everyday practice, this is not feasible, and in only 12% of hospitals nationwide is there complete embedding of radical prostatectomy tissue.3 There are a number of viable approaches to routine measurement of tumor size in partially embedded radical prostatectomy specimens, including assessment of percentage carcinoma and maximum tumor size. Determination of percentage carcinoma is an approach that has been applied to needle biopsy tissue,4,5 transurethral resection of prostate (TURP) chips,6 and radical prostatectomy tissues.1,7 In needle biopsy tissue, percentage carcinoma has been linked to pathologic stage.4,5 In TURP chips, percentage of tissue involvement is central to staging of incidentally-detected prostatic carcinoma.8 In our studies, percentage carcinoma in radical prostatectomy tissues, assessed by a grid morphometric technique or visual inspection, has been related to progression and survival after surgery.7,9–11 The grid method is reproducible8 and may be more quantitative, but the visual inspection method is just as strongly linked to tumor volume and is related to clinical progression after surgery.7

We concur with Dr. Renshaw that prostate carcinoma size should be provided in radical prostatectomy specimen reports. Currently, the Association of Directors of Anatomic and Surgical Pathology recommends reporting tumor amount in radical prostatectomy specimens as “percentage of the prostate involved by carcinoma in relation to the weight of the specimen.”12 The College of American Pathologists (CAP) suggests the following: “In subtotal and radical prostatectomy specimens, the percentage of tissue involved by tumor can also be eyeballed. Additionally, in these latter specimens it may be possible to measure a dominant tumor nodule in at least two dimensions and to indicate the number of blocks involved by tumor over the total number of blocks submitted.”13 The CAP recommends, for protocol reporting on all prostatic tissues, that “at the very least, the proportion (percentage) of prostatic tissue involved by tumor be included for all specimens.”13

REFERENCES


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DOI 10.1002/cncr.10467

De Novo Establishment and Cost-Effectiveness of Papanicolaou Cytology Screening Services in the Socialist Republic of Vietnam

Suba et al.1 recently presented a study regarding the cost-effectiveness of cervical cytology screening services in Vietnam. We would like to congratulate the authors on helping to focus attention on the problem of cervical carcinoma. The purpose of this letter is to outline methodologic issues that make it difficult to generalize the study findings to other settings. It should be noted that a lack of transparency in the data presented and key assumptions of the model often made it difficult to evaluate the article’s findings.

As your readers know, cost-effectiveness analysis is used to inform the optimal resource allocation in
health program planning. To determine an accurate average or unit cost per health outcome, the cost and health outcome data used in an analysis must be accurate, comprehensive, and transparent. The study by Suba et al.\(^1\) appeared to be missing some important information. For example, on the effectiveness side, it was not clear what assumptions were used to establish the sensitivity and specificity of cytology, or ultimately what sensitivity and specificity values were used in the model. Available data regarding the sensitivity and specificity of cytology for detecting cervical dysplasia suggest that these values can vary widely from setting to setting.\(^2\)

On the cost side, the study includes the costs for personnel categories, disposable supplies and equipment, and space and overhead costs. However, the authors describe these categories in limited detail and fail to explain how salaries, prices, and quantities were aggregated to determine total program costs (and unit costs) for a nationwide program over a 10-year period. There were no tables or figures available to provide detailed information on the cost profiles for the different categories, making it very difficult to evaluate the validity of the final cost figures. Information concerning the total number of centers for primary screening and for cytology reading and the staged expansion of the program over 10 years was not given. More information regarding program implementation could help to evaluate whether the costs and outcomes of the program were valid.

Another apparent weakness is the omission of start-up costs. Full start-up costs to establish the program in Vietnam included both international and on-site training, yet these costs were not included in the analysis. The authors assume that international donors will cover these costs. Clearly, regardless of where these resources originate, their valuation should be included in the total cost of the program. Although maintenance costs of the program were calculated, it was not clear whether these included important activities, such as ongoing training and quality control of providers and cytologists, that are key to program success.

Another area of concern is the estimation of recruitment costs. Although these costs are included (under Papanicolaou smear collection), we believe they are greatly underestimated, and fail to capture logistical expenses accurately, as well as the value of community outreach workers’ or volunteer workers’ time to increase women’s participation in remote rural areas. Women who should be targeted for cervical carcinoma screening (those age approximately 30–55 years) belong to an age group whose health needs typically are not well addressed by available health services and in most settings additional efforts and resources will be needed to reach these women.\(^3\) Furthermore, the assumption that recruitment in Vietnam will result in > 70% coverage of women most likely is unrealistic. Experience has shown that this would be the exception rather than the rule, unless increased resources were spent to achieve such rates; nevertheless, even with additional expenditures, a recruitment rate of > 70% is doubtful.\(^4\)

We have three final concerns that are not addressed in the article by Suba et al.\(^1\) The first is failure to include cancer treatment costs in the model, which also has serious implications for the total cost of the program. In establishing this program over 10 years, many prevalent cases of cervical carcinoma will be detected in the women screened, thereby generating increased costs to the health care system. Second, we believe it is unrealistic to assume that constant costs will prevail during expansion of the project. Although Vietnam is small and densely populated, it is a poor country and resources are unevenly distributed nationwide. Given differential access to transportation, rural infrastructure, and health care services, we anticipate differences in cost structures, as well as variability in the quality of screening services, test performance, and treatment. Therefore, the marginal cost required to gain a year of life expectancy per patient is likely to be higher in more remote areas in which the infrastructure is poor, and the presence and quality of health services are limited. Finally, given the cost omissions that we have described, and the uncertainty that surrounds many of the authors’ assumptions, presenting the results from a sensitivity analysis would have been appropriate. Sensitivity analysis would allow the reader to evaluate how stable and robust the results are when critical assumptions concerning the costs and effectiveness are varied.

In short, although we believe that the study by Suba et al. makes an important contribution to the awareness of cervical carcinoma screening issues, the findings are less useful for providing information regarding the policies and programs for cervical carcinoma screening and prevention in other low-resource settings.

REFERENCES


Author Reply

We maintain that Papanicolaou (Pap) screening in developing countries is an idea whose time has come.¹

We maintain that sociopolitical barriers to building working coalitions from groups with shared interests but competing incentives constitute the most critical real-world obstacles to achieving successful cervical carcinoma prevention, and that technological challenges are of lesser importance. Therefore, we do not find it appropriate to blame the Pap test for the failures of political will so often inherent to low-resource settings. Greater than 50 years of global clinical experience have established Pap screening to be both inexpensive and highly effective, although, as exemplified by this correspondence, details regarding cost-effectiveness continually will be debated. We maintain that no useful alternatives to the Pap test currently exist, and that it is unconscionable to delay the establishment of Pap screening programs pending the investigation of experimental technologies. The future of cervical carcinoma vaccines is a matter for speculation. The usefulness of human papillomavirus (HPV) assays for primary screening is debated. HPV assays, either alone or in combination with the Pap test, could be phased into preexisting Pap screening programs while the building of coalitions continues. To our knowledge the clinical effectiveness of visual screening methods has not been established to date. Visual screening methods used in combination with the Pap test and/or HPV assays also could be phased in at a later date without causing delays to coalition-building processes. Because visual screening methods combined with immediate ablative treatment produce no physical evidence on which to base meaningful program audits, it appears that it will not be possible to demonstrate the benefit or to rule out the harm of single-visit visual screening outside of controlled research settings. We therefore consider single-visit visual screening to be inappropriate public health policy and have advocated that it not be adopted.

Adherence to evidence-based medical principles places us in direct conflict with the Program for Appropriate Technology in Health (PATH) and other partner organizations of the Alliance for Cervical Cancer Prevention, which was established in 1999 with a gift of $50 million from the Bill and Melinda Gates Foundation. Senior medical advisors to the Alliance opine that the role of the Pap test in successful cervical screening programs is limited,² and are “loathe” to recommend the establishment of Pap screening services in high-risk communities with no cervical screening programs currently in place.³ The Alliance has incentives to focus on technological challenges and currently is conducting randomized trials comparing cervical screening with no screening among groups of Indian women at high risk for the development of cervical carcinoma.² Because the Pap test remains the archetype of a successful preventive intervention,⁴ any negative results from such trials will not be generalizable to other settings. Premature advocacy for visual screening methods caused needless delays in the establishment of Pap screening in Vietnam. The Alliance is promoting single-visit visual screening throughout the developing world,⁵,⁶ with the Royal Thai College of Obstetrics and Gynecology recently adopting single-visit visual screening as a safe and acceptable policy.²

Drs. Levin and Sellors of PATH challenge the transparency of the cost data we reported for Pap screening in Vietnam, although their own assumption that Pap tests cost between $3–10 in developing countries⁷ provides no reference to its origin. We maintain that costs of personnel salaries, supplies, equipment, space, and overhead for Pap screening in Vietnam were documented adequately given the space limitations in peer-reviewed medical journals for the description of methods. Because Pap screening is labor-intensive, salaries are a central component of Pap screening costs. A Pap test (currently one of the most expensive tests in American medicine) costs $15 in the U.S.⁸ and < 40 cents in Vietnam,¹ largely because pathologists earn > $150,000 annually in the U.S. and < $1200 annually in Vietnam. The relatively low cost of Pap screening in Vietnam should be no more surprising to readers of our report than the knowledge that people in much of the world, including Vietnam, earn on average < $1 per day.

To our knowledge, there is no consensus regarding all the items to include in cost-effectiveness analyses. Drs. Levin and Sellors object that costs for inter-
national training, on-site training, ongoing training, quality control, recruitment, differential access to transportation, differential access to infrastructure, and differential access to health care services either were not included or were underestimated in our analysis. A double standard is implied, because none of these items are included in cost-effectiveness analyses of cervical screening performed by the Alliance. In our analysis, recruitment costs specifically were included. Costs of start-up training, on-going training, and quality control were included as additional full-time equivalents in each relevant personnel category, although these inclusions were not indicated specifically due to space limitations. We did not include the costs of training provided by international consultants, because those costs are assumed by international donors rather than by Vietnamese society. We made no assumptions regarding what levels of program participation are realistic in Vietnam. We assumed two centralized screening networks had been established. Constant costs were not assumed; rather, costs were discounted at a fixed annual rate of 3%. Health care costs in rural areas generally are lower than those in urban settings. Space limitations precluded extensive sensitivity analyses. Our report did note that, even assuming large increases in all costs, Pap screening in Vietnam still would be inexpensive and affordable.

We assumed that Pap screening services would not be established in communities without access to curative treatment services. Cost-effectiveness analyses of cervical screening, including those performed by the Alliance, usually do not include establishment costs for curative treatment infrastructure such as surgical operating rooms and radiation therapy units. The decision not to include maintenance costs for curative treatment in our analysis constituted a bias against the cost-effectiveness of Pap screening in Vietnam. Pap screening in a variety of settings has been associated with an increased proportion of invasive tumors detected at earlier, more curable stages of disease progression, and with reduced maintenance costs for curative treatment in screened populations relative to unscreened populations. Because the performance of the Pap test varies in different settings, we deliberately assumed poor diagnostic performance on the part of Vietnamese cytology laboratories. As a result, our analysis projected 37–57% reductions in cervical carcinoma mortality for 5-year interval Pap screening in Vietnam. In reality, 5-year interval Pap screening in Finland has achieved 80% reductions in mortality from this disease. We expressed Pap test performance as rates of call for specific Pap diagnoses, and probabilities for specific cervical lesions given each Pap diagnosis, rather than as percentages of lesions detected or missed, to link Pap test performance to numeric personnel requirements, using time-motion assessments to create that linkage. Personnel requirements then were linked to salary, disposable supply, equipment, space, and overhead requirements to arrive at screening and preventive treatment costs per woman. The assumption that the screening program would be phased in over 10 years was required to infer the numeric size of the target screening population from available Vietnamese census data. Costs per woman to establish screening and preventive treatment services were multiplied by the number of women in the target screening population to calculate total program costs.

When reasonable questions arise regarding scientific validity, studies should be replicated in different settings for confirmation. Our organization’s clinical practitioners (Vietnamese joined by American) are willing to work with Alliance theoreticians, anywhere in the world, to demonstrate directly that medical realities do in fact conform to those we described in our article.

REFERENCES
Author Reply to Previously Published Correspondence

We thank Dr. Vordermark for his specific comments.1 We agree that our study2 did not provide a thorough analysis of the patterns of recurrence in relation to the plannings target volume (PTV) for brachytherapy or external beam radiation therapy (EBRT). We also agree that tumor outlining using magnetic resonance imaging (MRI) may differ substantially from that using computed tomography (CT) imaging. Because MRI could not be incorporated into the planning system at the beginning of our study, we continued to determine the PTV for brachytherapy or EBRT using CT for the duration of the study. Although MRI, single photon emission CT (SPECT), and positron emission tomography (PET) studies were performed during follow-up, the pattern of recurrence also was determined based on CT scan to guarantee maximum uniformity. The PTV for EBRT was defined as the contrast-enhancing region plus a margin of 2.0 cm in the study institution in Amsterdam, The Netherlands. This information was not provided in our article. We considered these data to be of minor importance because the article focused on brachytherapy. For brachytherapy the PTV was defined as the contrast region itself in Cologne and as 0.5 cm beyond the contrast-enhancing region in Amsterdam. In Cologne recurrence occurred outside the brachytherapy isodose (PTV) in nearly all cases. In Amsterdam, all recurrences occurred at the original site, which was within the PTV for brachytherapy (as measured by CT scan).

We agree that a more thorough analysis of patterns of recurrence in patients with glioblastoma multiforme after they receive higher-than-conventional doses is an interesting issue. At the current time, every patient is implanted using MRI, and follow-up after the interstitial implantation includes MRI, SPECT, and PET.

Although there are published reports that describe a shift from central recurrences to more marginal or distant ones in patients treated with brachytherapy, a local recurrence within the PTV remains the major cause of treatment failure in the majority of the large series examining brachytherapy that have been published to date.3–6 Furthermore, no apparent survival advantage after brachytherapy was reported in what to our knowledge is the only randomized study published to date regarding this subject.6 Although Phase II studies have demonstrated some differences with regard to the pattern of recurrence, to our knowledge the majority of these studies have not reported a survival benefit of >3 months, indicating only a minor impact of brachytherapy on the clinical outcome. With the techniques currently in use, Dr. Vordermark’s comments are mainly of scientific interest.

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DOI 10.1002/cncr.10465