Overtreatment and cost-effectiveness of the see-and-treat strategy for managing cervical precancer

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Running title: Cost-effectiveness of see-and-treat

Keywords: Cost-effectiveness analysis, cervical cancer, cervical intraepithelial lesions, screening, diagnosis

Financial support: This study was funded in part by grant numbers P01 CA082710 (S.B. Cantor, K.R. Davies, M. Follen) and P30 CA006927 (J.R. Beck) from the National Cancer Institute/National Institutes of Health (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.

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There are no potential conflicts of interest.

Word count: 3504, number of tables: 3, number of figures: 3
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 evaluate 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 (QALYs). We estimated incremental cost-effectiveness ratios (ICERs) 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 to 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, i.e. those with low treatment adherence.
INTRODUCTION

Cervical cancer has been largely control 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 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 non-adherence, the see-and-treat protocol was introduced in the mid-1990s as an alternative clinical strategy, i.e., 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), healthcare 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) histological 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 the present study, we conducted an economic evaluation by examining 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 (LSIL), 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 based on 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 (QALYs), 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 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 healthcare expenses for cervical cancer screening, diagnosis, and treatment. Claim databases included MarketScan for a privately insured young population (aged 20-64 years) and Medicare for a publicly insured senior population (aged 65 years or older) (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 histological finding of CIN-1 or normal. Most commonly, in usual practice, LEEP treatment was justified with respect to a lack of agreement between cytological interpretations and histological results, e.g., when the cytological finding was HSIL and the histological 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

Since 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). Based on the collected data, we recalculated the point estimates and plausible ranges for the diagnostic abilities of colposcopy among women with previous abnormal cytological findings (Table 1).

Assumptions

Our model included the following key assumptions: 1) 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) (19); 2) 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; 3) colposcopy had perfect diagnostic ability to identify patients with a true health state of cancer (12); and under usual care, 50% of patients with an abnormal histological 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).

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 analytical 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 2-3 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 were 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 (ICERs) 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 amongst 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 histological 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 versus 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., Williamstown, MA).

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).

**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 (Figure 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%). Based on 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 (5, 22) (Figure 2).
Harm-and-benefit tradeoff

We present the harm-and-benefit tradeoff with average estimates for the hypothetical cohort of 10,000 females in Figure 3. We found a positive relationship between the number of overtreatments and the number of QALYs gained of the see-and-treat strategy compared to 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 to 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 paper 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 quality-adjusted life years, 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 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 to 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 for 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 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 to 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 cutpoints 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, e.g., 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. Additionally, inherent in our study design, our model estimates the consequences of overtreatment (incorporating costs and some burden of treatment). While 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.
ACKNOWLEDGEMENTS

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

DISCLAIMER

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


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<td>Papanicolaou smear, sensitivity</td>
<td>0.84</td>
<td>0.69 – 0.88</td>
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<td>Papanicolaou smear, specificity</td>
<td>0.88</td>
<td>0.77 – 0.93</td>
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<td>Colposcopy, probability of normal result given normal histology</td>
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<td>0.51 – 0.62</td>
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<td>Colposcopy, probability of LSIL result given CIN-1 histology</td>
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<td><strong>Treatment parameters</strong></td>
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<td>Treatment adherence after a biopsy positive for HSIL</td>
<td>50%</td>
<td>30% – 90%</td>
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<td>Loss of quality of life from LEEP treatment (QALY)</td>
<td>0.01</td>
<td>0.00 – 0.04</td>
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<td>Estimate</td>
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<td>$292</td>
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<td>$44 – $252</td>
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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%)

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<th>Strategy</th>
<th>Cost</th>
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<th>Incremental effectiveness (QALYs)</th>
<th>ICER ($/QALY)</th>
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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)

<table>
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<tr>
<th>Disutility of LEEP treatment</th>
<th>Biopsy-directed treatment adherence = 30%</th>
<th>Biopsy-directed treatment adherence = 50%</th>
<th>Biopsy-directed treatment adherence = 90%</th>
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<td>0 QALY</td>
<td>$38,077</td>
<td>$56,210</td>
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<td>Dominated</td>
</tr>
</tbody>
</table>

*: Base-case

LEEP: loop electrosurgical excision procedure, ICER: incremental cost-effectiveness ratio.
FIGURE LEGENDS

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.

Figure 2. Overtreatment 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 quality-adjusted life years (QALYs) gained and the number of overtreatments in the see-and-treat strategy compared to 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.
Figure 2

% iterations with overtreatment rate below threshold

Overtreatment rate threshold for the see-and-treat strategy

- Average overtreatment rate (7.1%)
- Standard overtreatment rate (10%)

- 47.7%
- 78.8%
Overtreatment and cost-effectiveness of the see-and-treat strategy for managing cervical precancer


Cancer Epidemiol Biomarkers Prev Published OnlineFirst February 29, 2016.

Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-15-1044

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