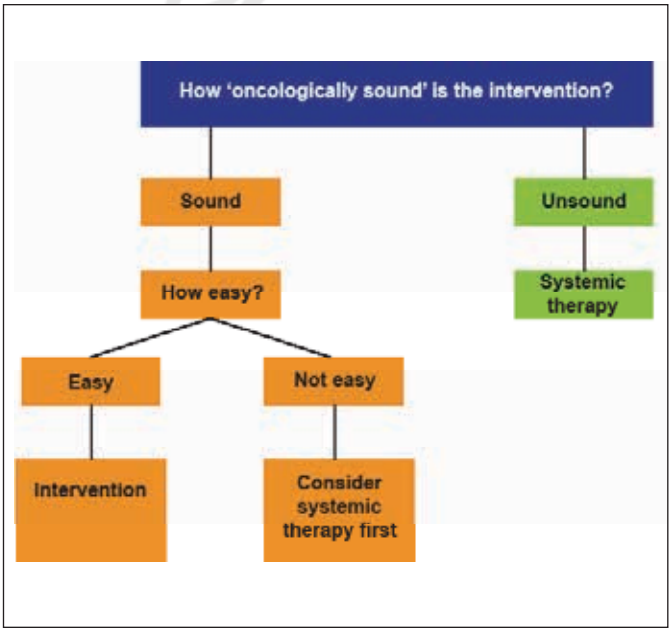
Achieving NED for at least 12 months gives patients hope for a cure, and is considered beneficial and relevant, whereas the value of achieving NED for 6 months is questionable and for <6 months, can be harmful. In a highly selected population of patients treated with surgery for liver metastases, 5- and 10-year survival rates were 40% and 20% for overall survival (OS), and 20% and 10% for relapse-free survival (RFS). Among unselected patients, the actual cure rate ranged from 1% to 4%.

Prof. Sobrero cautioned against using overly aggressive local treatment approaches because of the high rate of failure to achieve a NED state, the typically very short RFS, possible acceleration of the clinical course, treatment complications, and high mortality. Verwaal et al. [*Ann Surg Oncol* 2005] concluded that the key issue in selecting patients for cytoreduction and adjuvant therapy is selecting patients in whom it is feasible to reach complete cytoreduction. Laparotomy to diagnose peritoneal carcinomatosis provides the best information for selecting such candidates. According to Prof. Sobrero, this is an example of a simplified approach that can be generalized and used to determine the chance of achieving relevant NED, by evaluating the "soundness" of an intervention and the ease of performing the intervention (Figure 2).

Figure 2. A Simplified Approach to Determine Chance of Achieving Relevant No Evidence of Disease.



Reproduced with permission from A Sobrero, MD.

High originality and relevance coupled with low intrinsic and external validity of the results are the classic features and limits of most trials in this patient population. The main hurdles facing clinical trials in this field are poor feasibility and methodology. Trials must be designed to minimize bias (systematic error) and variability (random error). Bias can be minimized by randomization, treatment masking, eligibility criteria, and intention-to-treat analysis. Variability can be minimized by randomization, the number of patients, target delta, and patient stratification. However, these methods of minimizing bias and variability can be difficult to implement in this field.

Prof. Sobrero concluded that achieving the NED condition in patients with advanced CRC is very relevant. Physicians should not deceive themselves and patients but should, instead, aim for plausible results. The goal includes identifying appropriate patients for this approach, recognizing but not being paralyzed by the limitations of clinical trials in this field, and taking into consideration the toxicities associated with local therapy.

Eliminating Cervical Cancer: Novel Options in Vaccination and Screening

Written by ***Toni Rizzo***

The recognition that cervical cancer is caused by human papillomavirus (HPV) has opened new opportunities for preventing this devastating cancer. Jack Cuzick, PhD, Saint Bartholomew's Medical School, London, United Kingdom, presented evidence for the feasibility of eliminating cervical cancer through combined screening and HPV vaccination.

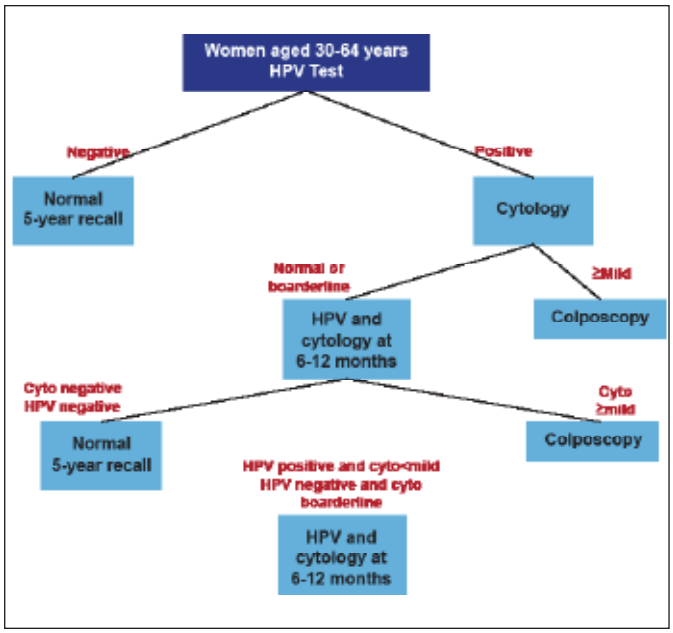
HPV and Cytology Screening for Cervical Cancer

To detect cervical cancer, European and North American screening studies have suggested primary HPV screening as a better method than traditional cytological methods. In a large pooled analysis which included 60,000 women included, HPV screening was more sensitive than cytology (96.1% vs 53%) in detecting cervical intraepithelial neoplasia grade 2 or greater (CIN2+) but less specific (90.7% vs 96.3%) [Cuzick J et al. *Int J Cancer* 2006]. In a multinational cohort, the cumulative incidence of cervical intraepithelial neoplasia grade 3 or cancer (CIN3+) after 6 years was considerably lower among women negative for HPV at baseline than among women with negative cytology at baseline [Dillner J et al. *BMJ* 2008]. The data support the use of HPV testing as the primary screening test for cervical cancer.

Figure 1 shows a proposed new screening algorithm beginning with HPV testing, followed by cytology screening for those with positive HPV results and

colposcopy for patients with abnormal cytology. In the future, the algorithm may be modified and simplified by including HPV-16 typing and testing for p16 overexpression to reduce referrals for nonprogressive HPV infections.

Figure 1. Proposed New Screening Algorithm.



Cyto=cytology; HPV=human papillomavirus.

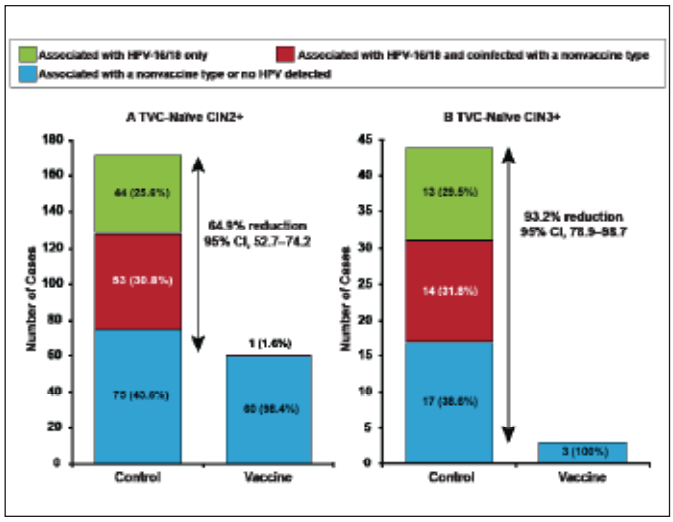
Reproduced with permission from J Cuzick, PhD.

HPV Vaccination

Primary prevention of cervical cancer is possible with HPV immunization of adolescents and young women. The Cervical Intraepithelial Neoplasm (CIN) in Women [FUTURE II; NCT00092534] trial of a quadrivalent vaccine against HPV-6/11/16/18 included a per-protocol susceptible population of 5305 women in the vaccine group and 5260 women in the placebo group [FUTURE II Study Group. *N Engl J Med* 2007]. At 36 months median follow-up, the vaccine efficacy for preventing the composite endpoint of CIN2-3, adenocarcinoma in situ, or HPV16/18-related cervical cancer was 98% (95.89% CI, 86 to 100). Nonavalent vaccines against HPV-16/18, HPV-6/11 (for prevention of genital warts), and 5 new oncogenic types (31, 33, 45, 52, and 58) are currently under development.

The HPV Vaccine Efficacy Trial Against Cervical Precancer in Young Adults with GlaxoSmithKline (GSK) Biologicals HPV-16/18 [PATRICIA; NCT00122681] trial randomized 18,644 women to HPV-16/18 vaccine versus control [Lehtinen M et al. *Lancet Oncol* 2012]. After a mean follow-up of 44.2 months, vaccine efficacy against CIN3+ associated with HPV-16/18 was 100% (95% CI, 85.5 to 100) in the total vaccine cohort-naïve. Vaccine efficacy against all CIN3+ was 93.2% (95% CI, 78.9 to 98.7; Figure 2).

Figure 2. Vaccine Efficacy in the Total Vaccine Cohort-Naïve.



CIN2+=cervical intraepithelial neoplasia grade 2 or greater; CIN3+=CIN grade 3 or greater; TVC=total vaccine cohort.

Reprinted from Lehtinen M et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncology*;13(1):89-99. Copyright 2012, with permission from Elsevier.

Issues associated with HPV vaccination include the need for 3 doses, cross-protection against other HPV types, durability of protection, the focus on adolescent girls, vaccination of boys, the need for vaccines not requiring cold storage, and lack of effectiveness after HPV infection. Vaccination coverage can be improved in the future by extending the age range for vaccination to children and adult women, and by alternative dose schedules (eg, 2 doses) [Kreimer AR et al. IPvC 2010]. Cervical cancer rates can be further reduced by screening older women to eliminate all current disease and vaccinating with polyvalent vaccines to prevent future disease. Next-generation HPV vaccines include polyvalent L1 virus-like particle (VLP) vaccines, L2 peptide vaccines, chimeric L1/L2 VLP vaccines, and combined prophylactic and therapeutic HPV vaccination [Kanda T and Kondo K. *Hum Vaccin* 2009; Stanley M. *Curr Opin Infect Dis* 2010].

Cervical cancer is the only cancer with a single, known cause: HPV. Vaccination can prevent infection but not eliminate it or impact subsequent cancer once it occurs. Cytology screening can identify treatable precursor lesions in women who are found to have HPV infection. Prof. Cuzick concluded that combined screening and vaccination in women aged 25 through 50 years offers the best chance of eliminating cervical cancer.