GYNECOLOGY

Survival implications of time to surgical treatment of endometrial cancers

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BACKGROUND: Optimal care for women with endometrial cancers often involves transfer of care from diagnosing physicians (eg, obstetrician-gynecologists) to treating physicians (eg, gynecologic oncologists.) It is critical to determine the effect of time to treatment on cancer outcomes to set best practices guidelines for referral processes.

OBJECTIVE: We sought to determine the impact of time from diagnosis of endometrial cancer to surgical treatment on mortality and to characterize those patients who may be at highest risk for worsened survival related to surgical timing.

STUDY DESIGN: The National Cancer Database was queried for incident endometrial cancers in adults from 2003 through 2012. Cancers were classified as low risk (grade 1 or 2 endometrioid histologies) or high risk (nonendometrioid and grade 3 endometrioid histologies) and analyzed separately. Demographic, clinicopathologic, and health system factors were collected. Unadjusted and adjusted hazard ratios for mortality were calculated by interval between diagnosis and surgery. Linear regression of patient and health care system characteristics was performed on diagnosis-to-surgery interval.

RESULTS: For low-risk cancers (N = 140,078), surgery in the first and second weeks after diagnosis was independently associated with mortality risk (hazard ratio, 1.4; 95% confidence interval, 1.3—1.5; and hazard ratio, 1.1; 95% confidence interval, 1.0—1.2, respectively). The 30-day postoperative mortality was significantly higher among patients undergoing surgery in the first or second week postdiagnosis, compared to patients treated in the third or fourth week postdiagnosis (0.7% vs 0.4%; $P < .001$). Mortality risk was also significantly higher than baseline when time between diagnosis and surgery was >8 weeks. Independent associations with added time to surgery of at least 1 week were seen with black race (1.1 weeks; 95% confidence interval, 0.9—1.4), uninsurance (1.3 weeks; 95% confidence interval, 1.1—1.5), Medicaid insurance (1.7 weeks; 95% confidence interval, 1.5—1.9), and Charlson-Deyo comorbidity score >1 (1.0 weeks; 95% confidence interval, 0.8—1.2). For high-risk cancers (N = 68,360), surgery in the first and second weeks after diagnosis was independently associated with mortality risk (hazard ratio, 1.5; 95% confidence interval, 1.3—1.6; and hazard ratio, 1.2; 95% confidence interval, 1.1—1.2, respectively). The 30-day postoperative mortality was significantly higher among patients undergoing surgery in the first or second week postdiagnosis, compared to patients treated in the third or fourth week postdiagnosis (2.5% vs 1.0%; $P < .001$). Surgery after the third week postdiagnosis was not associated with a statistically significant increase in the adjusted risk of mortality. Independent associations with added time to surgery of at least 1 week were seen with uninsurance (1.4 weeks; 95% confidence interval, 0.9—1.9) and Medicaid insurance (1.4 weeks; 95% confidence interval, 1.1—1.7).

CONCLUSION: Surgery in the first 2 weeks after diagnosis of endometrial cancer was associated with worsened survival associated with elevated perioperative mortality and treatment in low-volume hospitals. Delay in surgical treatment was a risk factor for mortality in low-risk cancers only and was likely associated with poor access to specialty care. We suggest that the target interval between diagnosis and treatment of endometrial cancers be ≤8 weeks; however, referral to an experienced surgeon and adequate preoperative optimization should be prioritized over expedited surgery.

Key words: cancer care delivery research, endometrial cancer, health policy

Introduction

Delay between diagnosis and surgical treatment of endometrial cancer may result in worsened overall survival, potentially as a consequence of disease progression or difficulty accessing care.[1] A relationship between surgical delay and survival disadvantage has been demonstrated in breast,[2,3] rectal,[4] and bladder[5] cancers; this relationship does not clearly exist for esophageal,[6] gastric,[4] renal cell,[7] or cervical[8] cancers. For endometrial cancer, findings to date have been mixed. Early work suggested that time to definitive treatment did not correlate with disease stage[9] or survival[10,11]; however, these studies were limited by small sample sizes, mixed tumor histologies, and a focus on time from onset of abnormal uterine bleeding rather than from definite diagnosis of malignancy.

Recently, 3 studies readdressed this issue with larger sample populations. A 2013 report of >9000 patients in Canada associated longer wait times with lower overall survival at 5 years.[12] Although this study was criticized for including high-risk histologies, a subsequent subset analysis of >3000 patients included only endometrioid cancers undergoing simple hysterectomy and excluded patients receiving chemotherapy or radiation. A survival disadvantage was confirmed for women undergoing surgery <2 weeks after diagnosis or waiting >12 weeks for hysterectomy.[13] In contrast, a study of 435 patients in California with grade 1-2 endometrioid-type endometrial cancer did not show an impact of wait time on overall survival, but was criticized for being

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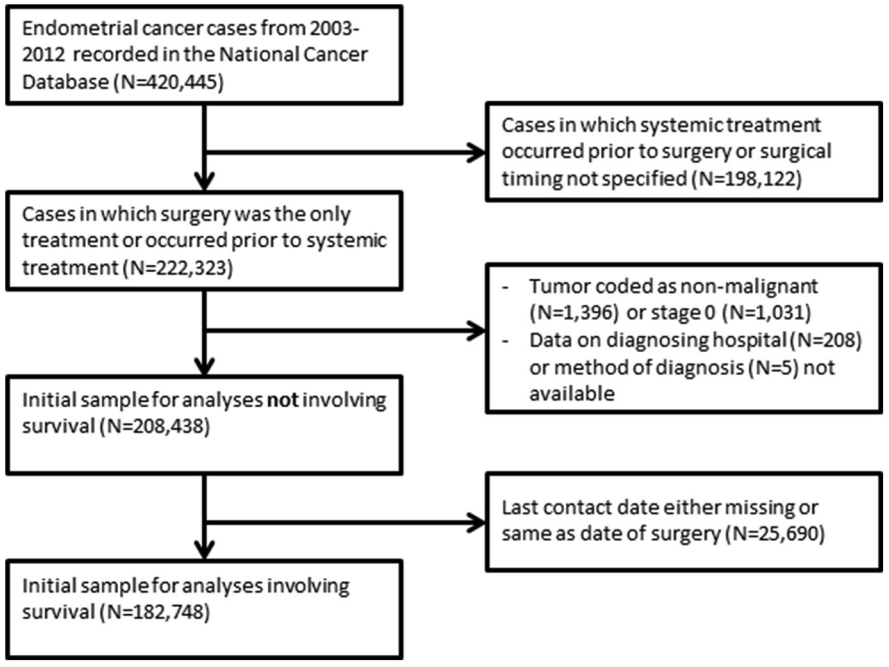
underpowered to do so adequately.[14,15] A third study using the National Cancer Database (NCDB) associated a diagnosis-to-surgery interval of ≥6 weeks with worsened outcomes; however this study analyzed a single time point and combined high- and low-risk histologies.[16]

Based on available data, we hypothesized that delayed or early surgical intervention may be associated with poor outcomes. Furthermore, the relationship between surgical interval and outcomes is likely to be different for low- and high-risk cancers. We therefore analyzed a large patient sample drawn from the NCDB to determine whether and when time from diagnosis of endometrial cancer to surgical treatment affects mortality and to characterize those patients who may be at highest risk for worsened survival related to timing of surgery.

Materials and Methods

The NCDB, maintained by the American College of Surgeons and the American Cancer Society, captures approximately 70% of cancer cases in the United States from 1500 Commission on Cancer (CoC)-accredited institutions nationwide.[17] The NCDB was queried for cases of endometrial cancer from 2003 through 2012. Cases included in the uterine corpus database with epithelial histologies were considered to be of endometrial origin. Low-risk (grade 1 and grade 2 endometrioid histologies) and high-risk (grade 3 endometrioid and all other epithelial histologies) tumors were analyzed separately. Uterine carcinosarcoma was included in the high-risk epithelial group, as this tumor likely originates from a dedifferentiated carcinoma.[18] There were 420,445 patients in the initial sample. We limited our analysis to cases for which there was evidence that surgery was the only modality pursued, or occurred prior to any hormonal therapy, radiation, or chemotherapy. We excluded those for whom time between diagnosis and surgery was unavailable or diagnosis was made at the time of surgery. In all, 222,323 cases met initial inclusion criteria. We then excluded cases for which the tumor was coded as nonmalignant (N = 1396) or stage 0 (N = 1031), or for which diagnostic confirmation (N = 5) or hospital identifier (N = 208) were invalid. For analyses not including survival time, the sample consisted of 208,438 patient-level observations. For analyses involving survival, we further excluded cases for which the last contact date was missing or equaled the treatment date, leaving 182,748 patients (Figure 1).

FIGURE 1
Study population flow diagram



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Variables

Covariates included patient, facility, and geographic area characteristics. Patient characteristics included age (<45, 45–54, 55–64, 65–74, 75–84, ≥85 years), race (white, black, American Indian, Asian/Pacific Islander, other, and unknown), ethnicity (Hispanic vs not), primary payer (not insured, private, Medicaid, Medicare, other government), stage (1, 2, 3, or 4 based on the higher of pathologic and clinical stages; or unknown), grade (1, 2, 3, or unknown), receipt of systemic (chemotherapy or hormonal therapy) or radiation therapy within 60 days after surgery, treatment and/or diagnosis in the reporting facility, Charlson-Deyo comorbidity score (0, 1, 2+, excluding cancer), performance of lymphadenectomy, and year of diagnosis. Facility characteristics included type (community cancer program, comprehensive community cancer program, academic/research program) and quartile of annual endometrial cancer cases (calculated prior to sample exclusions). Geographic area characteristics included facility's census region, quartile of straight-line distance from patient's residential ZIP code to facility, metropolitan location of patient's ZIP code (yes/no), and quartile of patient's ZIP code–level median household income (based on 2000 US Census). Lymphadenectomy was collected as a proxy for gynecologic oncologist involvement in surgical treatment and was not expected to be independently associated with survival in these cases, although controversy exists on this point.[19,20] The location of lymph nodes removed (eg, pelvic vs paraaortic) was not

TABLE 1
Descriptive characteristics of included cases

	Overall (N = 208,438)	Low risk (N = 140,078)	High risk (N = 68,360)	*P* value
Age at diagnosis, y				<.001
Mean (SD)	62.86 (11.63)	61.82 (11.59)	64.97 (11.44)	
Age category, y, N (%)				<.001
<45	11,926 (5.7%)	9138 (6.5%)	2788 (4.1%)	
45–54	34,529 (17%)	25,891 (18%)	8638 (13%)	
55–64	72,751 (35%)	50,688 (36%)	22,063 (32%)	
65–74	53,645 (26%)	33,463 (24%)	20,182 (30%)	
75–84	28,857 (14%)	17,018 (12%)	11,839 (17%)	
≥85	6730 (3.2%)	3880 (2.8%)	2850 (4.2%)	
Patient race, N (%)				<.001
White	179,598 (86%)	123,913 (88%)	55,685 (81%)	
Black	18,880 (9.1%)	9332 (6.7%)	9548 (14%)	
American Indian	584 (0.3%)	414 (0.3%)	170 (0.2%)	
Asian/Pacific Islander	4972 (2.4%)	3369 (2.4%)	1603 (2.3%)	
Other	1511 (0.7%)	1024 (0.7%)	487 (0.7%)	
Unknown	2893 (1.4%)	2026 (1.4%)	867 (1.3%)	
Hispanic ethnicity, N (%)				.032
No	181,666 (87%)	122,039 (87%)	59,627 (87%)	
Yes	10,023 (4.8%)	6659 (4.8%)	3364 (4.9%)	
Unknown	16,749 (8.0%)	11,380 (8.1%)	5369 (7.9%)	
Insurance coverage, N (%)				<.001
Not insured	7235 (3.5%)	4921 (3.5%)	2314 (3.4%)	
Private insurance	102,789 (49%)	73,658 (53%)	29,131 (43%)	
Medicaid	9095 (4.4%)	6020 (4.3%)	3075 (4.5%)	
Medicare	83,771 (40%)	51,913 (37%)	31,858 (47%)	
Other government	1783 (0.9%)	1258 (0.9%)	525 (0.8%)	
Unknown insurance	3765 (1.8%)	2308 (1.6%)	1457 (2.1%)	
Tumor stage, N (%)				<.001
1	145,628 (70%)	107,468 (77%)	38,160 (56%)	
2	15,196 (7.3%)	9608 (6.9%)	5588 (8.2%)	
3	26,777 (13%)	13,623 (9.7%)	13,154 (19%)	
4	8953 (4.3%)	2685 (1.9%)	6268 (9.2%)	
Unknown	11,884 (5.7%)	6694 (4.8%)	5190 (7.6%)	
Charlson-Deyo score,[a] N (%)				.40
0	155,646 (75%)	104,509 (75%)	51,137 (75%)	
1	43,068 (21%)	29,057 (21%)	14,011 (20%)	
2+	9724 (4.7%)	6512 (4.6%)	3212 (4.7%)	

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documented in the NCDB. The interval from diagnosis to surgery was coded as the week postdiagnosis during which surgery occurred; for example, surgery on days 1-7 postdiagnosis was coded as occurring during week 1, and on days 8-14 as week 2. The date of diagnosis was originally recorded as either the date a confirmatory test (eg, biopsy) was

TABLE 1
Descriptive characteristics of included cases *(continued)*

	Overall (N = 208,438)	Low risk (N = 140,078)	High risk (N = 68,360)	*P* value
Facility type, N (%)				<.001
Community cancer program	12,048 (5.8%)	7860 (5.6%)	4188 (6.1%)	
Comprehensive community cancer program	107,244 (51%)	72,399 (52%)	34,845 (51%)	
Academic/research program	88,747 (43%)	59,524 (42%)	29,223 (43%)	
Other	399 (0.2%)	295 (0.2%)	104 (0.2%)	
Annual hospital volume quartile, N (%)				<.001
1 Lowest	40,735 (20%)	26,767 (19%)	13,968 (20%)	
2	44,106 (21%)	29,409 (21%)	14,697 (21%)	
3	56,861 (27%)	38,434 (27%)	18,427 (27%)	
4 Highest	66,736 (32%)	45,468 (32%)	21,268 (31%)	
Distance traveled to recording institution, miles[b]				
Mean (SD)	30.52 (89.29)	30.10 (86.67)	31.40 (94.43)	.002
Median (IQR)	11.70 (25.40)	11.80 (25.10)	11.40 (25.80)	<.001
Metro or adjacent to metro, N (%)[b]				<.001
No	22,094 (11%)	14,583 (10%)	7511 (11%)	
Yes	186,344 (89%)	125,495 (90%)	60,849 (89%)	
Median income quartile, N (%)[b]				<.001
1 Lowest	30,131 (15%)	18,953 (14%)	11,178 (17%)	
2	42,060 (21%)	28,107 (21%)	13,953 (21%)	
3	56,284 (28%)	38,207 (28%)	18,077 (27%)	
4 Highest	74,498 (37%)	51,208 (38%)	23,290 (35%)	
Household education, quartile, N (%)[b]				<.001
1 Lowest	31,766 (16%)	20,125 (15%)	11,641 (18%)	
2	49,073 (24%)	32,453 (24%)	16,620 (25%)	
3	60,232 (30%)	41,311 (30%)	18,921 (28%)	
4 Highest	61,932 (31%)	42,603 (31%)	19,329 (29%)	
Lymphadenectomy, N (%)				<.001
No	54,719 (26%)	38,477 (27%)	16,242 (24%)	
Yes	153,719 (74%)	101,601 (73%)	52,118 (76%)	
Adjuvant systemic therapy, N (%)				<.001
No	182,641 (88%)	130,821 (93%)	51,820 (76%)	
Yes	25,797 (12%)	9257 (6.6%)	16,540 (24%)	
Adjuvant radiation therapy, N (%)				<.001
No	178,496 (86%)	120,644 (86%)	57,852 (85%)	
Yes	29,942 (14%)	19,434 (14%)	10,508 (15%)	

IQR, interquartile range.

[a] Excludes cancer as comorbidity; [b] Determined by ZIP code of patient's residence.

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performed or the date that a clinical diagnosis was documented, whichever came first.

Statistical analysis

The unit of analysis was the individual patient. Covariate and outcome values were compared across the 2 tumor categories (high or low risk) using χ^2 tests for categorical variables and

TABLE 2
Five-year crude survival by interval between diagnosis and surgery

Low risk			High risk		
Time to surgery, wk[a]	Patients	5-y Survival (95% CI)	Time to surgery, wk[a]	Patients	5-y Survival (95% CI)
1	2057	73.0% (70.6–75.3%)	1	1551	46.5% (43.5–49.5%)
2	5665	85.0% (83.8–86.2%)	2	3398	60.7% (58.8–62.6%)
3	10,409	87.4% (86.5–88.2%)	3	5153	66.9% (65.3–68.4%)
4	12,593	86.2% (85.4–86.9%)	4	5786	67.6% (66.0–69.1%)
5	11,736	86.5% (85.7–87.3%)	5	4994	67.1% (65.4–68.7%)
6	9350	85.4% (84.4–86.4%)	6	3975	66.7% (64.8–68.6%)
7	6559	85.8% (84.7–86.9%)	7	2675	65.0% (62.5–67.3%)
8	4655	84.5% (83.1–85.9%)	8	1905	66.3% (63.5–68.9%)
9	3045	83.0% (81.0–84.8%)	9	1224	62.5% (58.8–66.0%)
10	2061	84.7% (82.4–86.8%)	10	817	64.5% (60.0–68.7%)
11	1367	82.1% (79.2–84.7%)	11	638	66.0% (61.1–70.5%)
12	972	79.7% (75.9–82.9%)	12	398	60.5% (53.8–66.5%)
13	673	81.9% (77.5–85.5%)	13	296	55.9% (47.9–63.2%)
14	540	81.0% (76.0–85.1%)	14	243	57.8% (47.8–66.5%)
15	402	78.6% (72.5–83.5%)	15	197	57.7% (47.4–66.7%)
16	326	71.1% (63.4–77.4%)	16	153	49.6% (37.8–60.3%)
17	250	77.2% (69.9–83.0%)	17	119	57.5% (44.0–68.8%)
18	201	72.9% (63.5–80.2%)	18	113	51.0% (35.7–64.3%)
19	174	69.7% (58.2–78.6%)	19	71	47.6% (30.4–63.0%)
20	141	77.0% (63.5–86.0%)	20	72	61.2% (44.7–74.1%)
>20	898	74.5% (70.3–78.3%)	>20	462	55.7% (49.3–61.7%)

Five-year survival and 95% CI generated via Kaplan-Meier method.

CI, confidence interval.

[a] Surgery in wk 1 implies interval between diagnosis and surgery of 1–7 d; in wk 2, 8–14 d, etc.

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nonparametric equality of medians tests for continuous variables. To assess the association between surgical delay and postsurgical time to death or censoring separately for high- and low-risk cancers, the Kaplan-Meier method was used to calculate crude 5-year survival for each week of delay and Cox proportional hazard models were used to estimate crude and adjusted hazard ratios (HR). Linear regression was used to identify independent predictors of time between cancer diagnosis and definitive surgery. To account for the possible role of outliers in the distribution of time from diagnosis to surgery, we also estimated quasimaximum likelihood Poisson models. We report only the linear regression results because the Poisson results are qualitatively identical. In all models, SE were adjusted to account for the clustering of patients within centers. All analyses used software (Stata, Version 14.2; Stata Corp, College Station, TX). Two-tailed $P < .05$ was considered statistically significant. As the NCDB is a deidentified database, this study was exempted from institutional review board review.

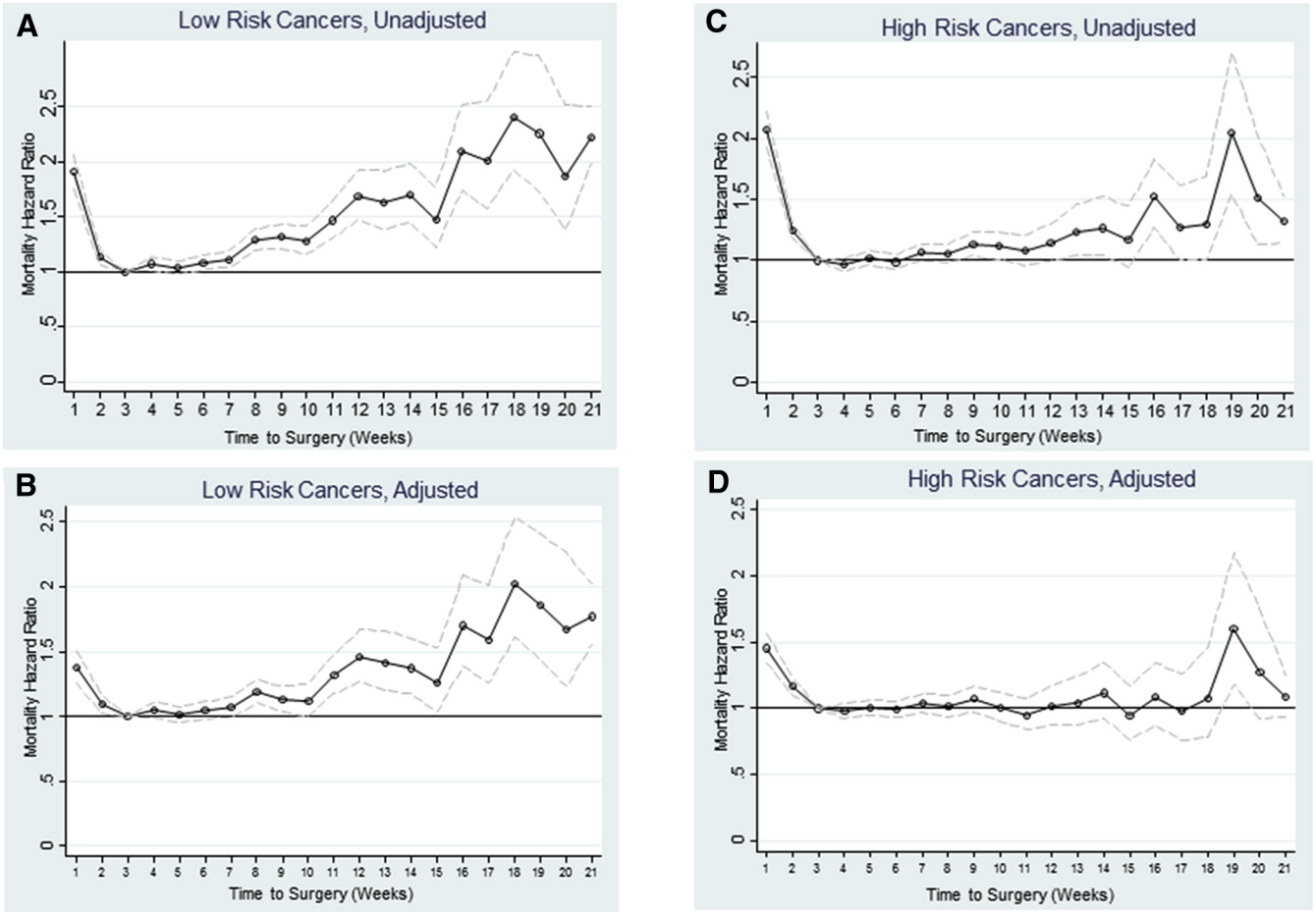
Results

In all, 140,078 low-risk and 68,360 high-risk endometrial cancers were included in the descriptive analysis (Table 1). As expected, low-risk cancers occurred comparatively more frequently in younger women and less frequently in black women.[21] Women with low-risk cancers were more likely to be diagnosed with stage I or II disease than women with high-risk cancers. Women with high-risk cancers were more likely to have Medicare insurance and less likely to be privately insured compared to women with low-risk cancers. Hispanic ethnicity, comorbidity score, and annual hospital case volume were not significantly different between low- and high-risk cancer cases.

Survival analyses for low-risk cancers

For patients with low-risk cancers, median survival time was 47.6 months (interquartile range 25.8-73.6), and

FIGURE 2
Unadjusted and adjusted hazard ratios for mortality, by histology



Dashed lines indicated 95% confidence interval. Hazard ratios adjusted for patient's age, race/ethnicity, insurance status, stage, Charlson-Deyo score, distance traveled to care; income/education quartile and rurality of patient's home ZIP code; reporting hospital type/location/case volume, year of diagnosis, receipt of lymphadenectomy and adjuvant treatment, location of diagnosis and treatment.

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14.3% of cases were censored. Five-year crude survival was highest when surgery was performed in the third week after diagnosis, with a linear decline in survival thereafter (Table 2; Supplemental Figure 1). Relative to patients who underwent surgery in the third week after diagnosis, the 11.7% of patients undergoing surgery during the first and second weeks after diagnosis had a higher risk of death (HR, 1.9; 95% confidence interval [CI], 1.7−2.1; and HR, 1.1; 95% CI, 1.1−1.2, respectively). When adjusted for age, stage, race, year of diagnosis, and additional clinical and health system characteristics, surgery in the first and second weeks after diagnosis remained independently associated with death (HR, 1.4; 95% CI, 1.3−1.5; and HR, 1.1; 95% CI, 1.0−1.2, respectively). Mortality risk was significantly higher than baseline when surgery was performed in the eighth week postdiagnosis and worsened as time to surgery increased (Figure 2, A and B).

Survival analyses for high-risk cancers

For patients with high-risk cancers, median survival time was 38.6 months (interquartile range 18.9-67.1), and 14.3% of cases were censored. Five-year crude survival was highest when surgery was performed in the third week after diagnosis, with a linear decline in survival thereafter (Table 2; Supplemental Figure 1). Relative to patients who underwent surgery in the third week after diagnosis, the 15.9% of patients undergoing surgery during the first and second weeks after diagnosis had HR for death of 2.1 (95% CI, 1.9−2.2) and 1.3 (95% CI, 1.2−1.3), respectively. When adjusted for age, stage, race, year of diagnosis, and additional clinical and health system characteristics, surgery in the first and second weeks after diagnosis remained independently associated with death (HR, 1.5; 95% CI, 1.3−1.6; and HR, 1.2; 95% CI, 1.1−1.2, respectively). Apart from an isolated increase seen in the 19th week

postdiagnosis, surgery after the third week postdiagnosis was not associated with a statistically significant increase in the adjusted risk of mortality (Figure 2, C and D).

Characteristics of recipients of early surgery

Given the finding of increased mortality risk accompanying surgery in the first 2 weeks after diagnosis, we compared clinical and process-based factors for patients undergoing surgery in this time period with patients undergoing surgery 3 and 4 weeks postdiagnosis. Patients with low-risk cancers who underwent surgery in the first week after diagnosis were more likely to be at the extremes of age (<45 or >85 years), black, uninsured or with Medicaid insurance, have advanced stage disease, and undergo both diagnosis and treatment at the reporting CoC hospital. These patients were less likely to be treated at high-volume hospitals or undergo lymphadenectomy (Supplemental Table 1A). Patients with high-risk cancers who underwent surgery in the first week after diagnosis were more likely to be elderly (age >85 years), black, uninsured or with Medicaid insurance, have advanced stage disease, and undergo both diagnosis and treatment at the reporting CoC hospital. These patients were likewise less likely to be treated at high-volume hospitals or undergo lymphadenectomy (Supplemental Table 1B). Additionally, 30-day postoperative mortality was significantly higher among patients treated in the first or second week postdiagnosis, compared to patients treated in the third or fourth week postdiagnosis. For low-risk cancers, this difference was 0.7% vs 0.4% ($P < .001$); for high-risk cancers the difference was 2.5% vs 1.0% ($P < .001$).

Factors associated with surgical delay

Given significant differences in the characteristics and outcomes of patients undergoing surgery <2 weeks after diagnosis, this group was excluded from the linear regression of the diagnosis-to-surgery interval on clinical and process-based characteristics. For patients with low-risk cancers, independent associations with added time to surgery of at least 1 week were seen with black race (1.1 weeks; 95% CI, 0.9−1.4), uninsurance (1.3 weeks; 95% CI, 1.1−1.5), Medicaid insurance (1.7 weeks; 95% CI, 1.5−1.9), and Charlson-Deyo comorbidity score >1 (1.0 weeks; 95% CI, 0.8−1.2) (Table 3). For patients with high-risk cancers, independent associations with added time to surgery of at least 1 week were seen with uninsurance (1.4 weeks; 95% CI, 0.9−1.9) and Medicaid

TABLE 3
Association of case factors with incremental change in interval between diagnosis and surgery (weeks)

	Low-risk histology	High-risk histology
	Estimate [95% CI]	Estimate [95% CI]
Age, y		
<45	Reference	Reference
45−54	−0.65 [−0.80 to −0.49][c]	−0.81 [−1.12 to −0.49][c]
55−64	−0.60 [−0.75 to −0.44][c]	−0.90 [−1.19 to −0.61][c]
65−74	−0.86 [−1.03 to −0.68][c]	−1.16 [−1.47 to −0.85][c]
75−84	−0.71 [−0.90 to −0.53][c]	−1.01 [−1.33 to −0.68][c]
≥85	−0.34 [−0.57 to −0.11][c]	−0.56 [−0.93 to −0.20][c]
Race		
White	Reference	Reference
Black	1.14 [0.94 to 1.35][c]	0.88 [0.69 to 1.06][c]
American Indian	0.53 [−0.35 to 1.42]	0.58 [−0.40 to 1.56]
Asian/Pacific Islander	0.02 [−0.31 to 0.35]	0.04 [−0.28 to 0.35]
Other	0.34 [−0.10 to 0.78]	−0.20 [−0.62 to 0.21]
Unknown	−0.23 [−0.50 to 0.05]	0.04 [−0.40 to 0.49]
Hispanic		
No	Reference	Reference
Yes	0.68 [0.46 to 0.89][c]	0.84 [0.53 to 1.16][c]
Unknown	0.03 [−0.13 to 0.18]	0.11 [−0.06 to 0.28]
Insurance		
Not insured	1.29 [1.05 to 1.54][c]	1.36 [0.87 to 1.86][c]
Private insurance	Reference	Reference
Medicaid	1.68 [1.46 to 1.90][c]	1.41 [1.11 to 1.71][c]
Medicare	0.58 [0.46 to 0.69][c]	0.46 [0.31 to 0.61][c]
Other government	0.49 [0.17 to 0.81][c]	0.31 [−0.09 to 0.71]
Unknown	0.75 [0.34 to 1.15][c]	1.41 [0.88 to 1.94][c]
Stage		
1	Reference	Reference
2	0.51 [0.39 to 0.63][c]	0.29 [0.14 to 0.45][c]
3	0.08 [0.00 to 0.17]	−0.05 [−0.16 to 0.05]
4	−0.14 [−0.38 to 0.10]	−0.39 [−0.56 to −0.22][c]
Unknown	0.35 [0.17 to 0.53][c]	0.00 [−0.20 to 0.20]

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(continued)

TABLE 3
Association of case factors with incremental change in interval between diagnosis and surgery (weeks) *(continued)*

	Low-risk histology	High-risk histology
	Estimate [95% CI]	Estimate [95% CI]
Diagnosis/treatment at reporting facility		
Diagnosis only	Reference	Reference
Diagnosis and treatment	−0.70 [−0.91 to −0.49][c]	−0.45 [−0.75 to −0.16][c]
Treatment only	−0.33 [−0.54 to −0.11][c]	0.08 [−0.22 to 0.39]
Charlson-Deyo comorbidity score[a]		
0	Reference	Reference
1	0.38 [0.30 to 0.46]	0.33 [0.22 to 0.44][c]
2+	0.99 [0.83 to 1.15][c]	0.85 [0.65 to 1.05][c]
Facility type		
CCP	Reference	Reference
Comprehensive CCP	−0.01 [−0.22 to 0.20]	0.10 [−0.18 to 0.37]
Academic/research program	0.47 [0.21 to 0.73][c]	0.53 [0.21 to 0.84][c]
Other	−0.42 [−0.73 to −0.12][c]	−0.59 [−0.94 to −0.24][c]
Facility location		
New England	Reference	Reference
Middle Atlantic	0.28 [0.00 to 0.57]	0.32 [−0.06 to 0.70]
South Atlantic	−0.18 [−0.46 to 0.11]	−0.06 [−0.45 to 0.33]
East North Central	−0.10 [−0.37 to 0.18]	−0.03 [−0.39 to 0.34]
East South Central	−1.03 [−1.36 to −0.70][c]	−0.80 [−1.30 to −0.29][c]
West North Central	−0.58 [−0.91 to −0.25][c]	−0.52 [−0.95 to −0.09][c]
West South Central	−0.41 [−0.75 to −0.08][c]	−0.36 [−0.78 to 0.05][c]
Mountain	−0.17 [−0.49 to 0.14]	−0.27 [−0.69 to 0.14]
Pacific	0.67 [0.24 to 1.10][c]	0.87 [0.29 to 1.45][c]
Hospital case volume quartile		
1 Lowest	Reference	Reference
2	0.00 [−0.14 to 0.13]	−0.06 [−0.24 to 0.11]
3	−0.03 [−0.20 to 0.15]	−0.25 [−0.47 to −0.03][c]
4 Highest	−0.14 [−0.33 to 0.05]	−0.42 [−0.65 to −0.18][c]
Distance traveled to care, quartile, miles[b]		
1 Lowest	Reference	Reference
2	0.00 [−0.08 to 0.08]	0.13 [0.02 to 0.25][c]
3	0.00 [−0.09 to 0.09]	0.07 [−0.05 to 0.19]
4 Highest	0.05 [−0.07 to 0.18]	−0.03 [−0.19 to 0.12]

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insurance (1.4 weeks; 95% CI, 1.1−1.7). Compared to age <45 years, ages 65-74 and 75-84 years were associated with 1.1 (95% CI, 0.9−1.5) and 1.0 (95% CI, 0.7−1.3) weeks decrease in time to surgery, respectively (Table 3).

For patients with either low- or high-risk cancers, disease stage was not consistently associated with the interval between diagnosis and surgery. Compared to stage I disease, stage II disease was associated with a 2- to 4-day longer time to surgery; stage IV disease was associated with a 1- to 3-day shorter time to surgery.

Comment

We identified 2 populations of endometrial cancer patients at risk for decreased survival related to the interval between diagnosis and surgery. First, patients who underwent surgery in the first or second week after diagnosis had consistently worse survival outcomes than patients treated in the third or fourth week after diagnosis, even after adjustment for observed clinical, demographic, and process-based factors. Crude survival at 5 years was decreased by 14% for low-risk patients and by 20% for high-risk patients (Table 2). Second, delay of ≥8 weeks in surgical treatment of low-risk endometrial cancers was independently associated with worsened 5-year survival. For example, 5-year survival for patients undergoing surgery 16 weeks postdiagnosis was 16% worse than for patients undergoing surgery 3 weeks postdiagnosis (Table 2). In contrast, delay of up to 21 weeks in surgical treatment of high-risk endometrial cancers did not appear to independently affect survival outcomes.

Elit et al[12] previously noted an increased mortality associated with surgery <2 weeks after diagnosis, but were unable to identify contributing factors to this phenomenon given relatively small case numbers. As there is not a cancer-specific reason that patients receiving rapid, appropriate surgical care would have worsened survival, this finding is likely related to the delivery of care. We found that patients treated earliest were more likely than patients treated 3 or 4 weeks postdiagnosis to have no insurance or Medicaid, have advanced disease, be black, be diagnosed and treated at the same hospital, be treated in hospitals with the lowest case-volume quartile, and not undergo lymphadenectomy. These findings suggest that access to care, delays in presentation (resulting in

TABLE 3
Association of case factors with incremental change in interval between diagnosis and surgery (weeks) *(continued)*

	Low-risk histology	High-risk histology
	Estimate [95% CI]	Estimate [95% CI]
Household education, quartile[b]		
1 Lowest	Reference	Reference
2	−0.21 [−0.33 to −0.08][c]	−0.38 [−0.56 to −0.21][c]
3	−0.33 [−0.47 to −0.19][c]	−0.60 [−0.80 to −0.40][c]
4 Highest	−0.57 [−0.74 to −0.40][c]	−0.80 [−1.03 to −0.57][c]
Lymphadenectomy		
No	Reference	Reference
Yes	−0.53 [−0.62 to −0.44][c]	−0.86 [−1.01 to −0.71][c]
Unknown	−0.07 [−0.63 to 0.49]	0.22 [−0.56 to 1.01]

Linear regression model also includes year of diagnosis, metropolitan/nonmetropolitan location, median household income of patient ZIP code of residence.

CCP, community cancer program; *CI*, confidence interval.

[a] Excludes cancer as comorbidity; [b] Determined by ZIP code of patient residence; [c] $P < .05$.

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advanced disease), and lack of referral to a specialty center may factor into this group's relatively poor outcomes. Additionally, the increased risk seen after adjustment for observable characteristics may indicate inadequate preoperative workup or clinical acuity not captured by comorbidity score, potentially reflected in this population's elevated rate of mortality in the first 30 postoperative days.

Likewise, for patients experiencing a time to surgery >2 weeks, the association of race and insurance status with prolonged time to surgery suggests that access to specialty care may contribute to delay. These findings are consistent with prior studies.[1,14,22] For patients with low-risk cancers, the association between high comorbidity scores and treatment delay suggests that differences in patients' need for preoperative medical optimization may also delay definitive surgical treatment. Interestingly, the finding that an increased interval between diagnosis and surgery was not independently associated with advancing stage suggests that extent of disease at diagnosis contributes more to survival outcomes than progression of disease during the wait for surgery.

Three major processes contribute to the interval between diagnosis and surgery. First, many patients require referral for definitive surgical treatment. Transfer of care carries the burden of insurance/financial access to a referral center and the logistics of coordinating and obtaining an appointment with a specialist. In some areas of the United States, distance to the closest referral center may significantly delay treatment or increase the probability that patients are treated by nonspecialists.[23] Second, preoperative medical optimization and logistics may affect the timing of surgical treatment. Patients with comorbid disease may require specialty medical clearance prior to surgery, some of which may involve imaging or other procedures (eg, cardiac stress testing). Third, after preoperative evaluation and optimization, surgical schedule availability is likely to be highly surgeon- and institution-dependent. Indeed, surgical wait times at referral institutions appear to be longer than at community hospitals.[24] Perhaps as a consequence of the benefits and burdens associated with referral, previous reports regarding the association between subspecialty care and outcomes for endometrial cancer patients have been mixed.[25-27]

What should be the target interval between diagnosis and treatment of endometrial cancers? For patients who experience treatment delay as a result of poor access to care, decreasing time to surgery through improved access may also improve outcomes. However, for some patients, complex presurgical optimization may require prolongation of the diagnosis-to-surgery interval. For the latter group, more rapid surgical intervention may increase risk of mortality, as seen in the patient population undergoing surgery in the first 2 weeks postdiagnosis.

We suggest that the recommended interval between diagnosis and treatment of endometrial cancers should be ≤8 weeks, especially for patients with low-risk histologies on biopsy. In the majority of cases, this interval should allow adequate time for: (1) pathologic analysis of the diagnostic biopsy, (2) subspecialty referral if needed, (3) preoperative evaluation and medical optimization, and (4) surgical scheduling. However, we emphasize that medical optimization should not be abbreviated to attempt to shorten time to surgery. Additionally, as the outcomes of patients with high-risk histologies appear less sensitive to delays in surgical treatment, referral to a gynecologic oncologist should not be neglected out of concern over surgical wait time. Patients with high-risk histologies on initial biopsy, or other known adverse clinical predictors (eg, significant medical comorbidity or evidence of extrauterine disease) should be triaged to centers with expertise in the management of gynecologic cancers. These patients are likely to require specialized surgical care (eg, lymphadenectomy or cytoreduction) in addition to adjuvant therapy, consistent with the standard of care for their disease.[28]

Approximately 37% of endometrial cancer cases were excluded from this analysis because of missing values for the interval between diagnosis and surgery. Survival data were also not available for these cases, suggesting that the original date of diagnosis may not have been documented. Although there was no a priori reason to suspect that the primary outcome of interest (ie, the effect of time

to surgery on survival) was affected by these exclusions, we were limited in our ability to determine whether significant bias occurred. For low-risk histologies, the stage distribution between included and excluded cases was statistically different given the large patient sample, but clinically identical. For high-risk histologies, slightly more cases were stage I/II in the excluded group than in the included group (71% vs 64%, respectively) (Supplemental Table 2). As the survival data contained in the NCDB are not cancer-specific, we selected 5-year survival as the outcome of interest, since the greatest risk for death from endometrial cancer occurs in this interval.[29] Our survival analyses were limited by the extent to which patient follow-up was recorded in the NCDB. Additionally, our results reflect average relationships across patients and may mask important clinical and nonclinical heterogeneity.

While retrospective analyses can help identify populations that are vulnerable to worsened survival as a result of surgical timing, prospective investigation is required to identify points in the process of care that are amenable to intervention. In the meantime, gynecologic oncologists and policy makers should use available data to develop national practice standards for endometrial cancer care delivery in the United States, following similar efforts internationally.[12,30] Priority should be given to policies that minimize morbidity from disparities in access to the standard of gynecologic cancer care. ■

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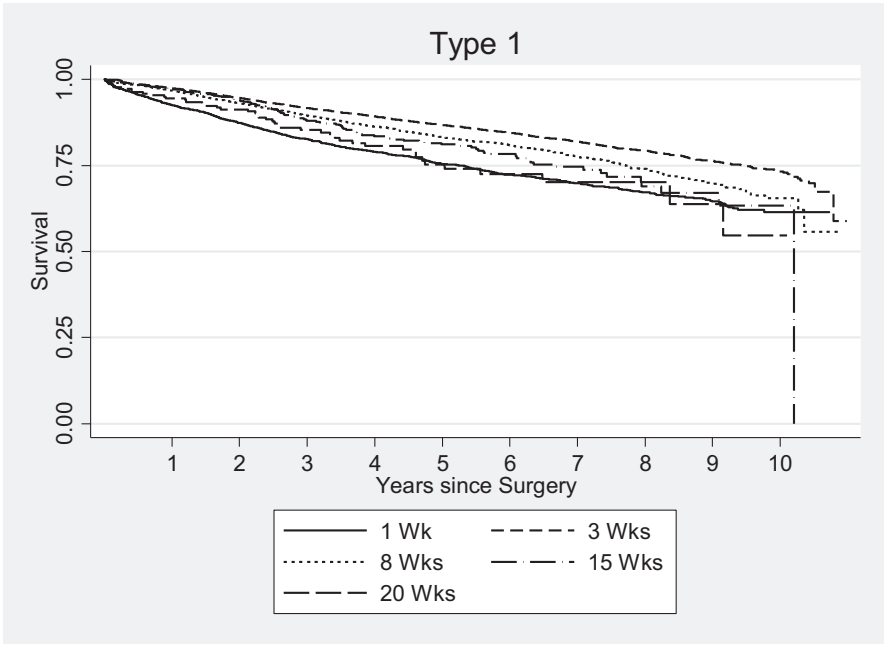
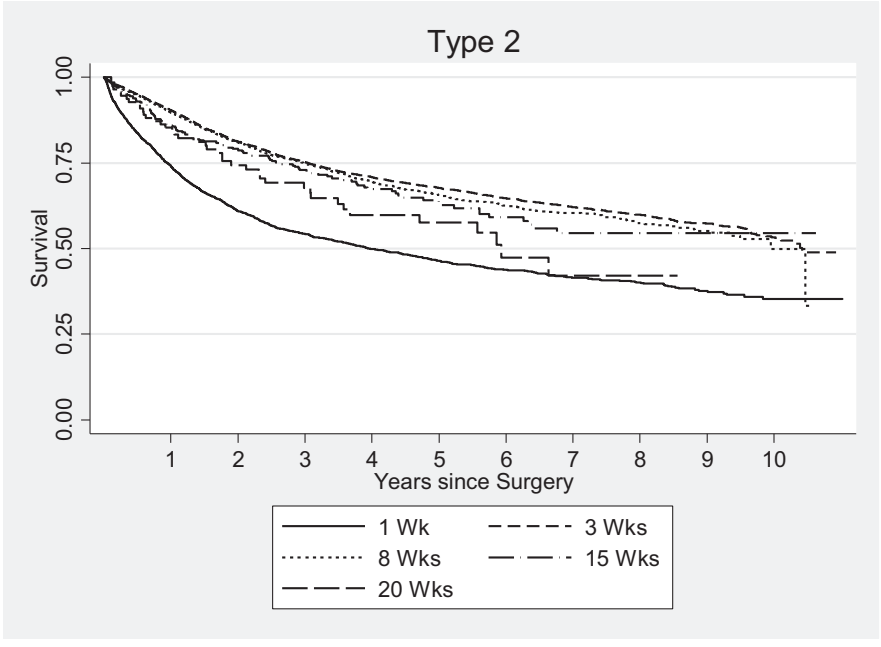
SUPPLEMENTAL FIGURE 1
Kaplan-Meier survival curves for selected delay times by patient risk level





Type 1 = low risk; type 2 = high risk.

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SUPPLEMENTAL TABLE 1A

Characteristics of cases with time to surgery <2 weeks—low-risk histologies

	0–1 wk N = 4264	1–2 wk N = 11,702	2–4 wk N = 44,375	*P* value
Age category, N (%)				<.001
<45 y	322 (7.6%)	689 (5.9%)	2565 (5.8%)	
45–54 y	889 (21%)	2383 (20%)	8443 (19%)	
55–64 y	1412 (33%)	4128 (35%)	16,375 (37%)	
65–74 y	898 (21%)	2777 (24%)	10,697 (24%)	
75–84 y	576 (14%)	1422 (12%)	5212 (12%)	
≥85 y	167 (3.9%)	303 (2.6%)	1083 (2.4%)	
Patient race, N (%)				<.001
White	3751 (88%)	10,626 (91%)	40,089 (90%)	
Black	300 (7.0%)	540 (4.6%)	2218 (5.0%)	
American Indian	6 (0.1%)	24 (0.2%)	110 (0.2%)	
Asian/Pacific Islander	108 (2.5%)	259 (2.2%)	1007 (2.3%)	
Other	43 (1.0%)	84 (0.7%)	284 (0.6%)	
Unknown	56 (1.3%)	169 (1.4%)	667 (1.5%)	
Hispanic ethnicity, N (%)				<.001
No	3732 (88%)	10,382 (89%)	39,038 (88%)	
Yes	242 (5.7%)	388 (3.3%)	1637 (3.7%)	
Unknown	290 (6.8%)	932 (8.0%)	3700 (8.3%)	
Primary payor, N (%)				<.001
Not insured	204 (4.8%)	261 (2.2%)	1147 (2.6%)	
Private insurance	2124 (50%)	6591 (56%)	25,024 (56%)	
Medicaid	226 (5.3%)	322 (2.8%)	1253 (2.8%)	
Medicare	1550 (36%)	4196 (36%)	15,887 (36%)	
Other government	38 (0.9%)	103 (0.9%)	387 (0.9%)	
Insurance status unknown	122 (2.9%)	229 (2.0%)	677 (1.5%)	
Tumor stage, N (%)				<.001
1	2703 (63%)	8807 (75%)	34,338 (77%)	
2	360 (8.4%)	741 (6.3%)	2769 (6.2%)	
3	665 (16%)	1304 (11%)	4386 (9.9%)	
4	341 (8.0%)	306 (2.6%)	806 (1.8%)	
Unknown	195 (4.6%)	544 (4.6%)	2076 (4.7%)	
Diagnosis/treatment at reporting facility, N (%)				<.001
Diagnosis only	48 (1.1%)	242 (2.1%)	1086 (2.4%)	
Both	2677 (63%)	6231 (53%)	21,274 (48%)	
Treatment only	1539 (36%)	5229 (45%)	22,015 (50%)	

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SUPPLEMENTAL TABLE 1A
Characteristics of cases with time to surgery <2 weeks—low-risk histologies *(continued)*

	0—1 wk N = 4264	1—2 wk N = 11,702	2—4 wk N = 44,375	*P* value
Charlson-Deyo score,[a] N (%)				.004
0	3273 (77%)	9208 (79%)	34,405 (78%)	
1	807 (19%)	2112 (18%)	8383 (19%)	
2+	184 (4.3%)	382 (3.3%)	1587 (3.6%)	
Facility type, N (%)				<.001
Community cancer program	329 (7.7%)	879 (7.5%)	2621 (5.9%)	
Comprehensive community cancer program	2391 (56%)	6826 (58%)	24,438 (55%)	
Academic/research program	1536 (36%)	3965 (34%)	17,186 (39%)	
Other	8 (0.2%)	32 (0.3%)	130 (0.3%)	
Facility location, N (%)				<.001
New England	211 (4.9%)	628 (5.4%)	3006 (6.8%)	
Middle Atlantic	677 (16%)	1510 (13%)	6172 (14%)	
South Atlantic	839 (20%)	2173 (19%)	8767 (20%)	
East North Central	762 (18%)	2386 (20%)	9560 (22%)	
East South Central	318 (7.5%)	973 (8.3%)	3032 (6.8%)	
West North Central	409 (9.6%)	1282 (11%)	4223 (9.5%)	
West South Central	450 (11%)	1105 (9.4%)	3080 (6.9%)	
Mountain	246 (5.8%)	673 (5.8%)	2414 (5.4%)	
Pacific	352 (8.3%)	972 (8.3%)	4121 (9.3%)	
Annual hospital volume quartile, N (%)				<.001
1 Lowest	1112 (26%)	2909 (25%)	8931 (20%)	
2	1017 (24%)	2728 (23%)	9453 (21%)	
3	1161 (27%)	3090 (26%)	12,109 (27%)	
4 Highest	974 (23%)	2975 (25%)	13,882 (31%)	
Distance traveled to care quartile,[b] N (%)				<.001
1 Lowest	1171 (28%)	2981 (26%)	10,820 (25%)	
2	1064 (25%)	2960 (26%)	10,984 (25%)	
3	1001 (24%)	2880 (25%)	11,144 (26%)	
4 Highest	941 (23%)	2682 (23%)	10,673 (24%)	
No high-school degree quartile,[b] N (%)				<.001
1 Lowest	659 (16%)	1435 (13%)	5495 (13%)	
2	953 (23%)	2477 (22%)	9765 (23%)	
3	1216 (29%)	3397 (30%)	13,073 (30%)	
4 Highest	1306 (32%)	4073 (36%)	14,879 (34%)	

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SUPPLEMENTAL TABLE 1A

Characteristics of cases with time to surgery <2 weeks—low-risk histologies *(continued)*

	0—1 wk N = 4264	1—2 wk N = 11,702	2—4 wk N = 44,375	*P* value
Year of diagnosis, N (%)				<.001
2003	444 (10%)	1194 (10%)	3654 (8.2%)	
2004	467 (11%)	1306 (11%)	4070 (9.2%)	
2005	485 (11%)	1323 (11%)	4323 (9.7%)	
2006	489 (11%)	1253 (11%)	4488 (10%)	
2007	429 (10%)	1180 (10%)	4494 (10%)	
2008	433 (10%)	1146 (9.8%)	4569 (10%)	
2009	403 (9.5%)	1073 (9.2%)	4594 (10%)	
2010	407 (9.5%)	1105 (9.4%)	4748 (11%)	
2011	361 (8.5%)	1097 (9.4%)	4776 (11%)	
2012	346 (8.1%)	1025 (8.8%)	4659 (10%)	
Lymphadenectomy, N (%)				<.001
No	1369 (32%)	3196 (27%)	11,331 (26%)	
Yes	2895 (68%)	8506 (73%)	33,044 (74%)	

[a] Excludes cancer as comorbidity; [b] Determined by ZIP code of patient residence.

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SUPPLEMENTAL TABLE 1B
Characteristics of cases with time to surgery <2 weeks—high-risk histologies

	0–1 wk N = 3399	1–2 wk N = 7243	2–4 wk N = 22,185	*P* value
Age category, N (%)				<.001
<45 y	132 (3.9%)	279 (3.9%)	770 (3.5%)	
45–54 y	493 (15%)	952 (13%)	2912 (13%)	
55–64 y	1034 (30%)	2332 (32%)	7197 (32%)	
65–74 y	942 (28%)	2202 (30%)	6804 (31%)	
75–84 y	619 (18%)	1230 (17%)	3703 (17%)	
≥85 y	179 (5.3%)	248 (3.4%)	799 (3.6%)	
Patient race, N (%)				<.001
White	2645 (78%)	6078 (84%)	18,759 (85%)	
Black	588 (17%)	820 (11%)	2433 (11%)	
American Indian	10 (0.3%)	18 (0.2%)	53 (0.2%)	
Asian/Pacific Islander	84 (2.5%)	174 (2.4%)	513 (2.3%)	
Other	29 (0.9%)	54 (0.7%)	149 (0.7%)	
Unknown	43 (1.3%)	99 (1.4%)	278 (1.3%)	
Hispanic ethnicity, N (%)				<.001
No	3016 (89%)	6398 (88%)	19,644 (89%)	
Yes	166 (4.9%)	262 (3.6%)	789 (3.6%)	
Unknown	217 (6.4%)	583 (8.0%)	1752 (7.9%)	
Primary payor, N (%)				<.001
Not insured	179 (5.3%)	210 (2.9%)	567 (2.6%)	
Private insurance	1323 (39%)	3276 (45%)	10,170 (46%)	
Medicaid	203 (6.0%)	235 (3.2%)	692 (3.1%)	
Medicare	1577 (46%)	3311 (46%)	10,226 (46%)	
Other government	24 (0.7%)	54 (0.7%)	160 (0.7%)	
Unknown	93 (2.7%)	157 (2.2%)	370 (1.7%)	
Tumor stage, N (%)				<.001
1	1187 (35%)	3714 (51%)	12,753 (57%)	
2	255 (7.5%)	545 (7.5%)	1648 (7.4%)	
3	768 (23%)	1452 (20%)	4207 (19%)	
4	849 (25%)	981 (14%)	1916 (8.6%)	
Unknown	340 (10%)	551 (7.6%)	1661 (7.5%)	
Class of case, N (%)				<.001
Diagnosis only	61 (1.8%)	155 (2.1%)	582 (2.6%)	
Both	2243 (66%)	3791 (52%)	10,389 (47%)	
Treatment only	1095 (32%)	3297 (46%)	11,214 (51%)	
Charlson-Deyo score,[a] N (%)				.064
0	2603 (77%)	5688 (79%)	17,124 (77%)	
1	651 (19%)	1289 (18%)	4228 (19%)	
2+	145 (4.3%)	266 (3.7%)	833 (3.8%)	

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SUPPLEMENTAL TABLE 1B
Characteristics of cases with time to surgery <2 weeks—high-risk histologies *(continued)*

	0–1 wk N = 3399	1–2 wk N = 7243	2–4 wk N = 22,185	*P* value
Facility type, N (%)				<.001
Community cancer program	252 (7.4%)	488 (6.7%)	1436 (6.5%)	
Comprehensive community cancer program	1829 (54%)	4055 (56%)	11,881 (54%)	
Academic/research program	1315 (39%)	2688 (37%)	8817 (40%)	
Other specified types of cancer programs	3 (0.1%)	12 (0.2%)	51 (0.2%)	
Facility location, N (%)				<.001
New England	174 (5.1%)	366 (5.1%)	1422 (6.4%)	
Middle Atlantic	497 (15%)	946 (13%)	3307 (15%)	
South Atlantic	775 (23%)	1458 (20%)	4606 (21%)	
East North Central	556 (16%)	1290 (18%)	4045 (18%)	
East South Central	328 (9.6%)	746 (10%)	1851 (8.3%)	
West North Central	300 (8.8%)	781 (11%)	2139 (9.6%)	
West South Central	313 (9.2%)	646 (8.9%)	1539 (6.9%)	
Mountain	153 (4.5%)	361 (5.0%)	986 (4.4%)	
Pacific	303 (8.9%)	649 (9.0%)	2290 (10%)	
Annual hospital volume quartile, N (%)				<.001
1 Lowest	815 (24%)	1721 (24%)	4738 (21%)	
2	811 (24%)	1659 (23%)	4613 (21%)	
3	890 (26%)	1914 (26%)	5927 (27%)	
4 Highest	883 (26%)	1949 (27%)	6907 (31%)	
Distance quartile,[b] N (%)				<.001
1 Lowest	992 (30%)	1891 (27%)	5666 (26%)	
2	821 (25%)	1652 (23%)	5242 (24%)	
3	706 (21%)	1664 (23%)	5280 (24%)	
4 Highest	809 (24%)	1877 (26%)	5571 (26%)	
Median income quartile (unified), N (%)				<.001
1 Lowest	612 (18%)	1088 (15%)	3292 (15%)	
2	692 (21%)	1452 (21%)	4465 (21%)	
3	919 (28%)	1898 (27%)	5884 (27%)	
4 Highest	1088 (33%)	2583 (37%)	7956 (37%)	
No high-school degree quartile (unified),[b] N (%)				<.001
1 Lowest	641 (19%)	1140 (16%)	3270 (15%)	
2	849 (26%)	1654 (24%)	5162 (24%)	
3	908 (27%)	1931 (28%)	6219 (29%)	
4 Highest	915 (28%)	2294 (33%)	6951 (32%)	

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SUPPLEMENTAL TABLE 1B
Characteristics of cases with time to surgery <2 weeks—high-risk histologies *(continued)*

	0—1 wk N = 3399	1—2 wk N = 7243	2—4 wk N = 22,185	*P* value
Year of diagnosis, N (%)				<.001
2003	415 (12%)	860 (12%)	2231 (10%)	
2004	375 (11%)	804 (11%)	2143 (9.7%)	
2005	335 (9.9%)	766 (11%)	2097 (9.5%)	
2006	324 (9.5%)	692 (9.6%)	2050 (9.2%)	
2007	339 (10.0%)	705 (9.7%)	2193 (9.9%)	
2008	317 (9.3%)	689 (9.5%)	2193 (9.9%)	
2009	355 (10%)	705 (9.7%)	2246 (10%)	
2010	316 (9.3%)	704 (9.7%)	2295 (10%)	
2011	331 (9.7%)	669 (9.2%)	2410 (11%)	
2012	292 (8.6%)	649 (9.0%)	2327 (10%)	
Lymphadenectomy, N (%)				<.001
No	1206 (35%)	1778 (25%)	4679 (21%)	
Yes	2193 (65%)	5465 (75%)	17,506 (79%)	

[a] Charlson-Deyo score excludes cancer as comorbidity; [b] Determined by ZIP code of patient residence.
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SUPPLEMENTAL TABLE 2
Stage comparison of included and excluded cases

A: Low-risk histologies

Stage	Included	Excluded	Total
1	107,468	43,147	150,615
%	76.72	75.49	76.36
2	9608	4564	14,172
%	6.86	7.99	7.19
3	13,623	5280	18,903
%	9.73	9.24	9.58
4	2685	1316	4001
%	1.92	2.30	2.03
Unknown	6694	2848	9542
%	4.78	4.98	4.84
Total	140,078	57,155	197,233
%	100.00	100.00	100.00
Pearson χ^2 (4) = 123.0128			$P < .001$

B: High-risk histologies

Stage	Included	Excluded	Total
1	38,160	40,106	78,266
%	55.82	63.76	59.63
2	5588	4736	10,324
%	8.17	7.53	7.87
3	13,154	7932	21,086
%	19.24	12.61	16.06
4	6268	3843	10,111
%	9.17	6.11	7.70
Unknown	5190	6284	11,474
%	7.59	9.99	8.74
Total	68,360	62,901	131,261
%	100.00	100.00	100.00
Pearson χ^2 (4) = 1900			$P < .001$

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