Incidence of Initial Local Therapy Among Men With Lower-Risk Prostate Cancer in the United States

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Background: **The frequently indolent nature of early-stage prostate cancer in older men and in men with low- or moderate-grade tumors and the demonstration that the survival benefits of radical prostatectomy are primarily among men younger than 65 years have led to concerns about prostate cancer overtreatment.** ***Methods:*** **Using data from 13 Surveillance, Epidemiology, and End Results registries, we performed a retrospective cohort study of 71 602 men who were diagnosed with localized or regional prostate cancer between 2000 and 2002. We quantified the incidence of initial curative therapy (i.e., surgery or radiation therapy) among men with lower-risk cancers as defined by their limited likelihood of either dying from expectantly managed prostate cancer or achieving a survival benefit from local therapy. Stratified analyses and multinomial logistic regression models were used to quantify the absolute and relative rates of curative therapy among men in various age–grade strata. All statistical tests were two-sided.** ***Results:*** **We identified 24 405 men with lower-risk prostate cancers and complete data for the first course of treatment. Initial curative therapy was undertaken in 13 537 of these men (55%); 81% of treated men received radiation therapy. The likelihood of curative therapy, relative to expectant management, varied statistically significantly among lower-risk age–grade strata (all $P<.05$). Assuming that initial expectant management is appropriate for all lower-risk cancers, 2564 men (10%) in this population-based sample were overtreated with radical prostatectomy and 10 973 (45%) with radiation therapy.** ***Conclusions:*** **These data quantify a target population for whom greater use of expectant approaches may reduce overtreatment and improve the quality of localized prostate cancer care. [J Natl Cancer Inst 2006;98:1134–41]**

Recent declines in prostate cancer mortality rates suggest that early diagnosis and treatment of localized prostate cancer may improve patient survival *(1–3)*. This possibility is strongly supported by results of a randomized controlled trial in which patients with clinically detected early-stage prostate cancers who were assigned to radical prostatectomy had better survival than those assigned to expectant (i.e., conservative) management (watchful waiting) *(4)*. However, several observational studies have confirmed the potentially indolent natural history of expectantly managed localized prostate cancer, particularly among older men with clinically detected low- and moderate-grade tumors *(5–7)*. The clinical behavior of tumors diagnosed by prostate-specific antigen (PSA) screening may be even less ominous than that of tumors detected clinically, given the prolonged lead time and length-bias sampling that have been attributed to PSA-based screening protocols *(8)*. Recent reports of increases in the prevalence of treatment among patients with low-risk clinical characteristics (i.e., clinical stage ≤ T2a, PSA ≤ 10, Gleason sum [GS] ≤ 6) *(9)*, as well as the declining prevalence of latent prostate cancers detected at autopsy *(10)*, have prompted renewed concerns about prostate cancer overdiagnosis and overtreatment *(9,11–16)*.

Just as a failure to treat a potentially lethal prostate cancer is generally considered inappropriate from a quality-of-care perspective, aggressive treatment of indolent cancers (i.e., overtreatment) may also reflect suboptimal care in that it confers risk to patients and increases costs without providing health benefits *(17)*. In particular, for some men with localized prostate cancer, the use of "curative" therapy (i.e., surgery or radiation therapy) may result in substantial morbidity without a consequent survival benefit *(18,19)*. To date, however, most research on quality of care in urology has focused on the skill with which such care is provided (e.g., surgical technique) *(20–22)*, with a more limited emphasis on the appropriateness of treatment. In this context, and recognizing the mounting evidence that supports expectant management as an evidence-based initial treatment option for men with early-stage prostate cancer *(5,23,24)*, we sought to estimate the potential overtreatment burden among men with newly diagnosed prostate cancer by using population-based data to quantify the incidence of initial curative therapy among men with lower-risk cancers.

Methods

Data Source and Study Population

The Surveillance, Epidemiology, and End Results (SEER) registries are a set of geographically defined, population-based central cancer registries in the United States that were established and are maintained by the National Cancer Institute. The demographic composition of the SEER registries and cancer incidence and mortality trends determined from SEER data are considered generally as representative of the entire US population *(25,26)*. We used the public-use files for 13 SEER registries (San Francisco, Connecticut, Metro Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, Alaska, San Jose, Los Angeles, and Rural Georgia) to identify 73 566 men who were diagnosed with localized or regional adenocarcinoma of the prostate (International Classification of Disease—Oncology 2 site code C61.9, histology codes 8140 and 8550) *(27)* from January 1, 2000, through December 31, 2002. We also identified 25 826 men who were diagnosed with localized

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or regional prostate cancer and for whom complete data for age and tumor grade were reported to nine SEER registries (San Francisco, Connecticut, Metro Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta) from January 1, 1988, through December 31, 1990. The men in this latter cohort (the historical cohort) were used to compare treatment patterns in the early PSA era (1988–1990) with those for patients diagnosed more recently (2000–2002).

Definition of Variables

Age at diagnosis, year of diagnosis, tumor grade, race/ethnicity (non-Hispanic white, African American, Hispanic, or other, as defined by the SEER program), marital status, and SEER registry were abstracted for each patient. For analytic purposes, each of these factors was treated as a categorical variable. We classified tumor grade as well differentiated (GS 2–4), moderately differentiated (GS 5–7), or poorly differentiated (GS 8–10).

To address our primary aim (i.e., quantifying the incidence of initial curative therapy among men with lower-risk prostate cancers), we identified patients with "lower-risk" prostate cancer as defined by the following age and grade criteria: men of any age at diagnosis with well-differentiated tumors or men 70 years or older at diagnosis with moderately differentiated tumors *(4–7)*. This approach identified 24 825 men (34.7% of the primary analytic cohort) who were diagnosed with lower-risk cancers from 2000 through 2002 and 15 480 men (59.9% of the historical cohort) who were diagnosed with lower-risk cancers from 1988 through 1990. In both cohorts, all other men were classified as having "higher-risk" cancers.

The SEER registries define the first course of therapy as all cancer-directed therapy that is either administered or planned within the first 12 months after diagnosis *(26)*. We used the SEER program variables for "site-specific surgery," "radiation therapy," and "radiation sequence with surgery" to assign each patient to one of three primary treatment groups: 1) surgery, 2) radiation, or 3) expectant management (i.e., watchful waiting). Specifically, patients who underwent radical or total prostatectomy (based on the "site-specific surgery" variable) were assigned to the surgery cohort. Men who were treated with external beam radiation, brachytherapy, and/or combination radiotherapy (based on the "radiation therapy" variable) were classified as having received radiation as their primary treatment. For patients who were treated with surgery and radiation, the initial intervention (as defined by the "radiation sequence with surgery" variable) was used to assign the primary treatment group. Men were classified as having had expectant management as the primary treatment if there was coded affirmation of no site-specific surgery and no radiation therapy. Because SEER registries lack explicit data regarding initial and longitudinal use of hormonal therapy, we could not specify a separate cohort of men that received primary androgen deprivation therapy (ADT). Therefore, as described in a previous study *(28)*, the expectant management group inevitably included some men who received ADT.

Statistical Analysis

The primary outcome in this study was the type of initial treatment (surgery, radiation, or expectant management/ADT) received by men diagnosed with localized or regional prostate cancer. For analytic purpose, we defined the receipt of initial local therapy for men in the lower-risk cohort as overtreatment. We used a general chi-square test to evaluate associations between the type of initial treatment received and various demographic (i.e., age at diagnosis, race/ethnicity, marital status, SEER registry, year of diagnosis) and cancer-specific (i.e., tumor grade) variables within each risk stratum.

Next, we used stratified analyses and multinomial regression models to quantify the absolute and relative propensity for initial curative therapy among men in various age–grade strata. With respect to the latter, we used a forward model-building approach to fit multinomial logistic regression models that evaluated associations between the type of initial therapy and patient age and tumor grade. The outcome variable for our regression model was receipt of initial local therapy (yes/no). The reference group for the multivariable analyses was men $\geq$75 years old with well-differentiated cancers; this group was chosen as the referent because, on average, men in this age-grade strata are the least likely to die from expectantly managed prostate cancer and/or to achieve a survival benefit from local therapy. We adjusted concurrently for race/ethnicity, marital status, year of diagnosis, and SEER registry. Each model also included a first-order variable for the interaction between categorical age and tumor grade. Given the high probability of the outcome (i.e., >10% of men treated with surgery or radiation) for our models, we calculated estimated relative risks (RRs) from the model-derived adjusted odds ratios according to the method of Zhang and Yu *(29)*. All analyses were two-tailed and were performed using SAS statistical software (version 9.1, SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant. In accordance with the Code of Federal Regulations Title 45, Subpart A, Section 46.101, institutional review board approval was waived for this study.

Results

We identified 73 566 men who were diagnosed with localized or regional prostate cancer from January 1, 2000, through December 31, 2002. Men with missing tumor grade (n = 1964) were excluded because they could not be assigned to a risk group. The remaining 71 602 men served as our primary analytic sample and were assigned to either the higher-risk (n = 46 777) or the lower-risk (n = 24 825) stratum. An additional 7490 men were excluded from subsequent multivariable analyses because of missing or unknown data for primary treatment (n = 966), race/ethnicity (n = 1831), and/or marital status (n = 4693). Thus, our final multivariable model included 64 112 men (87% of the original sample, 90% of the analytic sample) with complete data for treatment (the primary outcome), age at diagnosis and tumor grade (the primary covariates), race/ethnicity, marital status, year of diagnosis, and SEER registry.

There were some differences between men that were excluded from our multivariable model and those who were included. First, excluded men were older at diagnosis than included men (mean age = 70.1 versus 67.2 years; P<.001). Excluded men were also more likely than included men to have lower-risk cancers (43% versus 34%; P<.001) and to have received initial expectant management (64% versus 25%; P<.001). Finally, excluded men were more likely to be African American (14% versus 12%; P<.001) and less likely to be currently married (73% versus 78%; P<.001). There was no difference in tumor grade distribution between the two groups.

Table 1. Demographic and clinical characteristics of 71 602 men with higher- and lower-risk prostate cancers, 2000–2002*

Characteristic	Higher-risk cases (N = 46 777)				Lower-risk cases (N = 24 825)			
	Expectant management/ADT (n = 9544)	Radical prostatectomy (n = 19 876)	Radiation therapy† (n = 16 811)	*P*	Expectant management/ADT (n = 10 868)	Radical prostatectomy (n = 2564)	Radiation therapy† (n = 10 973)	*P*
Mean age at diagnosis, y (SD)	68.3 (10.5)	60.0 (6.6)	64.5 (7.4)	<.001‡	77.4 (6.1)	71.4 (5.2)	74.3 (4.1)	<.001‡
Age at diagnosis§, n (%)				<.001‖				<.001‖
<55 y	781 (12.0)	4175 (64.0)	1571 (24.0)		48 (36.1)	52 (39.1)	33 (24.8)	
55–59 y	1147 (13.3)	4932 (57.0)	2564 (29.7)		63 (35.2)	63 (35.2)	53 (29.6)	
60–64 y	1663 (15.3)	5299 (48.8)	3901 (35.9)		132 (45.7)	77 (26.6)	80 (27.7)	
65–69 y	2491 (19.2)	4711 (36.2)	5809 (44.6)		191 (48.8)	66 (16.9)	134 (34.3)	
70–74 y	693 (26.7)	583 (22.4)	1324 (50.9)		3007 (28.4)	1835 (17.3)	5749 (54.3)	
≥75 y	2769 (60.4)	176 (3.8)	1642 (35.8)		7427 (57.9)	471 (3.7)	4924 (38.4)	
Tumor grade¶, n (%)				<.001‖				<.001‖
Well differentiated	N/A	N/A	N/A		1291 (60.1)	319 (14.9)	538 (25.0)	
Moderately differentiated	5112 (15.7)	15 829 (48.7)	11 550 (35.6)		9577 (43.0)	2245 (10.1)	10 435 (46.9)	
Poorly differentiated	4432 (32.3)	4047 (29.4)	5261 (38.3)		N/A	N/A	N/A	
Race/Ethnicity#, n (%)				<.001‖				<.001‖
Caucasian	6127 (18.7)	14 692 (44.8)	11 962 (36.5)		7674 (42.3)	1968 (10.9)	8490 (46.8)	
African American	1448 (23.1)	2426 (38.6)	2408 (38.3)		1044 (48.5)	172 (8.0)	937 (43.5)	
Hispanic	702 (21.1)	1655 (49.6)	977 (29.3)		798 (47.8)	252 (15.1)	619 (37.1)	
Other	617 (21.8)	965 (34.1)	1246 (44.1)		661 (40.7)	158 (9.7)	807 (49.6)	
Marital status**, n (%)				<.001‖				<.001‖
Single	1112 (24.7)	1769 (39.3)	1621 (36.0)		815 (48.3)	179 (10.6)	692 (41.0)	
Married	5436 (16.2)	15 808 (47.1)	12 348 (36.7)		6669 (39.1)	2060 (12.1)	8325 (48.8)	
Separated	83 (24.3)	134 (39.2)	125 (36.5)		37 (41.6)	9 (10.1)	43 (48.3)	
Divorced	628 (20.5)	1165 (38.0)	1270 (41.5)		476 (46.2)	106 (10.3)	448 (43.5)	
Widowed	618 (37.0)	411 (24.6)	643 (38.4)		1165 (52.0)	140 (6.2)	937 (41.8)	
Year of diagnosis††, n (%)				.042‖				.008‖
2000	3078 (20.8)	6332 (42.7)	5418 (36.5)		3591 (44.4)	903 (11.2)	3593 (44.4)	
2001	3107 (20.0)	6702 (43.1)	5743 (36.9)		3590 (43.5)	870 (10.6)	3783 (45.9)	
2002	3359 (21.2)	6842 (43.2)	5650 (35.6)		3687 (45.7)	791 (9.8)	3597 (44.5)	
SEER site‡‡, n (%)				<.001‖				<.001‖
San Francisco	1049 (19.8)	1886 (35.6)	2364 (44.6)		989 (38.0)	258 (9.9)	1359 (52.1)	
Connecticut	1189 (23.4)	1918 (37.7)	1983 (38.9)		1252 (45.4)	150 (5.5)	1353 (49.1)	
Metro Detroit	1372 (21.2)	2808 (43.3)	2304 (35.5)		1622 (43.4)	283 (7.6)	1836 (49.1)	
Hawaii	294 (21.9)	333 (24.8)	714 (53.3)		217 (34.0)	26 (4.1)	396 (61.9)	
Iowa	785 (22.1)	1650 (46.6)	1110 (31.3)		1175 (51.0)	238 (10.3)	890 (38.7)	
New Mexico	554 (27.7)	911 (45.5)	536 (26.8)		599 (55.0)	116 (10.7)	373 (34.3)	
Seattle	788 (15.0)	2306 (43.9)	2158 (41.1)		1023 (38.4)	351 (13.2)	1291 (48.4)	
Utah	488 (21.1)	1133 (49.0)	692 (29.9)		646 (46.2)	236 (16.9)	517 (36.9)	
Atlanta	493 (15.5)	1255 (39.4)	1435 (45.1)		368 (31.9)	75 (6.5)	711 (61.6)	
Alaska	5 (14.3)	20 (57.1)	10 (28.6)		10 (66.7)	1 (6.7)	4 (26.7)	
San Jose	532 (20.4)	1025 (39.4)	1048 (40.2)		528 (45.5)	92 (7.9)	540 (46.6)	
Los Angeles	1965 (22.0)	4574 (51.3)	2383 (26.7)		2420 (50.2)	734 (15.2)	1669 (34.6)	
Rural Georgia	30 (18.6)	57 (35.4)	74 (46.0)		19 (33.3)	4 (7.0)	34 (59.7)	

*Risk stratification not possible for 1964 cases with missing/unknown tumor grade, resulting in an analytic sample of 71 602 cases. ADT = androgen deprivation therapy; SD = standard deviation; N/A = not applicable; SEER = Surveillance, Epidemiology, and End Results registry.

†Includes external beam radiation, brachytherapy, and combination radiation therapy.

‡Mean values (within risk strata) statistically significantly different in individual pairwise comparisons using Bonferroni method ($P<.05$).

§In all, 546 higher-risk cases and 420 lower-risk cases with missing/unknown treatment.

‖General (Pearson) chi-square test.

¶In all, 2930 cases with missing/unknown treatment and/or tumor grade (includes cases with undifferentiated tumors).

#In all, 1552 higher-risk cases and 1245 lower-risk cases with missing/unknown treatment and/or race/ethnicity.

**In all, 3606 higher-risk cases and 2724 lower-risk cases with missing/unknown treatment and/or marital status.

††In all, 546 higher-risk cases and 420 lower-risk cases with missing/unknown treatment.

‡‡In all, 546 higher-risk cases and 420 lower-risk cases with missing/unknown treatment.

Demographic and clinical characteristics for the 71 602 men assigned to risk strata (i.e., the analytic sample) are summarized in Table 1. Figure 1 compares the use of primary treatments, by age and grade strata, among patients for whom we had complete data for age at diagnosis, tumor grade, and primary treatment (n = 70 636; 98.7% of the analytic sample). Curative therapy (radical prostatectomy or radiation) was initially used to treat the majority (70%) of men diagnosed from 2000 to 2002 with prostate cancer regardless of their age at diagnosis or tumor grade, with the exception of men who were 75 years or older at diagnosis (irrespective of grade) and men who were 70–74 years old at diagnosis with well-differentiated tumors (Table 1, Fig. 1). Men in the latter age-grade strata were more likely to receive expectant management than curative local therapy.

Among the 24 405 men with lower-risk cancers and complete treatment data (98.3% of men assigned to the lower-risk cohort), 55% received initial curative treatment; 45% of men in the cohort received radiation therapy, and 10% were treated with radical prostatectomy (Fig. 1). To provide a context for initial treatment patterns during this period (2000–2002), we also determined the cumulative incidence of curative therapy among men with lower-risk cancers as reported to the SEER registries

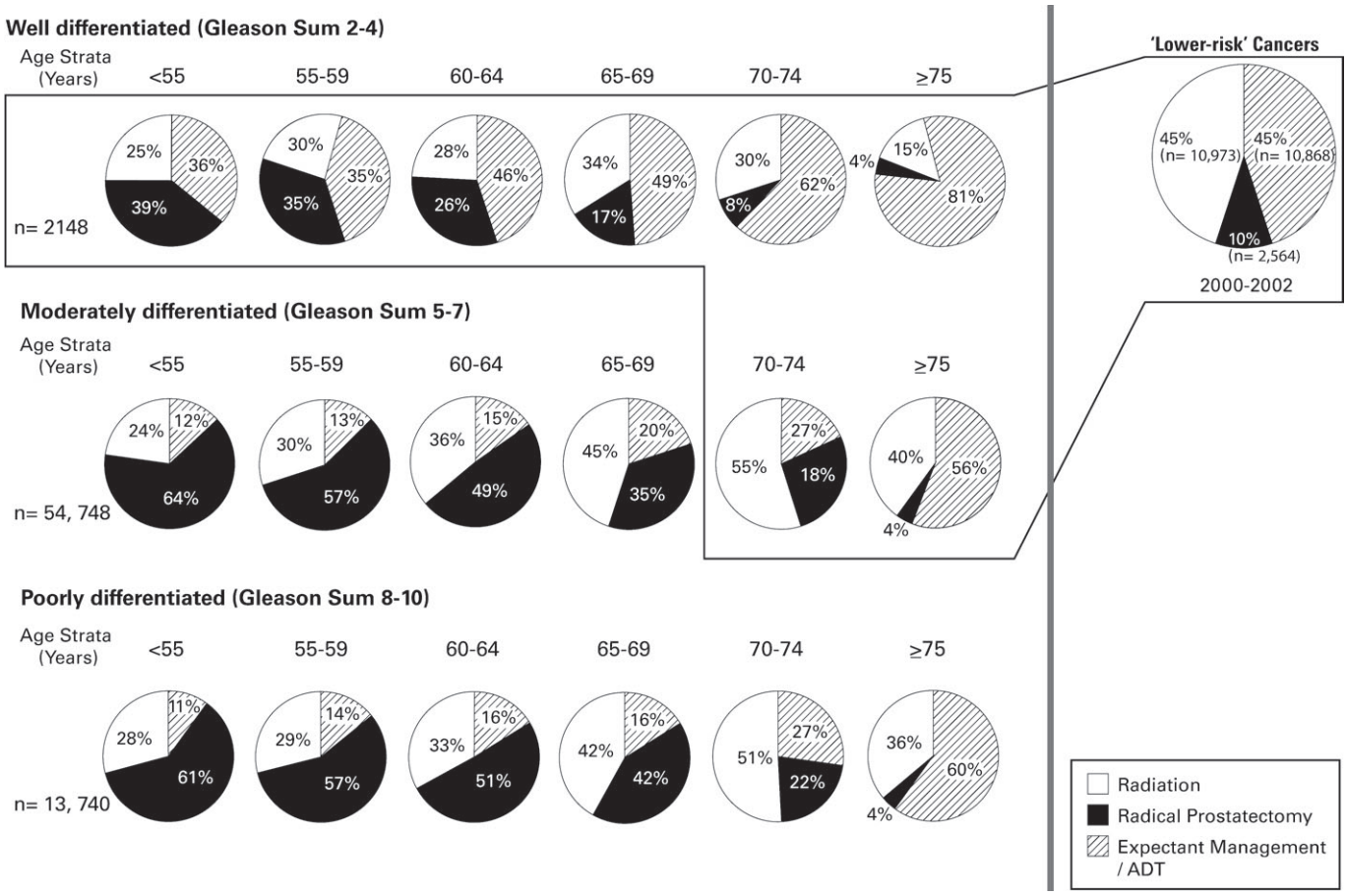

Fig. 1. Cumulative incidence of initial therapy for localized/regional prostate cancer by age (at diagnosis) and tumor grade strata (2000–2002). Age–grade strata comprising the lower-risk cohort are contained within the **black border**. The cumulative incidence of initial therapies among men with lower-risk cancers is summarized in the **top right pie chart**. The data for this figure come from 70 636 men with complete data for age at diagnosis (no cases missing), tumor grade (1964 cases missing/unknown), and primary treatment (additional 966 cases missing/unknown). ADT = androgen deprivation therapy.

from 1988 through 1990. In this historical cohort, initial local therapy was administered in only 48% of patients with lower-risk cancers; 31% of men in the historical cohort were treated with radiation therapy, and 17% were treated with radical prostatectomy.

The estimated relative risks presented in Table 2 highlight the joint effect of patient age and tumor grade on the rates of initial curative therapy among men who were diagnosed from 2000 to 2002 *(29)*. The likelihood of receiving initial surgery or radiation versus expectant management or ADT was greater for men with

Table 2. Estimated relative risk (95% confidence intervals) for initial treatment with radical prostatectomy or radiation therapy versus treatment with expectant management/androgen deprivation therapy by age at diagnosis and tumor grade strata, 2000–2002*

	Age at diagnosis, y					
Tumor grade	<55	55–59	60–64	65–69	70–74	≥75
Radical prostatectomy versus expectant management/androgen deprivation therapy						
Well differentiated	12.0 (9.15 to 14.6)†	10.8 (8.12 to 13.5)†	8.52 (6.25 to 11.0)†	5.83 (4.02 to 8.04)†	2.51 (1.54 to 3.94)†	1.00 (referent)†
Moderately differentiated	18.1 (17.2 to 18.7)	17.5 (16.4 to 18.3)	16.5 (15.1 to 17.5)	14.1 (12.3 to 15.7)	9.18 (7.23 to 11.2)†	1.51 (1.03 to 2.19)†
Poorly differentiated	18.4 (17.5 to 19.0)	17.5 (16.3 to 18.3)	16.6 (15.2 to 17.7)	15.7 (14.1 to 17.0)	10.2 (8.1 to 12.2)	1.52 (1.02 to 2.23)
Radiation therapy versus expectant management/androgen deprivation therapy						
Well differentiated	2.91 (2.15 to 3.70)†	3.05 (2.38 to 3.73)†	2.69 (2.15 to 3.25)†	2.76 (2.28 to 3.26)†	2.27 (1.85 to 2.73)†	1.00 (referent)†
Moderately differentiated	4.35 (4.02 to 4.64)	4.51 (4.21 to 4.77)	4.54 (4.26 to 4.80)	4.48 (4.20 to 4.74)	4.32 (4.02 to 4.60)†	2.75 (2.41 to 3.09)†
Poorly differentiated	4.87 (4.49 to 5.18)	4.52 (4.14 to 4.85)	4.47 (4.11 to 4.77)	4.64 (4.34 to 4.92)	4.17 (3.84 to 4.48)	2.45 (2.12 to 2.80)

*Adjusted for year of diagnosis, race/ethnicity, marital status, and Surveillance, Epidemiology, and End Results (SEER) registry site. From our primary analytic sample of 71 602 cases, an additional 7490 cases were excluded from multivariable analyses due to missing or unknown data for primary treatment (n = 966), race/ethnicity (n = 1831), and/or marital status (n = 4693). Thus, our final multivariable models include 64 112 cases (87% of the original sample, 90% of the analytic sample) with complete data for treatment (primary outcome), age, grade (primary covariates), race/ethnicity, marital status, year of diagnosis, and SEER registry.

†Lower-risk age–grade strata.

higher-risk cancers than for men with lower-risk cancers (Table 2). Assuming that the natural history of untreated prostate cancer should be similar for all men in the lower-risk cohort, it is reasonable to contend that the relative risk of treatment for each of the lower-risk age–grade strata should approach or equal 1.0 (i.e., for each low-risk stratum the likelihood of treatment with radical prostatectomy or radiation therapy versus expectant management or ADT should not be statistically significantly different from that in men with well-differentiated cancers who were 75 years or older at the time of diagnosis, i.e., the reference group). In this context, the data presented in Table 2 suggest that, among the entire lower-risk cohort, the relative risk of overtreatment with radical prostatectomy (versus expectant management/ADT) was greatest for men who had well-differentiated tumors and who were younger than 55 years at diagnosis (estimated RR = 12.0, 95% confidence interval [CI] = 9.15 to 14.6). The relative risk of overtreatment with radiation therapy (versus expectant management/ADT) among lower-risk patients was greatest for 70- to 74-year-olds with moderately differentiated cancers (RR = 4.32, 95% CI = 4.02 to 4.60).

We took this line of reasoning one step further by assuming that all men with lower-risk cancers should receive initial treatment with expectant management, and we quantified the absolute number of men in the 13 US SEER registries who were potentially overtreated in that they received initial treatment with radical prostatectomy or radiation therapy. A total of 13 537 men (55% of the 24 405 men with lower-risk cancer and complete treatment data in the SEER registries) were potentially overtreated with radical prostatectomy (n = 2564; 10%) or radiation therapy (n = 10 973; 45%) from 2000 through 2002. In absolute terms, the greatest burden of potential overtreatment (i.e., the largest number of lower-risk patients receiving initial local therapy) was among older men (≥70 years) with moderately differentiated cancers. Among this group, 12 680 men were potentially overtreated with initial surgery or radiation therapy from 2000 through 2002.

Discussion

This report builds on a growing literature that has examined the potential overtreatment of localized prostate cancer in the United States *(9,11,15)*. On the basis of explicit age and grade criteria, we identified more than 24 000 men who were diagnosed with prostate cancer from 2000 through 2002 and who were: 1) any age at diagnosis, with well-differentiated tumors [with a consequent relatively low risk of dying from conservatively managed prostate cancer over the next 20 years *(5)*], or 2) 70 years or older at diagnosis, with moderately or well-differentiated tumors [and thus less likely to experience an overall survival benefit from aggressive local therapy than younger men with similar tumors *(4,30)*]. Among this lower-risk group of men, 55% received local therapy within 12 months of diagnosis; most of the men treated for lower-risk tumors were 70 years or older at the time of diagnosis and received initial radiation therapy for a moderately differentiated (i.e., GS 5–7) cancer. Thus, despite mounting evidence supporting the safety of an expectant management approach *(4–7,30)*, patients who were diagnosed from 2000 through 2002 with lower-risk cancers appear to have initial treatment intensity that equaled or exceeded that for similar patients who were diagnosed during the early PSA era (1988–1990), according to our analysis of such men.

Our study is similar to other studies using population-based registry and/or administrative data *(31–33)* in that the data produced do not allow compelling inference regarding the appropriateness of care for individual patients. Nevertheless, our findings serve two useful purposes: 1) they quantify a target population for whom initial expectant management may be underutilized, and 2) they provide a useful context for examining, at a population level, factors that influence the use of initial expectant management among men with lower-risk prostate cancer. Given the cumulative health burden that is attributable to prostate cancer and its associated therapies and the recognition that unnecessary care is poor-quality care, efforts to better define these "upstream" determinants of initial expectant management are an important clinical and public health endeavor.

Among providers, an important barrier to their expanded use of initial expectant management may be skepticism, on the part of both physicians and patients, regarding the safety (in terms of cancer control) of this approach. We believe that the growing body of evidence should alleviate this concern, particularly regarding the safety of expectant management for older men (i.e., ≥70 years) who have well- or moderately differentiated tumors *(4–7)*. Indeed, robust observational data have established that older men who choose expectant management for well- or moderately differentiated (GS ≤ 6) cancers will most likely die from competing causes during the 20 years after their diagnosis *(5–7)*. In addition, a recent landmark clinical trial comparing survival among men randomly assigned to radical prostatectomy versus watchful waiting demonstrated that the overall survival benefit for surgery was seen mostly among men who were younger than 65 years at diagnosis *(4,30)*. Accurate dissemination of these data to frontline providers has the potential to further solidify expectant management as an evidence-based initial treatment option for men with lower-risk cancer as defined by their age, tumor grade, and other clinical criteria *(34,35)*. An important challenge, of course, will be to define and implement the optimal mechanisms by which to translate this evidence into practice-style modifications at a population level *(36)*.

However, we also recognize that there are gaps in the evidence base, that it is complex, and that there is potential for conflicting interpretations. For example, it is important to acknowledge that expectant management of localized prostate cancer, including the use of hormonal therapy, is not necessarily benign *(37)*. Therefore, the notion that expectant management inevitably avoids the adverse quality-of-life effects of local therapy will not hold for all patients, and this caveat must be considered by both patients and providers during the shared decision-making process.

It is also likely that some clinicians will disagree with our classification of lower-risk cancers and with the general notion that some prostate cancers require no initial intervention. For example, two studies *(39,40)* have used simulation techniques to demonstrate that curative therapy benefits healthy men older than 70 years. However, the survival gains projected by these data were concentrated among patients with high-grade tumors who would not be classified as lower-risk in the current analysis. The current absence of data from randomized controlled trials comparing radiation therapy (external beam radiation or brachytherapy) to watchful waiting among men with lower-risk cancers further obscures this issue. It is also unclear why, when comparing more contemporary patients with those diagnosed in the early PSA era, radiation therapy has become even more entrenched as the predominant local treatment among older men (≥70 years at diagnosis) with lower-risk cancers

(9). Although the reemergence of brachytherapy, with its reputation for easier short-term convalescence, is a possible explanation, further evaluation of patient- and provider-level determinants of this trend is clearly warranted *(9,41)*.

Providers face several additional challenges beyond interpreting the evidence base when exploring the option of forgoing, or even just delaying, potentially curative cancer therapy. For many patients, a cancer diagnosis is equated with the inevitable need for treatment; failure to provide treatment is perceived by many patients as inconsistent with the action-oriented approach that generally characterizes the behavior of clinicians and our medical care system in general *(42)*. Likewise, some patients who receive careful counseling about an expectant management approach continue to have specific treatment preferences that are both well-informed and nonmalleable. In addition, the fact that current financial incentives for providers are aligned with an interventionalist treatment approach (rather than an expectant management approach) cannot be overlooked *(43)*. Finally, physicians may also have justifiable concerns regarding the legal implications of what a patient may perceive to be their "inaction" following a prostate cancer diagnosis *(44)*. In our view, the financial and medicolegal barriers to recommending expectant management underscore the need to develop and prioritize novel policies that address malpractice reform in the setting of shared decision making, as well as innovative payment systems that provide specific incentives to physicians who practice high-quality, patient-centered decision making *(43)*.

Comprehensive efforts to limit overtreatment must synchronize provider-focused approaches with patient-centric initiatives such as greater understanding and accommodation of patients' preferences for localized prostate cancer therapy, as well as consideration of various social factors (e.g., partnership status, race/ethnicity, geography) that influence prostate cancer treatment decisions *(28,38,41,45–51)*. Progress in this area may require more extensive use of formal decision aids during the period immediately after a prostate cancer diagnosis is made; a growing literature, particularly concerning women with early-stage breast cancer, supports the ability of multidimensional decision aids to enhance patient knowledge regarding treatment options, satisfaction with treatment decisions, and concordance in treatment choice and personal values *(52–55)*. A versatile array of shared decision-making tools (including nomograms) may be required to ensure cultural competence among providers and to accommodate the substantial diversity in health literacy, risk perception, and other intrapersonal factors among men with newly diagnosed prostate cancer *(52,54–59)*. However, the potential benefits of such interventions are likely to depend on the ease with which they can be integrated into usual clinical practice and the degree to which they produce tangible improvements in the quality of care for patients with localized prostate cancer *(52)*.

Finally, we emphasize that initial expectant management need not be a permanent treatment choice and that some men, particularly younger patients, should eventually proceed to appropriate curative therapy after a period of asymptomatic expectant management *(15,60)*. In this context, refined watchful waiting strategies that are based on the concept of active surveillance with delayed intervention are an appealing approach to addressing overtreatment concerns among men with lower-risk prostate cancer *(32,61)*. Indeed, given that PSA screening advances the time of prostate cancer diagnosis *(8)*, active surveillance with delayed intervention provides a unique opportunity to exploit the presumed benefits of screening (i.e., early detection of lethal but curable tumors that are then selected out and treated based on surveillance findings) while simultaneously reducing overtreatment of indolent cancers that may be preferentially detected by contemporary screening practices *(23,62)*. Promising preliminary data for this approach have come from one study that reported that 60% of men remained under active surveillance during a median follow-up of nearly 5 years; the most common justification among men who came off surveillance and underwent treatment with curative therapy was patient's preference *(23)*. The prognostic applications of PSA kinetics have further strengthened the feasibility of an active surveillance paradigm *(63,64)*. Therefore, while clinicians await both improvements in focused prostate cancer therapies *(65,66)* and molecular advances that more precisely distinguish between indolent and lethal cancers *(67)*, active surveillance protocols represent a practical, and immediately applicable, strategy for reducing overtreatment.

This study has several limitations. First, we observed several relevant differences between cases that were excluded and those that were included in our multivariable models. Excluded patients were older at diagnosis than included patients and thus more likely to be classified as having lower-risk cancers and to undergo initial expectant management. The primary concern raised by these differences is that the relative risks of curative therapy presented herein may be biased away from the null (i.e., biased toward greater relative overtreatment with surgery or radiation). However, our principal finding was the absolute number of men that may have been overtreated. Unlike the model-derived relative risks, this figure was ascertained from the sample of 70 636 cases for which we had complete data for age, grade, and primary treatment (only 1.3% of cases had missing treatment data). Accordingly, whereas the exclusion of cases from the multivariable analysis may have inflated our estimates of relative overtreatment within various lower-risk age–grade strata, it does not affect our conclusions regarding the absolute number of men that may have been overtreated for lower-risk prostate cancer.

Second, our lower-risk cohort includes some patients with higher-grade cancers because we used the SEER registry tumor classification system, in which GS 7 cancers are classified as moderately differentiated. Given the greater risk of disease progression and/or death from prostate cancer among men with GS 7 tumors *(5)*, inclusion of these patients in the lower-risk cohort may inflate our estimates of potential overtreatment. A third and related limitation is that the absence of pretreatment PSA levels, biopsy GS, and other risk assessment criteria (e.g., tumor volume on biopsy) in the current SEER data set precludes creation of a meaningful moderate-risk stratum. However, the eventual availability of these data in the SEER public-use files will facilitate future population-based analyses of moderate-risk patients, among whom the optimal level of initial curative therapy remains controversial *(5,6,14,68,69)*. In the meantime, assessing potential overtreatment among men with lower-risk cancers is a reasonable place to start.

Fourth, the applicability of our findings to current patients is limited by the fact that very few men now present with GS 2–4 prostate cancers (well-differentiated tumors in this study) because Gleason patterns 1 and 2 are rarely, if ever, diagnosed on contemporary needle biopsy specimens *(70)*. Therefore, among patients diagnosed in 2006 and beyond, the prognostically important grade distinction, with respect to choice of therapy, will be primarily between GS 6 and more high-grade (i.e., GS 7–10)

tumors. A fifth limitation is that the histologic grades for radiation patients are based on a needle biopsy specimen alone. This may increase the potential for underestimation of the true tumor grade and inflate our estimates of overtreatment with radiation therapy among men with lower-grade cancers *(70)*. Sixth, our decision to combine brachytherapy and external beam radiation into a single radiation cohort may have obscured important trends in the use of individual therapies *(9)*. The impact of this concern is tempered, however, by our primary focus on the initial decision to use any curative treatment. Finally, we recognize that our ability to draw concrete conclusions regarding the "right rate" of expectant management is limited by an absence, in SEER public-use data, of detailed patient-level information regarding cancer severity, health status, life expectancy, and treatment preferences *(35,71)*.

Early local therapy remains common, and our findings suggest that its incidence may actually have increased since the early PSA era, among men with lower-risk prostate cancers. Given the substantial body of evidence supporting expectant management as an evidence-based option for the initial treatment of men with lower-risk prostate cancers, our data highlight the need to better define potential catalysts and barriers to the use of initial expectant management among carefully selected patients with newly diagnosed prostate cancer. Indeed, greater attention to the factors that influence the use of expectant management among men with lower-risk prostate cancer is essential insofar as initial patient counseling and shared decision making mark the most important role that physicians play during the course of caring for patients with localized prostate cancer. In our view, if the treatment decision is inappropriate for an individual patient, then, no matter how skillfully surgery is performed or radiation is delivered, it is poor-quality treatment. For this reason, efforts to reduce overtreatment should be a clinical and public health priority.

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NOTES

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