Research Article

Cancer Epidemiology, Biomarkers & Prevention

Overtreatment and Cost-Effectiveness of the See-and-Treat Strategy for Managing Cervical Precancer

Van T. Nghiem[1,2], Kalatu R. Davies[2], J. Robert Beck[3], Michele Follen[4], and Scott B. Cantor[2]

Abstract

Background: See-and-treat using loop electrosurgical excision procedure (LEEP) has been recommended as an alternative in managing high-grade cervical squamous intraepithelial lesions, but existing literature lacks evidence of the strategy's cost-effectiveness. We evaluated the overtreatment and cost-effectiveness of the see-and-treat strategy compared with usual care.

Methods: We modeled a hypothetical cohort of 40-year-old females who had not been screened for cervical cancer and followed them through their lifetimes using a Markov model. From a U.S. health-system perspective, the analysis was conducted in 2012 dollars and measured effectiveness in quality-adjusted life-years (QALY). We estimated incremental cost-effectiveness ratios (ICER) using a willingness-to-pay threshold of $50,000/QALY. The robustness of the see-and-treat strategy's cost-effectiveness and its overtreatment rates were further examined in various sensitivity analyses.

Results: In the base-case, the see-and-treat strategy yielded an ICER of $70,774/QALY compared with usual care. For most scenarios in the deterministic sensitivity analysis, this strategy had ICERs larger than $50,000/QALY, and its cost-effectiveness was sensitive to the disutility of LEEP treatment and biopsy-directed treatment adherence under usual care. Probabilistic sensitivity analysis showed that the see-and-treat strategy had a 50.1% chance to be cost-effective. It had an average overtreatment rate of 7.1% and a 78.8% chance to have its overtreatment rate lower than the 10% threshold.

Conclusion: The see-and-treat strategy induced an acceptable overtreatment rate. Its cost-effectiveness, compared with usual care, was indiscriminating at the chosen willingness-to-pay threshold but much improved when the threshold increased.

Impact: The see-and-treat strategy was reasonable for particular settings, that is, those with low treatment adherence. *Cancer Epidemiol Biomarkers Prev; 25(5); 807–14. ©2016 AACR.*

Introduction

Cervical cancer has been largely controlled in the United States with timely screening and early detection services. Despite such efforts, approximately 13,000 women would be newly diagnosed with cervical cancer in 2015. Expanded access to cervical cancer screening, increased human papillomavirus (HPV) vaccination, and identifying other missed opportunities (e.g., see-and-treat strategy) for early disease detection and treatment are needed to improve cervical cancer prevention. In usual practice, a woman with an abnormal result from the Papanicolaou smear test is referred for colposcopy-directed biopsy diagnosis and appropriate treatment: loop electrosurgical excision procedure (LEEP) for a finding of high-grade squamous intraepithelial lesions (HSIL) or surgery and radiation for a finding of cancer [the treatment protocol may be different for women younger than 25 years (1)]. However, there exist disparities in access to these programs among different groups of women. Multiple studies have found inadequate follow-up adherence (as low as 30% in certain populations) among patients with biopsy-proven high-grade cervical dysplasia (2, 3). In an attempt to overcome this nonadherence, the see-and-treat protocol was introduced in the mid-1990s as an alternative clinical strategy, that is, to perform a LEEP of the transformation zone when the colposcopic impression is suggestive of HSIL, at the same time of the colposcopy visit (4).

Recommendations for the see-and-treat strategy as a viable alternative for usual care are strengthened by several advantages. These include patients' saving of time and transportation, patient satisfaction (less anxiety and stress associated with medical visits), health care expense savings for reduced utilization of biopsies and other medical services, and improved treatment adherence. A key concern with this see-and-treat strategy centers on overtreatment when women are treated with LEEP, although their true (but unknown at the time) histologic findings are cervical intraepithelial neoplasia grade 1 (CIN-1) or normal (5). Previous studies have individually examined feasibility, efficiency, cost savings, or overtreatment of the see-and-treat protocol (3, 6, 7). However, a comprehensive assessment of this squamous intraepithelial lesion (SIL) management strategy has not been performed. In this study, we conducted an economic evaluation by examining

[1]Center for Health Promotion and Prevention Research, The University of Texas School of Public Health, Houston, Texas. [2]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas. [3]Cancer Prevention and Control Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania. [4]Department of Obstetrics & Gynecology, Brookdale University Hospital & Medical Center, Brooklyn, New York.

Corresponding Author: Scott B. Cantor, The University of Texas MD Anderson Cancer Center, Department of Health Services Research, Unit 1444, P.O. Box 301402, Houston, TX 77230-1402. Phone: 713-563-0020; Fax: 713-563-0059; E-mail: sbcantor@mdanderson.org

doi: 10.1158/1055-9965.EPI-15-1044

the cost-effectiveness of the see-and-treat strategy compared with usual care and estimated the overtreatment rate of the see-and-treat strategy in the U.S. setting.

Materials and Methods

Decision-analytic model

A state-transition Markov model was used to simulate the natural history of HPV infection and the potential development into cervical precursors and cancer; we previously used this model to compare DNA ploidy analysis and liquid-based cytology for cervical screening (8). The model included the following health states: well, benign hysterectomy, undetected HPV, detected HPV, low-grade squamous intraepithelial lesions, HSIL, unknown cancer (stages I–IV), detected cancer (stages I–IV), cancer survivor (stages I–IV), death from cervical cancer, and death from other causes. We derived estimates of HPV vaccine uptake and efficacy (9), the regression and progression through the precancerous stages, age-specific HPV prevalence and incidence rates, and the age-adjusted mortality rates from the literature (8, 10). The operating characteristics of the Papanicolaou smear test were updated on the basis of the findings by Goldie and colleagues (11). We built our model with a cycle length of one year. Further details of this model were published previously (8).

Effectiveness

In this study, we estimated the effectiveness in quality-adjusted life-years (QALY), which is a composite measure for both quality of life and survival of the study population. We assigned a value of 1 for perfect health and 0 for death (12). We also adjusted the effectiveness by age and health state (13). A short-term disutility for the LEEP treatment was assumed to be 0.01 QALY and was varied during the sensitivity analyses.

Costs

We derived cost inputs from both claims and secondary data sources that estimated health care expenses for cervical cancer screening, diagnosis, and treatment. Claim databases included MarketScan for a privately insured young population (ages 20–64 years) and Medicare for a publicly insured senior population (ages 65 years or older; refs.14, 15). We used the consumer price index (medical component) to transform our costs to 2012 U.S. dollars (15).

Overtreatment in the see-and-treat strategy

One of our concerns was whether this SIL management protocol induced an acceptable overtreatment rate (5, 7). In our study, we defined an occurrence of overtreatment when LEEP was performed on a woman with a true histologic finding of CIN-1 or normal. Most commonly, in usual practice, LEEP treatment was justified with respect to a lack of agreement between cytologic interpretations and histologic results, for example, when the cytologic finding was HSIL and the histologic result was CIN-1 or normal. In such cases, physicians may believe that LEEP treatment is appropriate because they believe a certain percentage of patients may have disease and "might be missed" (16).

Accuracy of colposcopy

As colposcopy served as a basis for the clinical decision in the see-and-treat protocol, our study attempted to acquire precise testing characteristics of colposcopy from a clinical trial (17, 18). On the basis of the collected data, we recalculated the point estimates and plausible ranges for the diagnostic abilities of colposcopy among women with previous abnormal cytologic findings (Table 1).

Assumptions

Our model included the following key assumptions: (i) women underwent the triennial screening with liquid-based Papanicolaou smear test as recommended by the U.S. Preventive Services Task Force (we opted for Papanicolaou smear test over other screening methods to simplify the modeling process and because this test has remained common in the U.S. setting; ref.19); (ii) for both of the management protocols, women could only have LEEP and other medical services, including follow-up diagnostic tests and treatments, in the same year they experienced the Papanicolaou smear test; (iii) colposcopy had perfect diagnostic ability to identify patients with a true health state of cancer (12); (iv) and under usual care, 50% of patients with an abnormal histologic finding failed to adhere to recommended treatment follow-ups. This value was chosen based on a wide range of treatment adherence reported in previous studies (2, 20, 21).

Table 1. Parameters for sensitivity analyses

Parameter	Mean	Plausible range	Distribution	Source
Testing operating characteristics				
Papanicolaou smear, sensitivity	0.84	0.69–0.88	Beta	(11)
Papanicolaou smear, specificity	0.88	0.77–0.93	Beta	(11)
Colposcopy, probability of normal result given normal histology	0.57	0.51–0.62	Beta	(17)
Colposcopy, probability of LSIL result given CIN-1 histology	0.48	0.40–0.55	Beta	(17)
Colposcopy, probability of HSIL result given CIN-2 histology	0.71	0.65–0.77	Beta	(17)
Treatment parameters				
Treatment adherence after a biopsy positive for HSIL	50%	30%–90%	Beta	(20, 2)
Loss of quality of life from LEEP treatment (QALY)	0.01	0.00–0.04	Beta	Estimate
Costs (2012 US$)				
Colposcopy	$292	$206–$371	Log-normal	(8)
Biopsy	$322	$227–$408	Log-normal	(8)
Papanicolaou smear	$88	$44–$252	Gamma	(11)
Treating HSIL	$4,996	$2,268–$6,887	Log-normal	(10)
Treating cancer stage I	$28,914	$15,467–$35,962	Log-normal	(10)
Treating cancer stage II	$44,357	$19,228–$47,667	Log-normal	(10)
Treating cancer stage III	$44,357	$19,228–$47,667	Log-normal	(10)
Treating cancer stage IV	$66,006	$20,762–$76,213	Log-normal	(10)

Abbreviation: LSIL, low-grade squamous intraepithelial lesions.

Target population

The target population for this study is one that might be seen in a colposcopy clinic, a sample of women who would be at elevated risk of cervical cancer. We artificially created a cohort of 40-year-old females at elevated risk by hypothetically simulating a cohort of 12-year-old females through the age of 40 without screening in a published validated model (8). At the end of this simulation, we obtained a distribution of "true" health states for these women, some of whom were infected with HPV, some who had developed SIL, and most who had not developed HPV or SIL. This heterogeneous disease-state cohort then entered our analytic model from the age of 40 and was followed throughout their lifetimes.

HSIL management with the see-and-treat protocol

We compared two management strategies for cervical precancer diagnosed after an abnormal Papanicolaou smear result and follow-up colposcopy procedure. In the usual care strategy, biopsy provides a confirmatory diagnosis 2 to 3 weeks after the diagnostic visit; patients would return to the clinic for treatment if there was histologically confirmed HSIL. In the alternative see-and-treat strategy, immediate treatment would occur at the colposcopy visit if the colposcopic impression was HSIL or worse. For both strategies, if cancer was found, subsequent clinical management with surgery and/or radiation would follow.

Analysis

We conducted the analysis from a U.S. health-system perspective. A discount rate of 3% was applied for both cost and effectiveness measures. In the base-case, we estimated and compared the total costs and total effectiveness of the two strategies. Our primary outcome measure was based on the calculation of the incremental cost-effectiveness ratios (ICER) of the see-and-treat strategy compared with usual care. In this study, we used a given willingness-to-pay threshold of $50,000/QALY to deem a strategy to be cost-effective.

In sensitivity analyses, we explored the potential impact of key parameters on the calculated ICER. These parameters included costs for the screening and diagnostic procedures, treatment costs, the operating characteristics of the Papanicolaou smear test and colposcopy, treatment adherence after a biopsy finding in usual care, and the disutility from LEEP treatment. These chosen parameters were varied individually in one-way sensitivity analyses. We also investigated the parameters' threshold values that switched the cost-effectiveness decision for the see-and-treat strategy at the willingness-to-pay threshold of $50,000/QALY. The simultaneous effect of the biopsy-directed treatment adherence in usual care and the disutility of LEEP treatment on the cost-effectiveness of the see-and-treat strategy were examined in a two-way sensitivity analysis. In this case, the biopsy-directed treatment adherence changed among 30%, 50%, and 90%. The disutility of LEEP treatment was varied between 0 and 0.04 QALY at increments of 0.01 QALY.

We ran 100,000 iterations in the probabilistic sensitivity analysis to examine the robustness of the cost-effectiveness of the see-and-treat strategy. Cost-effectiveness acceptability curves were used to compare this strategy with usual care across a wide range of willingness-to-pay thresholds, from $0 to $150,000 per QALY. We fit beta distributions on Papanicolaou smear testing characteristics, colposcopic probabilities, the biopsy-directed treatment adherence, and the disutility of LEEP treatment. We incorporated in the model the inverse correlation among colposcopic probabilities of normal and abnormal outcomes. Cost data followed either log-normal or gamma distributions as described previously (8).

For each of the two strategies, we estimated the probability that a 40-year-old woman would experience LEEP treatment in her lifetime. We ran 10,000 microsimulations to predict the probability to be treated with LEEP. Finally, we estimated the overtreatment rate of the see-and-treat protocol based on the number of LEEP treatments on women with a confirmed histologic diagnosis of CIN-1 or normal.

We implemented two-dimensional Monte Carlo simulations to estimate the probabilities that the see-and-treat strategy obtained an overtreatment rate lower than a range of overtreatment thresholds, from 0% to 15%. These simulations were comprised of probabilistic sensitivity analyses and microsimulations in a hypothetical cohort of 10,000 forty-year-old females throughout their lifetimes. Selected variables for these simulations were similar to those in the aforementioned probabilistic sensitivity analysis. We ran 10,000 iterations for the probabilistic sensitivity analysis. Within each of these iterations, we implemented 500 separate runs for the microsimulation.

We also varied the number of LEEP overtreatments to examine the harm-and-benefit tradeoff (presented by the number of overtreatments vs. the number of QALYs gained) in scenario analyses. Within the see-and-treat strategy, we varied the proportion of women who followed the see-and-treat protocol (with the remaining following usual care). The scenario analyses were performed by the aforementioned method of two-dimensional Monte Carlo simulations. Throughout these scenario analyses, usual care remained as the comparator.

We programmed our model and analyzed the data in TreeAge Pro 2015 software (TreeAge Software Inc).

Our decision-analytic simulation study was deemed exempt from human subject review because it only used previously published sources, and data were not obtained through intervention or interaction with individuals or included identifiable private information.

Results

Base-case

Compared with usual care, the see-and-treat strategy increased the quality-adjusted life expectancy by 0.006 QALY at an additional cost of $417. Overall, the see-and-treat strategy yielded an ICER of $70,774/QALY compared with usual care. At our given willingness-to-pay threshold of $50,000/QALY, the see-and-treat strategy was not cost-effective (Table 2).

Table 2. Discounted costs, discounted quality-adjusted life expectancy, and incremental cost-effectiveness ratio for the base-case analysis (assuming biopsy-directed treatment adherence of 50%)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ($/QALY)
Usual care	$1,276	—	17.943	—	—
See-and-treat	$1,692	$417	17.949	0.006	$70,774

Deterministic sensitivity analysis

We explored the robustness of the see-and-treat strategy's ICERs compared with usual care by varying each of the variables individually within their plausible ranges. We set the biopsy-directed treatment adherence in usual care at a fixed value of 50% and the disutility of LEEP treatment at 0.01 QALY. For most of the scenarios, the see-and-treat strategy had ICERs larger than $50,000/QALY. Lowering the cost of LEEP treatment to $3,819 or less or increasing the specificity of the Papanicolaou smear test to over 90.9% would result in reduced ICERs for the see-and-treat strategy and make it cost-effective. When the disutility of LEEP treatment was set at 0.01, varying the biopsy-directed treatment adherence in usual care was also influential to the cost-effectiveness of the see-and-treat strategy. When the treatment adherence was less than 36%, the see-and-treat strategy had ICERs less than the willingness-to-pay threshold.

We next performed a two-way sensitivity analysis by varying the biopsy-directed treatment adherence and the disutility of LEEP treatment. This analysis was demonstrated in twelve scenarios, of which the see-and-treat strategy was only cost-effective when the treatment compliance was the lowest (30%) and LEEP treatment resulted in a disutility of 0.01 or did not affect the quality-adjusted life expectancy at all (disutility of LEEP treatment equal to 0 QALY). In the remaining scenarios, compared with usual care, either the ICERs of the see-and-treat strategy were larger than $50,000 (up to $423,433) per QALY or this strategy was dominated by usual care. Table 3 shows that the ICERs of the see-and-treat strategy increased when the biopsy-directed treatment adherence in usual care increased or when the disutility of LEEP treatment increased.

At the willingness-to-pay threshold of $50,000/QALY, the see-and-treat strategy was not cost-effective in the deterministic sensitivity analyses.

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, the proportion of the iterations for which each strategy had the highest net benefit determined the cost-effectiveness probability. The probability of the see-and-treat strategy increased when the willingness-to-pay threshold increased. At the given threshold of $50,000/QALY, the see-and-treat strategy had a slightly better chance (50.1%) to be cost-effective compared with usual care. However, the probability of the see-and-treat strategy being cost-effective would substantially increase to 78.1% when the willingness-to-pay threshold reached $100,000/QALY (Fig. 1).

Overtreatment in the see-and-treat strategy

As expected, our model predicted a comparatively higher rate of LEEP treatment for the see-and-treat strategy than the rate for usual care. During their lifetimes, one sixth [16.6%; 95% confidence interval (CI), 15.7%–17.5%) of the women following the see-and-treat protocol would have undergone LEEP treatment. Meanwhile, only 5.8% (95% CI, 5.3%–6.3%) of the women given usual care would have undergone LEEP treatment.

The overtreatment rate under the see-and-treat management was 7.1% (95% CI, 6.5%–7.6%). On the basis of the two-dimensional Monte Carlo simulations, the see-and-treat strategy was determined to have a probability of 78.8% of having its overtreatment rate be lower than the 10% threshold as recommended by the Cochrane Colposcopy and Cervical Cytopathology Collaborative and the U.S. Standards and Quality in Colposcopy (Fig. 2; refs.5, 22).

Harm-and-benefit tradeoff

We presented the harm-and-benefit tradeoff with average estimates for the hypothetical cohort of 10,000 females in Fig. 3. We found a positive relationship between the number of overtreatments and the number of QALYs gained from the see-and-treat strategy compared with usual care. The higher the proportion of females within the see-and-treat strategy actually following the see-and-treat protocol, the more LEEP overtreatments the see-and-treat strategy incurred, and consequently, the higher QALYs the see-and-treat strategy would be obtained in the see-and-treat strategy in comparison with usual care. Approximately, after the proportion of females within the see-and-treat strategy actually following the see-and-treat protocol reached 50% or after the number of LEEP overtreatments reached 391, the marginal QALYs gained of the see-and-treat strategy compared with usual care was decreasing if the number of overtreatments continued to increase.

Discussion

This study of the see-and-treat strategy for cervical cancer diagnostic patients is, to our knowledge, based on a MEDLINE literature review, the first attempt to summarize the literature regarding this treatment strategy with a cost-effectiveness analysis. Previously, in 1999, a resource utilization analysis was performed; however, that article did not include details on the clinical effectiveness of the strategies (2). Another study included a cost-effectiveness analysis, but in that study, the outcome measure was evaluated in terms of cost per case of cervical precancer detected (23). Our study's approach, by using the clinical outcome measure of QALYs, is preferred by guidelines of economic evaluation (24). Furthermore, by employing a microsimulation analysis method, we were able to follow individual patient outcomes and provide an estimate of the percentage of patients who would be overtreated using this strategy.

In our study, the see-and-treat strategy was more costly than usual care. This finding contradicted previous studies from the late 1990s (2, 23). In our analysis, the cost savings from reduced utilization of biopsy were outweighed by the cost of the

Table 3. Cost-effectiveness analysis of the see-and-treat strategy compared with usual care in two-way sensitivity analyses (with respect to biopsy-directed treatment adherence and disutility of LEEP treatment)

	ICER ($/QALY)		
Disutility of LEEP treatment	**Biopsy-directed treatment adherence = 30%**	**Biopsy-directed treatment adherence = 50%**	**Biopsy-directed treatment adherence = 90%**
0 QALY	$38,077	$56,210	$423,433
0.01 QALY	$44,313	$70,774[a]	Dominated
0.02 QALY	$52,992	$95,526	Dominated
0.03 QALY	$65,900	$146,899	Dominated
0.04 QALY	$87,120	$317,822	Dominated

[a]Base-case

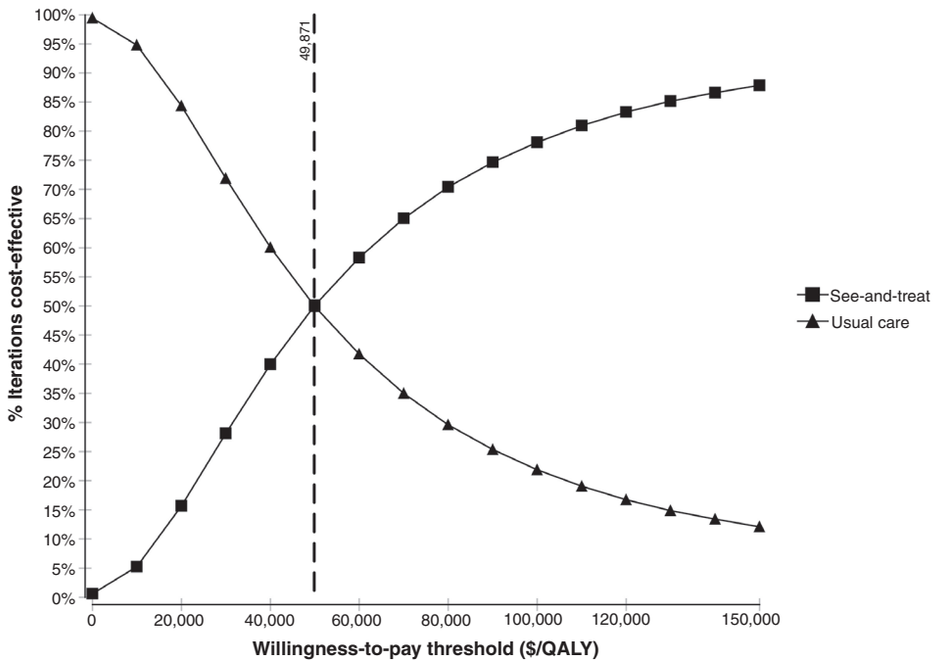

Figure 1.
Cost-effectiveness acceptability curves compared the see-and-treat strategy with usual care. At the given willingness-to-pay threshold of $50,000/QALY, the see-and-treat strategy had 50.1% chance of being cost-effective.

additional LEEP treatments, as expected by Monteiro and colleagues (4). Using the standard willingness-to-pay threshold of $50,000/QALY (25), our results show that the see-and-treat strategy is not cost-effective compared with usual care. The sensitivity analysis, in which treatment compliance was varied, revealed that the see-and-treat strategy had the potential to be cost-effective if treatment compliance was less than 36%. In addition, the overtreatment rate under the see-and-treat management strategy was estimated to be 7.1%, low in comparison to the overtreatment standard of 10% recommended by the Cochrane Colposcopy and Cervical Cytopathology Collaborative and the U.S. Standards and Quality in Colposcopy (5, 22). The see-and-treat strategy also performed well against this overtreatment threshold, obtaining a 78.8% chance to have its overtreatment rate lower than 10%. In the probabilistic sensitivity analysis, the see-and-treat strategy had a 50.1% probability of being

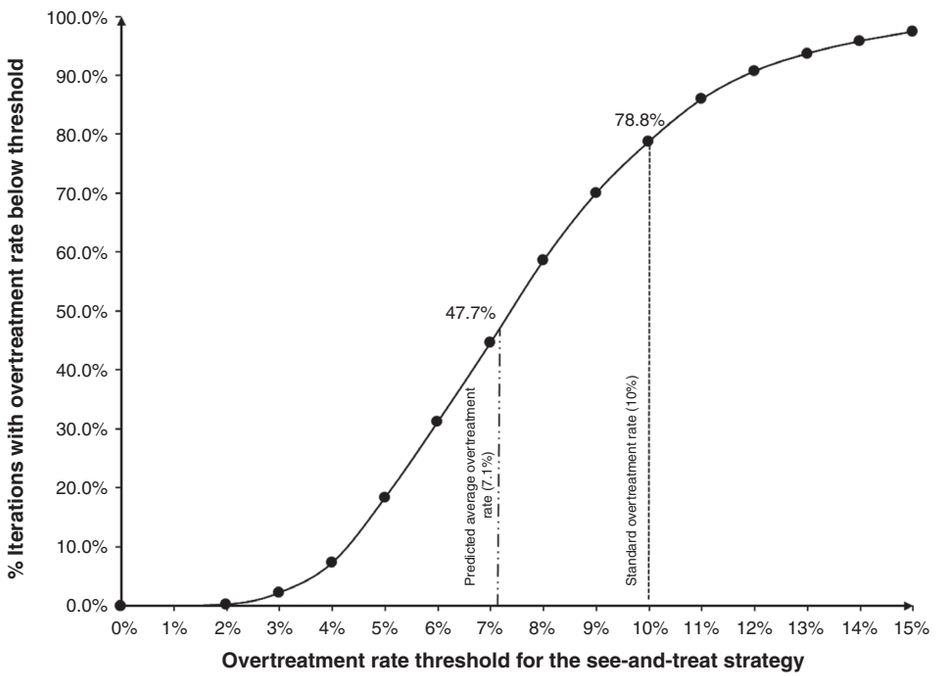

Figure 2.
Overtreament acceptability curve demonstrated the proportion of simulations when the see-and-treat strategy yielded a number of overtreatments below the given threshold. The *x*-axis showed potential thresholds for overtreatment. The rate of 10% is the standard threshold recommended by the Cochrane Colposcopy and Cervical Cytopathology Collaborative and the U.S. Standards and Quality in Colposcopy (5, 22). The see-and-treat strategy obtained a 78.8% chance to have an overtreatment rate lower than 10%.

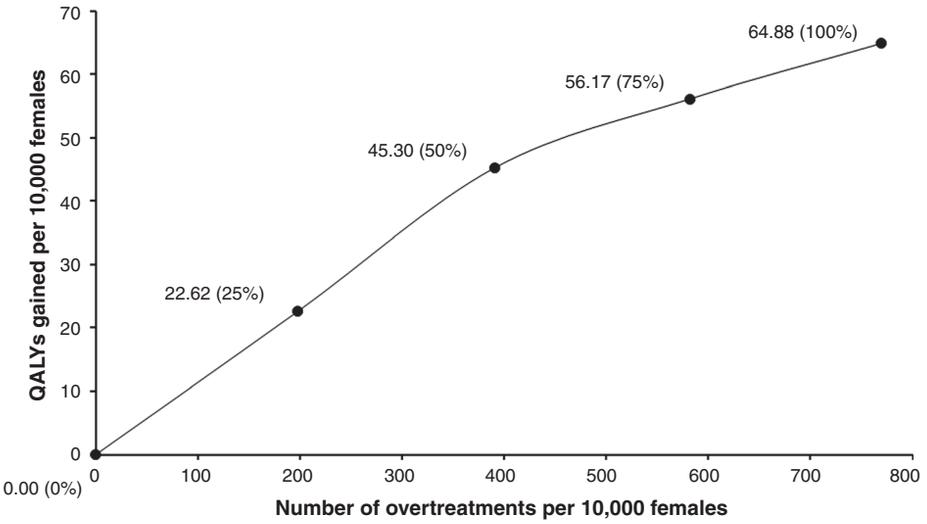

Figure 3.
Harm-and-benefit tradeoff curve compared the see-and-treat strategy with various proportions of females following the see-and-treat protocol (in parentheses) with usual care. There was a positive relationship between the number of QALYs gained and the number of overtreatments in the see-and-treat strategy compared with usual care in a cohort of 10,000 forty-year-old females. Note: 0% represents usual care and 100% represents the see-and-treat strategy.

cost-effective under the aforementioned threshold. With this type of analysis, influential variable values, including treatment compliance, are drawn from a distribution of possible values. These indiscriminating results are thus indicative of a wide range of reported patient compliance levels (2, 20, 21, 26) and estimates of the overtreatment rate (5, 7, 27).

Given the indiscriminate economic evaluation results, our study offered an alternative analysis approach, the harm-and-benefit tradeoff curve, to examine the performance of the see-and-treat strategy compared with usual care. We expect this approach would be helpful to clinicians, policy makers, and those who are not familiar with using economic willingness-to-pay thresholds in justifying certain medicinal decisions. The harm-and-benefit tradeoff is a proxy for resource allocation (28) that provided a rough estimate of the potential health benefits gained (QALYs gained) at the expense of the harm (LEEP overtreatments). With this analysis approach, individual decision makers can be provided a choice of cut-off points for the harm-and-benefit tradeoff as their rationale on the issue may differ significantly.

As noted previously (14), to conduct our analysis, we adapted an earlier published model for cervical cancer screening (10). Thus, similar to most decision analyses, ours is not without limitations. However, we amended the model to better mirror the current standard of care by incorporating utilities, diagnostic test operating characteristics, and the standard diagnostic protocols based on the recent literature. At this time, other management strategies, such as "see-and-treat Pap," in which treatment is based on the results of the Papanicolaou smear (29), have not been considered. We implemented a simple model structure to focus on the comparison of the see-and-treat strategy with the current standard of care. The see-and-treat strategy eliminated one medical visit and consequently saved transportation efforts and time of patient and caregivers. We opted for the health-system perspective, which may have underestimated the economic advantage of this strategy by not incorporating the patient time cost. Although we made a careful estimation for the short-term disutility of LEEP treatment, we did not account for long-term adverse health outcomes, for example, infertility and preterm delivery (30). However, our study focused on the 40-year-old female cohort, and these patients possibly would have a completed family or would soon depart the childbearing age (31); thus, the consideration of only short-term disutility of LEEP treatment was justifiable.

Mathematical models may assist clinical decision making by assessing new technologies and treatment strategies. In this study, we have utilized cost-effectiveness analysis to determine when the see-and-treat strategy may be optimal. We simulated a diagnostic population that one might see in a colposcopy clinic by running the model, beginning at age 12 years to age 40 years, without incorporating any cervical screening, resulting in a diagnostic cohort of 40-year-old women. In addition, inherent in our study design, our model estimates the consequences of overtreatment (incorporating costs and some burden of treatment). Although the results showed that the see-and-treat strategy is not cost-effective in the base-case analysis, the 50% compliance level was chosen somewhat arbitrarily, given the wide reported range. By methodically varying the compliance level and disutility of LEEP treatment, our decision model revealed that the see-and-treat strategy may be optimal in low-compliance settings, with minimal disutility associated with treatment.

Given that the usual care strategy is the widely accepted standard in the United States, a see-and-treat strategy would not be implemented. However, as reducing the burden of cervical cancer in lower resource settings has taken greater priority in recent years, a see-and-treat strategy may be feasible where treatment compliance is low (5, 32). Despite the overtreatment rate, this approach has been accepted for underserved communities internationally (2, 5, 26, 27, 33, 34). Nevertheless, our study findings are based on a U.S. framework and cannot be directly applied to additional settings without determining the epidemiology of cervical cancer and its management in a particular population.

Cervical cancer is often a leading cause of cancer mortality in limited resource settings, which typically do not adhere to the current standard of care (33). With this comparison of the see-and-treat approach to the usual standard of care, we conclude that a see-and-treat strategy is only cost-effective when compliance with the usual standard of care and disutility of LEEP treatment are low. Thus, in those particular settings, a see-and-treat strategy may be a reasonable alternative.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute (NCI) or the National Institutes of Health (NIH).

Authors' Contributions

Conception and design: V.T. Nghiem, K.R. Davies, M. Follen, S.B. Cantor
Development of methodology: V.T. Nghiem, K.R. Davies, J.R. Beck, S.B. Cantor
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): V.T. Nghiem, S.B. Cantor
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V.T. Nghiem, K.R. Davies, J.R. Beck, M. Follen, S.B. Cantor
Writing, review, and/or revision of the manuscript: V.T. Nghiem, K.R. Davies, J.R. Beck, M. Follen, S.B. Cantor
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.B. Cantor
Study supervision: S.B. Cantor

Acknowledgments

The authors thank Sunita C. Patterson for editorial contributions and Rana Banton for administrative assistance.

Grant Support

This study was funded in part by grant numbers P01 CA082710 (to S.B. Cantor, K.R. Davies, and M. Follen) and P30 CA006927 (to J.R. Beck) from the NCI/NIH. V.T. Nghiem was supported by a predoctoral fellowship from the Cancer Education and Career Development Program (NCI/NIH grant number R25 CA057712) and research funding from the Center for Health Promotion and Prevention Research at the University of Texas School of Public Health.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 5, 2015; revised February 11, 2016; accepted February 15, 2016; published OnlineFirst February 29, 2016.

References

1. American College of Obstetricians and Gynecologists. Practice Bulletin No. 140: Management of abnormal cervical cancer screening test results and cervical cancer precursors. Obstet Gynecol 2013;122:1338–67.
2. Holschneider CH, Ghosh K, Montz FJ. See-and-treat in the management of high-grade squamous intraepithelial lesions of the cervix: a resource utilization analysis. Obstet Gynecol 1999;94:377–85.
3. Irvin WPJr, Andersen WA, Taylor PTJr, Stoler MH, Rice LW. "See-and-treat" loop electrosurgical excision. Has the time come for a reassessment? J Reprod Med 2002;47:569–74.
4. Monteiro AC, Russomano F, Reis A, Camargo MJ, Fialho SA, Tristao MA, et al. Effectiveness of see-and-treat for approaching pre-invasive lesions of uterine cervix. Rev Saude Publica 2009;43:846–50.
5. Cardenas-Turanzas M, Follen M, Benedet JL, Cantor SB. See-and-treat strategy for diagnosis and management of cervical squamous intraepithelial lesions. Lancet Oncol 2005;6:43–50.
6. Fung HY, Cheung LP, Rogers MS, To KF. The treatment of cervical intraepithelial neoplasia: when could we 'see and loop'. Eur J Obstet Gynecol Reprod Biol 1997;72:199–204.
7. Bosgraaf RP, Mast PP, Struik-van der Zanden PH, Bulten J, Massuger LF, Bekkers RL. Overtreatment in a see-and-treat approach to cervical intraepithelial lesions. Obstet Gynecol 2013;121:1209–16.
8. Nghiem VT, Davies KR, Beck JR, Follen M, MacAulay C, Guillaud M, et al. Economic evaluation of DNA ploidy analysis vs liquid-based cytology for cervical screening. Br J Cancer 2015;112:1951–7.
9. Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13–17 years - United States, 2012. MMWR Morb Mortal Wkly Rep 2013;62:685–93.
10. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol 2000;151:1158–71.
11. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96:604–15.
12. Sawaya GF, Smith-McCune KK. Global library of women's medicine [updated 2010]. Available from: http://www.glowm.com/section_view/heading/Colposcopy/item/19#r2.
13. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13:28–41.
14. McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, et al. Evaluation of cervical cytology, summary. Evidence report/technology assessment . Rockville, MD: Agency for Healthcare Research and Quality; 1999.
15. The Council of Economic Advisers. Economic Report of the President. Washington, DC: U.S. Government Printing Office; 2013.
16. Moss EL, Moran A, Douce G, Parkes J, Todd RW, Redman CW. Cervical cytology/histology discrepancy: a 4-year review of patient outcome. Cytopathology 2010;21:389–94.
17. Cantor SB, Cardenas-Turanzas M, Cox DD, Atkinson EN, Nogueras-Gonzalez GM, Beck JR, et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. Obstet Gynecol 2008;111:7–14.
18. Davies KR, Cantor SB, Cox DD, Follen M. An alternative approach for estimating the accuracy of colposcopy in detecting cervical precancer. PLoS One 2015;10:e0126573.
19. Agency for Healthcare Research and Quality. Screening for cervical cancer: clinical summary of U.S. Preventive Services Task Force Recommendation. Available from: http://www.uspreventiveservicestaskforce.org/uspstf11/cervcancer/cervcancersum.htm.
20. Benard VB, Howe W, Royalty J, Helsel W, Kammerer W, Richardson LC. Timeliness of cervical cancer diagnosis and initiation of treatment in the National Breast and Cervical Cancer Early Detection Program. J Womens Health 2012;21:776–82.
21. Hartz LE, Fenaughty AM. Management choice and adherence to follow-up after colposcopy in women with cervical intraepithelial neoplasia 1. Obstet Gynecol 2001;98:674–9.
22. Aue-Aungkul A, Punyawatanasin S, Natprathan A, Srisomboon J, Kietpeerakool C. "See and treat" approach is appropriate in women with high-grade lesions on either cervical cytology or colposcopy. Asian Pac J Cancer Prev 2011;12:1723–6.
23. Cantor SB, Mitchell MF, Tortolero-Luna G, Bratka CS, Bodurka DC, Richards-Kortum R. Cost-effectiveness analysis of diagnosis and management of cervical squamous intraepithelial lesions. Obstet Gynecol 1998;91:270–7.
24. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276:1172–7.
25. Weinstein MC. How much are Americans willing to pay for a quality-adjusted life year? Med Care 2008;46:343–5.
26. Spitzer M, Chernys AE, Seltzer VL. The use of large-loop excision of the transformation zone in an inner-city population. Obstet Gynecol 1993;82:731–5.
27. Srisuwan S, Hamontri S, Kongsomboon K, Bhamarapravatana K, Suwannarurk K. See-and-treat approach to cervical intraepithelial lesions in HRH Princess Maha Chakri Sirindhorn Medical Center. Asian Pac J Cancer Prev 2014;15:3483–6.
28. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:659–69.

29. Meirovitz M, Gatt D, Dreiher J, Shaco-Levy R. Uterine cervix conization based on Pap smear results: the "see and treat" approach. Isr Med Assoc J 2014;16:303–6.
30. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006;367:489–98.
31. Bosgraaf RP, Mast PP, Struik-van der Zanden PH, Bulten J, Massuger LF, Bekkers RL. In reply. Obstet Gynecol 2013;122:1304–5.
32. Arbyn M, Castellsague X, de Sanjose S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675–86.
33. Chigbu CO, Onyebuchi AK. See-and-treat management of high-grade squamous intraepithelial lesions in a resource-constrained African setting. Int J Gynaecol Obstet 2014;124:204–6.
34. Nogara PR, Manfroni LA, Consolaro ME. Frequency of cervical intraepithelial neoplasia grade II or worse in women with a persistent low-grade squamous intraepithelial lesion seen by Papanicolaou smears. Arch Gynecol Obstet 2013;288:1125–30.