

The quarterly newsletter of Asia Oceania research organization on Genital Infections and Neoplasia - India



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From the editor's desk

Dear Readers,

We are back with yet another issue.

Cervical cancer remains one of the gravest threats to women's lives. Worldwide, every 2 minutes and in India every 7 minutes one woman dies of cervical cancer. In recognition of an acceptable burden, WHO Director-General, Dr Tedros Adhanom Ghebreyesus made a global call for action towards the elimination of cervical cancer. Although this thought has been enduring in the mind of all gynaecologic oncologists but now with the newer commitment it will soon be the reality. In this issue we have brought a glimpse of the speech of Dr Tedros Adhanom Ghebreyesus Director-General WHO that he delivered on 19th May 2018 at Geneva.

The issue has a lot of interesting features. Dr Nisha has reviewed the newer modalities available for screening. Dr Sabuhi has brought forth an interesting issue in the journal club. Three interesting case scenarios have been discussed by Dr Saritha Shamsunder. In this issue we have added a new segment to share the journey of champions with you in our column "Meet the champion".

It is really heart-warming to see all these contributions. We appreciate the time and effort that have been devoted by the different contributors and would like to thank them all. As always, suggestions and criticisms towards improving the newsletter content are welcome.

Happy reading !!!

Dr Seema Singhal



What's inside

Message from the president	2
Message from WHO Director-General	3
Expert Opinion	5
Journal Scan	7
Clinical Pearls	8
Meet the Champion	10

Message From the President

Dr Abraham Peedicayil, Professor and Head Department of Gynae Oncology, CMC Vellore



Dear Colleagues,

Greetings

Despite the important work done with secondary prevention and more recently primary prevention we still have much work to do in decreasing the burden and impact of cervical cancer. Any reduction in cervical cancer rates now will rely on a rapid roll out of a vaccination and screening program. As members of AOGIN India, we need to increase awareness among the general public and engage policy makers to institute the HPV vaccine in the national immunization programme. Furthermore, the State government where we live and work should be encouraged to implement a sustained screening programme. Follow up of screen positives and treatment of abnormalities is the key to success.

The WHO global call for action to reduce the suffering from cervical cancer is a wonderful opportunity that will enable AOGIN India to advance as an association and continue to be a leader in the field of cervical cancer prevention. The collaborations from national and international societies are more important than ever. We need to work together to demonstrate the relevance of our work and bring about change. I would like to encourage the young dynamic and proactive members of our society to move our mission ahead.

Best wishes,

Abraham Peedicayil

WHO Director - General calls to take action to eliminate cervical cancer



Dr Tedros Adhanom Ghebreyesus
Director-General

Cervical Cancer: An NCD We Can Overcome
Intercontinental Hotel, Geneva
19 May 2018

My sister Michelle Bachelet, Excellencies, distinguished guests, ladies and gentlemen,

It's a privilege to be here today.

You don't need me to remind you of the terrible toll taken by cervical cancer.

Cervical cancer affects over half a million women each year, and kills a quarter of a million. One woman dies of cervical cancer every two minutes, making it one of the greatest threats to women's health.

Each one is a tragedy, and we can prevent it.

Most of these women are not diagnosed early enough, and lack access to life-saving treatment.

If we don't act, deaths from cervical cancer will rise by almost 50% by 2030.

Cervical cancer strikes women in the prime of life. These women are raising children, caring for their families and contributing to the social and economic fabric of their communities.

Nine in 10 women who die from cervical cancer are in poor countries. This means some of the most vulnerable women in our world are dying unnecessarily. That cannot be fair or just.

But it doesn't have to be this way. Cervical cancer is one of the most preventable and treatable forms of cancer, as long as it is detected early and managed effectively.

Prevention and early treatment are also highly cost-effective.

HPV vaccines are truly wonderful inventions.

The fact that the research that led to the development of vaccines against HPV won a Nobel Prize speaks for itself.

If only we had vaccines against every form of cancer.

Our challenge is to ensure that all girls globally are vaccinated against HPV and that every woman over 30 is screened and treated for pre-cancerous lesions. To achieve that, we need innovative technologies and strategies.

We must improve access to diagnosis and treatment of invasive cancers at their earliest stages, and ensure the availability of palliative care for women who need it.

All of these services must be embedded in strong health systems aimed at delivering universal health coverage.

High-income countries have shown the way. In many of these countries, cervical cancer is becoming a thing of the past. Now is the time for global elimination.

During my campaign in 2016, I made a commitment to support the global elimination of cervical cancer. I reiterated that commitment when I was elected as Director-General a year ago.

We have the tools to turn that commitment into a reality. But crucially, we also have the political commitment.

Several countries and UN agencies have already joined forces under the UN Global Joint Programme on Cervical Cancer Prevention and Control.

But to succeed, we need everyone on board. We must expand our partnership to include anyone and everyone who can help us reach our goal.

That's why today I am calling for coordinated action globally to eliminate cervical cancer.

I'm encouraged that today we're joined by GAVI, the Global Fund, UNITAID, UICC and the World Bank.

As the manufacturers of life-saving vaccines, diagnostics and treatments, the private sector is also a key partner in this mission.

We cannot succeed without all of you.

Thank you for your everything you have already done. We still have a lot of hard work ahead of us. Please join us in making cervical cancer history.

Thank you.

Newer Screening Modalities for Cervical Cancer

Prof Nisha Singh, King George Medical University, Lucknow

Introduction

Till about two decades ago, cervical cancer screening was synonymous with Pap smear. Though cervical cancer screening has been well organized and universal in the western world, it has been only opportunistic in Indian Health system. Mortality reductions in excess of 50% have been achieved in many developed countries; however, the procedure is generally inefficient and unworkable in many parts of the world where the appropriate infrastructure is not achievable. The last two decades have seen enormous development in modalities for cervical cancer screening that can be used in both high and low resource settings. So much so, that Pap smear cytology is not the component of cervical cancer screening algorithm of any organization or guidelines. Let us learn about all the newer modalities available for cervical cancer screening today and possibilities in coming years.

HPV DNA Testing

Almost all organizations currently recommend HPV DNA testing as the primary screening modality in both high and low resource settings. (ACOG 2016, WHO 2013, ACS, USPSTF 2017). In April 2014, FDA approved one assay for primary HPV testing for women ≥ 25 . The HPV DNA tumor virus has over 150 genotypes. Oncogenic HPV causes cervical cancer and out of 40 types of genital HPV, 14-15 are oncogenic. The scientific evidence from numerous European and Canadian studies as well as the ATHENA trial clearly demonstrates that primary HPV testing outperforms cytology or Pap as a screening test. There are going to be fewer false negatives with HPV as compared to cytology. The test is particularly superior for diagnosis of adenocarcinoma, which is gradually increasing in proportion.

FDA approved HPV DNA Tests

The Hybrid Capture 2 test, approved by the FDA in 2003, detects 13 oncogenic HPV types (16/18/31/33/35/39/45/51/52/56/58/59/68) using full genome probes complementary to HPV DNA, specific antibodies, signal amplification, and chemiluminescent detection.

The Cervista HPV HR test, approved by the FDA in 2009, detects 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using a signal amplification method for detection of specific nucleic acid sequences. This method uses a primary reaction that occurs on the targeted DNA sequence and a secondary reaction that produces a fluorescent signal.

These tests have two limitations. First, neither test

differentiates between single HPV genotype infections and multiple concurrent HPV genotype infections. Second, neither test quantitates viral load.

The care HPV assay (QIAGEN, Gaithersburg, MD, USA) which uses a signal-amplification assay that detects 14 different high risk HPV DNA types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), requires only 25x50 cm of work space, does not require electricity or running water, and takes approximately 2.5 hours to perform. This assay time of 2.5 hours, as compared to the approximately 6 hours required for HC2 high-risk HPV testing, allows for evaluation and treatment the same day if needed. Care HPV is particularly advantageous in the low resource field settings because the woman can take her cervical sample on her own, it can be assessed in a short time and treatment may be provided in the same sitting.

HPV Self sampling – Studies have shown that there is no significant difference in the incidence of CIN2+ between provider and patient collected samples.

HPV DNA viral load assays

The development of HPV viral load assays that may reliably be used as an adjunct screening tool to identify women at increased risk of progression to CIN 2+ and cervical cancer remains a promising tool in cervical cancer screening.

HPV Genotyping

HPV Genotyping means identifying the specific viral genotype particularly HPV 16 and 18. Both DNA and mRNA tests are available. 5 year risk of CIN2+ if HPV 16+ is 10%. Risk of CIN2+ is lower if HPV 18 is detected, but there is an association with adenocarcinoma. ASCCP guidelines (2012) state HPV genotyping is acceptable without recommending for or against. The HPV DNA test, Cervista HPV 16/18, was approved by the FDA in 2009, and detects only HPV 16 and 18, the genotypes most commonly associated with cancer, using a similar method to the Cervista HPV HR assay.

HPV DNA Integration Tests

Screening for HPV integration into the host genome is a subcategory of HPV diagnostics. HPV integration is a key molecular event in the transition from an innocuous HPV infection to one that has oncogenic potential. HPV integration results in increased expression of the viral E6 and E7 proteins that ultimately results in the disruption of host cell proteins, p53 and pRb. Tests that detect the integration of HPV into the host cell and corresponding risk of CIN 2+ or cancer may provide a useful way of screening women at risk

Expert Opinion

for cervical cancer. Studies have demonstrated that viral integrants are detected in 100% of HPV 18 positive and 70-80% of HPV 16 positive cases of cervical carcinoma. A smaller subset of HSILs (15%) and 0% of LSILs contain transcriptionally active viral integrants.

The APTIMA HPV test (Gen-Probe) detects E6/E7 mRNA of 14 oncogenic types and **E6 STRIP TEST** is another biomarker that indicates viral integration. Both **APTIMA and PROOFER** (PreTect HPV-Proofer E6/E7 mRNA) assay have demonstrated a higher degree of agreement with LA genotyping than HC2. The Aptima test was as sensitive as HC2 but more specific for detecting CIN 2+ and can serve as a reliable test for both primary cervical cancer screening and the triage of borderline cytological abnormalities.

Liquid based cytology (LBC)

LBC is a technically better method of cytology than Pap smear due to the advantages like fewer reports of inadequate smears (1.9%), possibility of Reflex HPV testing and automated reading facility. Its overall sensitivity is same as conventional cytology (RR 1.1) but has 11% more sensitivity for LSIL+ lesions; its limitations is being expensive and not cost-effective. **LBC** Options available are - Thin Prep (Hologic), Sure Path (BD) and Autocyte computerized rescreening (PAPNET).

Biomarkers

Detection of p16 INK4a correlates tightly with viral integration. In a normal cell, p16 blocks cyclin-dependent kinases (CDK) 4/6. Increased expression of the E6 and E7 oncogenes disrupt cell cycle regulation, resulting in cell cycle progression. Increased expression of p16 in cells driven by viral oncogene-mediated cell-cycle dysregulation can be detected through cellular immunostaining. The available assays are: cintec (p16 INK4a) and cintec PLUS (p16 INK4a + Ki-67) (Roche). These biomarkers have the advantages of identifying transforming HPV infection. The sensitivity ranges from 64-92% and specificity ranges from 41-96% for low-grade smears. The limitations include wide variation in

reported sensitivity, lack of standardized reporting, need for substantial expertise and high false positive rates.

Methylation markers - Strategies Identifying Epigenetic Changes

Aberrant methylation of tumor suppressor genes is a known cause of cell cycle dysregulation. Many genes are currently being evaluated as potential methylation biomarkers for cervical cancer, but assay reliability for these methylation markers is highly variable. Some promising candidate genes include DAPK1, CADM1, and RARB.

Telomerase RNA component (TERC) identification by fluorescence in situ hybridization (FISH)

Most cervical cancers have an extra copy of the long arm of chromosome 3 and as a result demonstrate amplification of TERC (present on chromosome band 3q26), which appears to play a key role in progression from low-grade dysplasia to cancer.

Screening Methods Utilizing Proliferation Markers

Other biomarkers under early evaluation for cervical cancer screening include CDC6 and MCM5. These proteins are present in normal cells only during the activation of the cell cycle and help form pre-replicative DNA complexes during the G1 phase. Studies indicate that CDC6 may be a biomarker of high-grade and invasive lesions of the cervix, with limited use in low-grade dysplasia. MCM5 appears to be a biomarker that is expressed independent of high-risk HPV infection and may in the future serve as a useful marker for both HPV-dependent and HPV-independent cervical dysplasia.

Conclusion

At present HPV DNA test is the best suited, cost effective and widely recommended test for primary cervical cancer screening. The FDA approved options should be used. All other tests are under research to collect evidence in support.

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HPV-Testing in Follow-up of Patients Treated for CIN2 + Lesions

Prof Sabuhi Qureshi, Dept of Gynaecological Oncology, Super Speciality Cancer Institute, Lucknow, U.P.

Luciano Mariani, Maria Teresa Sandri, Mario Preti, Massimo Origoni, Silvano Costa, Paolo Cristoforoni, Fabio Bottari, Mario Sideri. *J Cancer*. 2016; 7(1): 107–114. doi: 10.7150/jca.13503

Persistent positivity of HPV-DNA testing is considered a prognostic index of recurrent disease in patients treated for CIN2+. HPV detection, and particularly genotyping, has an adequate high rate of sensitivity and specificity (along with an optimal reproducibility), for accurately predicting treatment failure, allowing for an intensified monitoring activity. Conversely, women with a negative HPV-test 6 months after therapy have a very low risk for residual/recurrent disease, which leads to a more individualized follow-up schedule, allowing for a gradual return to the normal screening

scheme. HPV testing should be routinely included (with or without cytology) in post-treatment follow-up of CIN2+ patients for early detection of recurrence and cancer progression. HPV genotyping methods, as a biological indicator of persistent disease, could be more suitable for a predictive role and risk stratification (particularly in the case of HPV 16/18 persistence) than pooled HPV-based testing. However, it is necessary to be aware of the performance of the system, adhering to strict standardization of the process and quality assurance criteria.

Are two doses of human papillomavirus vaccine sufficient for girls aged 15–18 years? Results from a cohort study in India

Dr Seema Singhal, AIIMS, New Delhi

Neerja Bhatla, Bhagwan M. Nene, Smita Joshi, Pulikottil O. Esmey, Usha Rani Reddy Poli, Geeta Joshi, Yogesh Verma, Eric Zomawia, Sharmila Pimple, Priya R. Prabhu, Partha Basu, Richard Muwonge, Sanjay Hingmire, Catherine Sauvaget, Eric Lucas, Michael Pawlita, Tarik Gheit, Kasturi Jayant, Sylla G. Malvi, Maqsood Siddiqi, Angelika Michel, Julia Butt, Subha Sankaran, Thiraviam Pillai Rameshwari Ammal Kannan, Rintu Varghese, Uma Divate, Martina Willhauck-Fleckenstein, Tim Waterboer, Martin Müller, Peter Sehro, Alka Kriplani, Gauravi Mishra, Radhika Jadhav, Ranjit Thorat, Massimo Tommasino, M. Radhakrishna Pillai, Rengaswamy Sankaranarayanan for the Indian HPV vaccine study group. *Papillomavirus Research* 2018 ;5:163-71.

Extending two-dose recommendations of HPV vaccine to girls between 15 and 18 years will reduce program cost and improve compliance. Immunogenicity and vaccine targeted HPV infection outcomes were compared between 1795 girls aged 15–18 years receiving two (1–180 days) and 1515 girls of same age receiving three (1–60–180 days) doses. Immunogenicity outcomes in 15–18 year old two-dose recipients were also compared with the 10–14 year old three-dose (N = 2833) and two-dose (N = 3184) recipients. The 15–18 year old two dose recipients had non-inferior L1-binding antibody titres at seven months against vaccine-targeted HPV types compared to three-dose recipients at 15–18 years and three-dose recipients at 10–14 years of age. Neutralizing antibody titres at 18 months in 15–18 year old two-dose recipients were non-inferior to same age three-dose recipients for all except HPV 18. The titres were inferior to those in the 10–14 year old three-dose recipients for all

targeted types. Frequency of incident infections from vaccine-targeted HPV types in the 15–18 year old two dose recipients was similar to the three dose recipients. None of the girls receiving two or three doses had persistent infection from vaccine-targeted types.

Conclusion: Adolescent girls vaccinated between 15 and 18 years of age with two doses of the quadrivalent HPV vaccine have similar antibody profiles as seen in girls vaccinated at the same age with three doses of the vaccine. The efficacy results in terms of protection against incident and persistent infections from the vaccine targeted HPV types in the girls getting two doses are also comparable to the girls receiving three doses at 15–18 years or even at younger age. The results justify extending the two-dose recommendation to the 15–18 year old healthy adolescents as well.

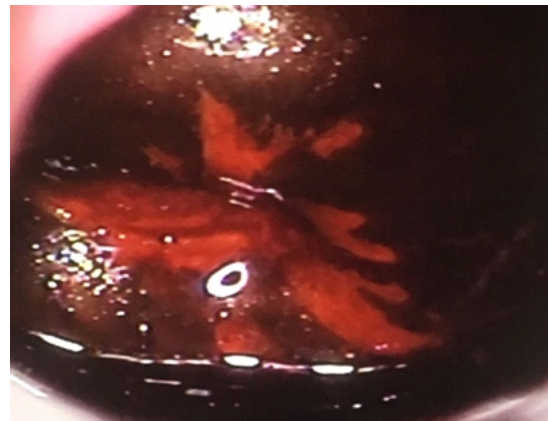
Challenging Cases in Colposcopy

Dr Saritha Shamsunder, Dr Sonu Agarwal, Dr Sunila Soni
Vardhman Mahavir Medical college and safdarjang hospital New Delhi.

Case 1

Mrs A, 40 yrs old P2L2, attended with heavy menstrual bleeding. Her colposcopy was done as she was VIA positive. The colposcopy was adequate. The transformation zone was type 1. Large acetowhite area in 2 quadrants which was distinct and opaque white. Margins were sharp and even. Vessels were fine and regular. Lugol's Iodine showed patchy yellow area. The Swede score was 6. A punch biopsy from the lesion showed CIN 1. Patient was scheduled for TAH for Abnormal uterine bleeding. The histology of the specimen of uterus showed leiomyoma and cervix showed CIN1.

Q Case1: Why was a cervical biopsy taken despite the plan for a hysterectomy?



Case 2

Mrs B, A 24 year old with primary infertility underwent colposcopic examination as she was VIA positive. The colposcopy was adequate, TZ was 1 and opaque acetowhite areas were seen at 12,4,9 O'clock position with distinct borders. Vessels were fine and regular. The Lugol's iodine showed patchy uptake. Thus the lesion was high grade with Swede score as 7. Biopsy was taken from all 3 areas and it showed CIN2.

Q: What will be your management?



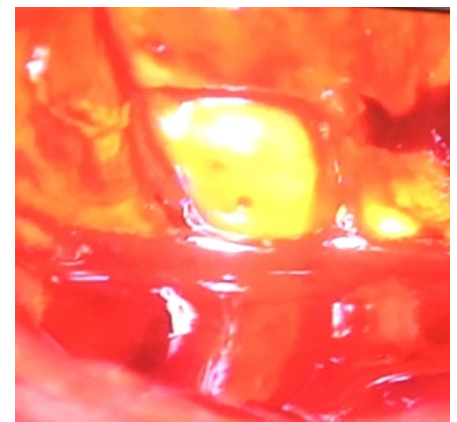
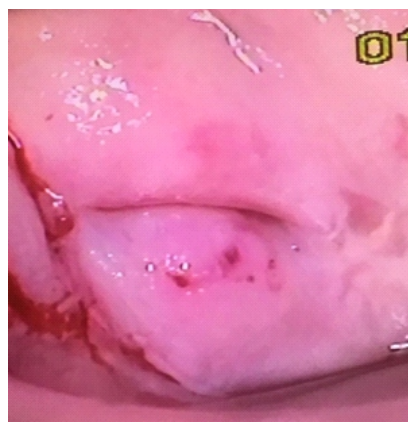
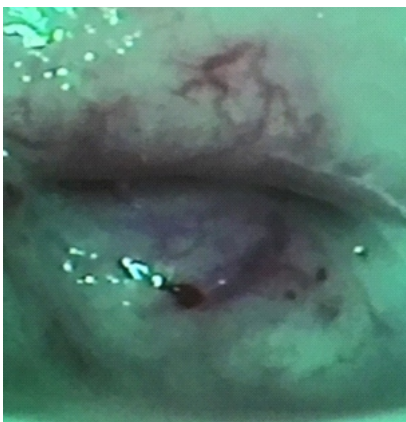
Case 3

Mrs C, D A 64 year old lady presented with history of post menopausal bleeding. Her abdominal examination was normal. On speculum examination the cervix was flushed with vagina with no obvious growth. However, there was a 1x1cm growth present on the posterior wall of vagina in the upper part which bleeds on touch. Vaginal examination revealed the growth to be hard in consistency, the cervix was flushed with vagina and uterus was atrophic. Rectal examination was done which revealed involvement of the parametrium upto the lateral pelvic wall and also of the rectal mucosa.

PAP smear was reported as squamous cell carcinoma and biopsy of the vaginal growth revealed moderately differentiated squamous cell carcinoma.

Colposcopy was adequate and showed coarse punctuations, a distinct, opaque aceto white area with sharp borders and a raised surface extending over two quadrants on the posterior lip of the cervix which turned distinct yellow on application of Lugol's iodine giving a Swede's score of 9 indicating a high grade lesion.

Q: How will you manage this patient?



Answers

Ans Case 1: In this case it is important to note that a biopsy is indicated if the patient is already planned for a hysterectomy? Yes, because if it shows micro invasion, a more extensive surgery will be required. This patient underwent hysterectomy for AUB. On screening she was found to be VIA positive. Colposcopy indicated a high grade lesion and a directed biopsy was indicated. Ideally the biopsy would have dictated the type of hysterectomy to be done. After hysterectomy the HPE of the cervix showed CIN 1, a vault smear is indicated at 6 and 18 months as CIN has been completely excised.

Ans Case 2: In this case a cryoablation was done as she was a case of primary infertility. She will require repeat cytology after 6 months and or a co test at 1 year. The follow up will continue till 20 years. In this case it is important to note that cryotherapy will not affect fertility. Cervical stenosis occurs in less than 1% of women who have undergone cryotherapy. Reduced mucus production is seen in 5 to 20% of women treated with cryotherapy. Pelvic inflammatory disease is also rarely reported if care has been taken to postpone cryotherapy till preexisting infection has been adequately treated.

Cryotherapy has no known adverse effect on fertility and pregnancy. This case also emphasizes the importance of opportunistic screening, the patient had come for treatment of infertility but was found to be VIA positive and biopsy showed CIN 2 which was treated.

Ans Case3: Carcinoma of the vagina is an uncommon tumor comprising 1% of female genital system cancers. According to the American Joint Committee on cancer, tumors in the vagina that involve the cervix with an intact uterus are classified as cervical cancers. In this case Colposcopy revealed a high grade lesion on the cervix though no growth was visible. Biopsy of the vaginal growth revealed a squamous cell carcinoma. Clinical staging was Stage 4A. So treatment would remain the same i.e radiotherapy regardless of whether the primary malignancy was cervical or vaginal.

Strength does not come from a physical capacity. It comes from an indomitable will.
- Anonymous



Meet the Champion

Women's health champion, Dr Riko Muranaka, awarded the 2017 John Maddox Prize for Standing up for Science. This prize is a joint initiative of the science journal "**Nature**" and the charity "**Sense about Science**", supported by the Kohn Foundation. The late Sir John Maddox, FRS, was editor of "**Nature**" for 22 years.

Dr Riko Muranaka has been awarded the international 2017 John Maddox Prize for promoting science and evidence on a matter of public interest, despite facing difficulty and hostility in doing so. A journalist and lecturer at Kyoto University, Dr Muranaka is recognised for her work championing the use of evidence in public discussions of the Human Papilloma Virus (HPV) vaccine. Dr Muranaka's work to put the evidence for the safety of the vaccine clearly before the public has continued in the face of attempts to silence her with litigation and undermine her professional standing. In persisting, she has tried to ensure that a scientific account of the weight of evidence is available not only for Japanese families but for public health globally.

Plan Your Schedule

CME on Cervical cancer control will be organized on 3rd November 2018 under the aegis of AOGIN by Department of Gynecologic Oncology, CMC Vellore. The event will be held at Jacob Chandy Hall, Paul Brand building, Christian Medical College Vellore.

The lighter Facet

- Wife returns from the clinics and tells her husband:
 - The doctor recommended me to spend one month at the sea, two weeks in the countryside and go for one week abroad. Where will you take me first?
 - To another doctor...
- Is it true that 5 minutes of laugh prolongs your life by 5 minutes?
 - It depends who you are laughing at – it may as well shorten it...