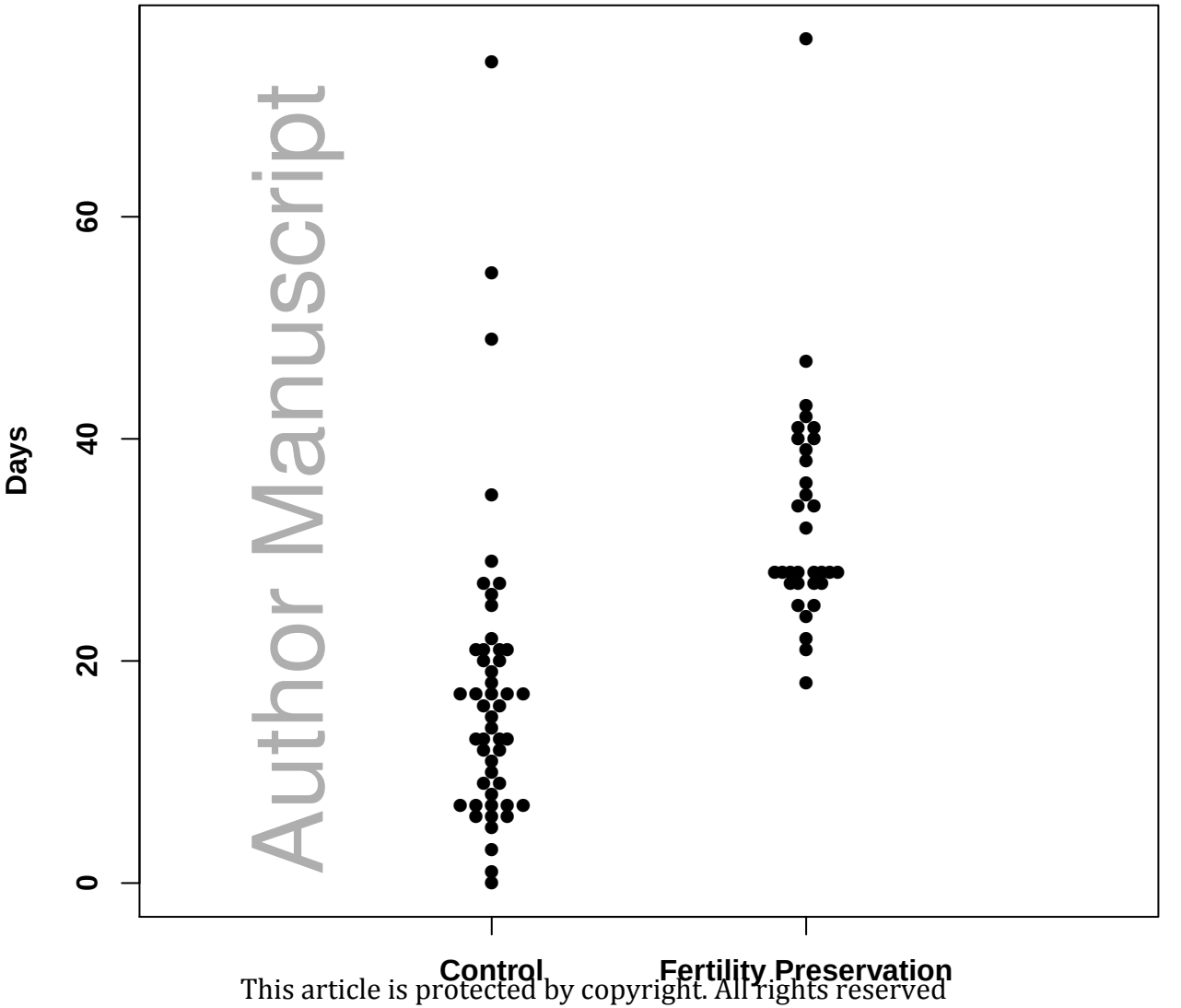
¥ ECOG PS missing for 3 HL patients in control group, and 2 HL and 2 NHL in the fertility preservation group

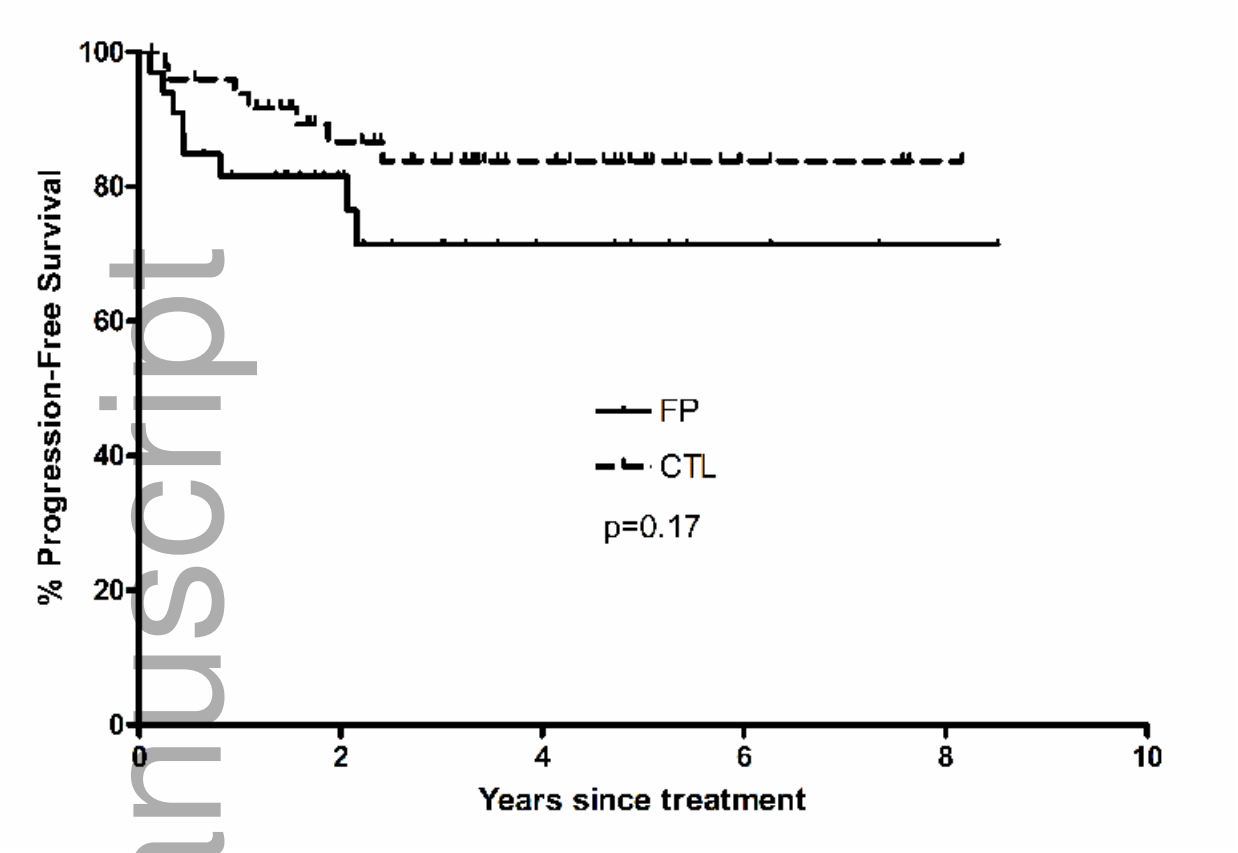
Figure legend

Figure 1

(A) Time to treatment among patients undergoing fertility preservation versus controls. Patients undergoing fertility preservation had longer time to treatment ($p < 0.001$). The median times to treatment were 28 and 15.5 days in patients undergoing and not undergoing fertility preservation respectively. (B) There was no difference in 5-year progression-free survival between patients undergoing or not undergoing fertility preservation ($p=0.11$).

CTL: control; FP: fertility preservation.





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