



Research Article

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Fertility-Sparing Management and Outcomes in Patients with Cervical Cancer in a Large Population-Based Health Care System

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Keywords

Objective: To evaluate patterns of fertility-sparing management for cervical cancer and factors associated with successful fertility-sparing management and pregnancy.

Methods: We conducted a retrospective cohort study of patient's ages 18-45 years with cervical cancer who were eligible for fertility-sparing management from January 1st, 2011 - December 31st, 2020. The primary outcome was fertility-sparing treatment. Secondary outcomes included subsequent need for definitive treatment, pregnancy, live birth, and demographic and clinical characteristics associated with these outcomes. Successful fertility-sparing management was defined as not requiring definitive management with hysterectomy or radiation over the follow-up period. Data were abstracted from the electronic medical record and chart reviewed. Multivariable logistic regression was performed to determine factors associated with initial and successful fertility-sparing treatment.

Results: Of the 128 patients that met eligibility criteria, the majority (52%) were non-Hispanic white, with a median age of 37 years at time of diagnosis, with median follow up of 72 months. Most patients had FIGO 2018 stage 1A1 cancer (43%), followed closely by stage 1B1 (40%). Fertility desires were documented for two-thirds of patients, with 41 (32%) having completed childbearing, and 40 (31%) desiring future fertility. Overall, 33 patients (26%) were treated with fertility sparing management. On multivariable analysis, younger age (OR 0.86, 95% CI 0.77-0.96), lower stage (OR 11.30, 95% CI 3.25-39.25), and nulliparity (OR 4.31, 95% CI 1.51-12.34) were associated with initial fertility-sparing management. Only six patients (18%) ultimately required definitive treatment over the study period. There were 13 pregnancies (39%) and 10 live births (30%) occurring a median of 19 months after cervical cancer diagnosis.

Conclusions: Documentation of fertility desires in a cohort of young patients with early-stage cervical cancer was poor. Few patients who elected fertility-sparing management required definitive treatment and a high proportion achieved pregnancy.

Keywords

Cervical cancer, Fertility-sparing treatment, Pregnancy

Introduction

Fortunately, due to widespread screening, many cervical cancers are detected at early stages when the goal of treatment can be curative [1]. As early detection and treatment have improved, survivorship issues have become more central to cancer care. Paramount among them for young cancer patients is fertility. Increasingly women are delaying childbearing, with first birth rates for women aged 40 to 44 years increasing fourfold between 1985 and 2012 [2]. According to recent data from Surveillance, Epidemiology and Ends Results (SEER) Program, 38% of cervical cancer is diagnosed in people <45 years old [3].

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According to the SEER Program, 41% of patients with cervical cancer have localized disease at diagnosis, thus having potential to be a candidate for fertility sparing surgery [2]. Overall, though, rates of pregnancy and utilization of fertility preservation services are low nationally among cancer patients [4]. Not much has been described regarding underlying reasons and barriers to accessing care [5].

The goal of this study was to evaluate patterns of fertility-sparing management for cervical cancer and factors associated with successful fertility-sparing management and pregnancy. The primary outcome was fertility-sparing treatment. Secondary outcomes included subsequent definitive treatment, pregnancy, live birth, and demographic and clinical characteristics associated with these outcomes.

Methods

We conducted a retrospective cohort study of patient's ages 18-45 years with cervical cancer who were eligible for fertility-sparing management from January 1st, 2011, through December 31st, 2020 in Kaiser Permanente Northern California (KP NCAL). KP NCAL serves ~4.6 million people and the demographic characteristics of these patients has been shown to be similar to the demographics of the general population in the region [6].

Cancer diagnosis was identified using the cancer registry and the diagnosis confirmed via chart review of the electronic medical record. Eligibility for fertility-sparing management was defined as squamous, adenocarcinoma or adenosquamous histology, tumors < 4 cm confined to the cervix, and a PET scan negative for extra-cervical disease. The primary outcome was fertility-sparing treatment. Secondary outcomes included subsequent definitive treatment, pregnancy, live birth and demographic and clinical characteristics associated with these outcomes. Subsequent definitive treatment was defined as requiring management with hysterectomy or radiation over the follow-up period. Data were abstracted from the electronic medical record and chart-reviewed. Wilcoxon-Mann-Whitney tests were used for continuous variables that did not meet normality conditions, and Chi-Square and Fisher's exact tests performed on categorical variables depending on cell counts. Multivariable logistic regression was performed to determine factors associated with initial fertility-sparing management and need for definitive treatment. Both multivariable models adjust for age, race and ethnicity, and parity.

Results

A total of 128 patients met eligibility criteria with a median age of 37 years. The majority were white (52%), and 33% were nulliparous (Table 1). There was no documentation of fertility desires for 36% of patients. Of those where documentation occurred, 50% had completed childbearing and 50% desired fertility. A total of 26% (33/128) patients had fertility-sparing management and were followed for a median of 71 months.

On bivariate analysis, those who had initial fertility-sparing management were more likely to be younger in age (median 34 years vs. 37 years, $p < 0.001$), have lower stage of disease (76% vs. 32% were stage 1A1, $p < 0.001$), and be

nulliparous (58% vs. 24%, $p < 0.001$) compared to those who did not have fertility-sparing management. On multivariable analysis, younger age (OR 0.86, 95% CI 0.77-0.96), lower stage (OR 11.30, 95% CI 3.25-39.25), and nulliparity (OR 4.31, 95% CI 1.51-12.34) remained associated with initial fertility-sparing management (Table 2).

Most patients were treated with a LEEP or cone (91%), with few having a radical trachelectomy (9%). Only six patients (6/33, 18%) required subsequent definitive treatment during the study period and all of these patients had stage 1A1 cancer (Table 3). Two of these patients had children and completed childbearing after fertility sparing surgery. They then proceeded with a completion hysterectomy during the study period. The other four patients ultimately decided that they did not want children so they proceeded with definitive treatment. None of these patients had recurrence of their cancer as the reason for definitive treatment. There were no factors on bivariate or multivariate analysis that were associated with needing definitive treatment (Table 4). Thirteen pregnancies (39%) and 10 live births (30%) occurred a median of 19 months after cervical cancer diagnosis. The three pregnancies that did not end in a live birth ended in a first trimester miscarriage or abortion for undesired pregnancies. Of note, one of those patients did go on to have a term (≥ 37 week gestation) live birth down the line. Of the ten live births, two patients delivered at < 34 week gestation (though the indication for one delivery was abruption thus not a complication in relation to the prior cone), three patients delivered between 34w0d and 36w6d, and five patients delivered at ≥ 37 week gestation. The most common reason for preterm delivery was Preterm Prelabor Rupture of Membranes (PPROM).

Discussion

Many studies have documented the oncologic safety of fertility-sparing surgeries for cervical cancer, with a range of pregnancy outcomes depending on the radicality of surgery [7-10]. Despite these data, many patients still do not have discussions regarding fertility sparing management options, consistent with our data demonstrating lack of documentation of fertility desires for 36% of patients and initial pursuit of fertility-sparing treatment in only 26% of patients.

While lack of documentation does not correlate directly with lack of provider discussion or offering, it does imply that there could be a gap in the type of patients offered fertility-sparing procedures for cervical cancer. When comparing those who underwent initial fertility-sparing surgery vs. definitive treatment, younger age, nulliparity, and lower stage were associated with those undergoing fertility-sparing surgery. However, none of these factors were then predictive of needing subsequent definitive management or of attaining pregnancy in the future.

Interestingly, when looking at those who required subsequent definitive treatment during the study period, all cases were stage 1A1 cancers.

Providers may be more likely to discuss in more depth the option of fertility sparing surgery with those that are

Table 1: Overall cohort (N = 128), demographics and clinical characteristics of patients with fertility sparing versus definitive treatment.

	Overall N = 128	Fertility Sparing Treatment n = 33 (25.8%)	Definitive treatment n = 95 (74.2%)	P value
Age at diagnosis (yrs), Median (IQR)	36.5 (34.0-39.8)	34.4 (30.2-36.5)	37.2 (35.0-40.4)	< 0.001
Stage, N (%) IA1 IA2 IB1 IB2	55 (43.0) 16 (12.5) 51 (39.8) 6 (4.7)	25 (75.8) < 5 < 5 < 5	30 (31.6) 12 (12.6) 47 (49.5) 6 (6.3)	< 0.001†
Histology, N (%) Adenocarcinoma Squamous	65 (50.8) 63 (49.2)	14 (42.4) 19 (57.6)	51 (53.7) 44 (46.3)	0.27*
Race/ethnicity, N (%) Asian Hispanic White Non-Hispanic Black Non-Hispanic White Other/Unknown	26 (20.3) 15 (11.7) 7 (5.5) 67 (52.3) 13 (10.2)	7 (21.2) 5 (15.2) < 5 19 (57.6) < 5	19 (20.0) 10 (10.5) 7 (7.4) 48 (50.5) 11 (11.6)	0.48†
BMI (kg/m ²), Median (IQR)	27.5 (22.6-31.6)	26.4 (21.8-29.0)	27.8 (23.0-31.8)	0.13
Neighborhood Deprivation Index, N (%) Q1 (Least Deprived) Q2 Q3 Q4 (Most Deprived)	19 (14.8) 48 (37.5) 35 (27.3) 26 (20.3)	5 (15.2) 16 (48.5) < 5 8 (24.2)	14 (14.7) 32 (33.7) 31 (32.6) 18 (19.0)	0.12†
Parity, N (%) Nulliparous Parous	42 (32.8) 86 (67.2)	19 (57.6) 14 (42.4)	23 (24.2) 72 (75.8)	<0.001*
Years of Diagnosis, N (%) 2011-2013 2014-2017 2018-2020	29 (22.7) 56 (43.8) 43 (33.6)	6 (18.2) 13 (39.4) 14 (42.4)	23 (24.1) 43 (45.3) 29 (30.5)	0.43

Wilcoxon performed on continuous variables that are not normally distributed. Some cells may have exact frequencies and percentages suppressed due to small cell size.

*: Chi-Square performed on categorical variables

†: Fisher's Exact performed on categorical variables with cell counts less than 5

Table 2. Overall cohort (N = 128), adjusted odds of initial fertility-sparing treatment.

	Adjusted OR	95% CI	P-Value
Age (years)	0.86	0.77-0.96	0.006
Race and Ethnicity			
Asian	0.80	0.23-2.77	0.73
Hispanic White	1.58	0.35-7.06	0.55
Non-Hispanic White	Referent	Referent	Referent
Other/Unknown	0.50	0.09-2.81	0.43
Stage			
1A	11.30	3.25-39.25	< 0.001
1B	Referent	Referent	Referent
Parity			
Nulliparous	4.31	1.51-12.34	0.007
Parous	Referent	Referent	Referent

younger, haven't had a child before, or have a lower cancer stage because there may be implicit bias that these are characteristics of someone who may be more motivated to have children in the future. The risks and pregnancy complications associated with radical trachelectomy may be discouraging to both providers and patients.

The landscape of fertility-sparing management has changed in recent years with the publication of the ConCerv trial, demonstrating a low rate of recurrence of 3.5% after cone in selective low risk patients with stage IA2-IB1 cervical cancer [11]. Complications of radical trachelectomy include infertility, increased second trimester loss, preterm delivery

Table 3: Fertility-sparing treatment cohort (N = 33), demographics and clinical characteristics of patients with continued fertility sparing treatment versus subsequent definitive treatment.

	Overall N = 33	Fertility Sparing Treatment Continued n = 27 (81.8%)	Subsequent Definitive Treatment n = 6 (18.2%)	P value
Age at diagnosis (yrs), Median (IQR)	34.4 (30.2-36.5)	34.4 (30.3-36.5)	32.3 (29.2-38.2)	0.76
Stage, N (%) IA1 IA2 IB1	25 (75.8) < 5 < 5	19 (70.4) < 5 < 5	6 (100.0) < 5 < 5	0.43†
Histology, N (%) Adenocarcinoma Squamous	14 (42.4) 19 (57.6)	10 (37.0) 17 (63.0)	< 5 < 5	0.36†
Race/ethnicity, N (%) Asian Hispanic White Non-Hispanic White Other/Unknown	7 (21.2) 5 (15.2) 19 (57.6) < 5	6 (22.2) < 5 15 (55.6) < 5	< 5 < 5 < 5 < 5	> 0.99†
BMI (kg/m ²), Median (IQR)	26.4 (21.8-29.0)	27.6 (22.8-32.3)	21.4 (18.1-26.4)	0.05
Neighborhood Deprivation Index, N (%) Q1 (Least Deprived) Q2 Q3 Q4 (Most Deprived)	5 (15.2) 16 (48.5) < 5 8 (24.2)	< 5 13 (48.2) < 5 7 (25.9)	< 5 < 5 < 5 < 5	> 0.99†
Parity, N (%) Nulliparous Parous	19 (57.6) 14 (42.4)	16 (59.3) 11 (40.7)	< 5 < 5	>0.99†

Wilcoxon performed on continuous variables that are not normally distributed. Some cells may have exact frequencies and percentages suppressed due to small cell size.

†: Fisher's Exact performed on categorical variables with cell counts less than 5.

Table 4. Fertility-sparing treatment cohort (N = 33), adjusted odds of continued successful fertility-sparing treatment.

	Adjusted OR	95% CI	P-Value
Age (years)	1.02	0.84-1.25	0.84
Race and Ethnicity			
Asian	1.55	0.14-17.57	0.73
Non-Hispanic White	Referent	Referent	Referent
Other/Unknown	1.52	0.13-17.14	0.74
Parity			
Nulliparous	1.42	0.23-8.68	0.71
Parous	Referent	Referent	Referent

and need for cesarean section [12-14]. Rates of fertility have been demonstrated to be higher in patients undergoing cone or simple trachelectomy vs. radical trachelectomy (63% vs. 26%) [15]. This is consistent with the pregnancy rate of 39% in our study as the majority of patients had undergone a cone or LEEP. Also, half of patients with a live birth went on to have a full-term delivery. Four out five patients had a preterm delivery after PPROM, a known possible pregnancy complication after a cone. Only one of these patients though were extremely premature, born at < 34 weeks which overall means that these patients had a good pregnancy outcome. There were no postnatal mortalities among the live births.

Limitations of our study include the small sample size of those undergoing fertility-sparing management and an even smaller size of those achieving pregnancy, making it difficult to be able to detect differences between groups. Also, the study was conducted over a long period of time, with changes in the staging system for cervical cancer and potential shifts in

practice patterns. Strengths include the robust long standing medical record and patient retention over time. Our study builds on prior data that have assessed pregnancy and cancer outcomes related to fertility-sparing management of cervical and adds data on whether fertility desires are discussed and the patient characteristics associated with this treatment strategy.

Conclusion

Thirty-six percent of patients eligible for fertility-sparing treatment of cervical cancer lacked documentation of fertility desires and 26% underwent fertility-sparing treatment. While younger age, lower stage, and nulliparity were associated with undergoing fertility-sparing management, there were no factors predictive of requiring subsequent definitive treatment. Future studies need to address the barriers to fertility-sparing management and understanding how broadening the option of more conservative surgery will change this landscape.

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