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CONTENTS

Editorial <i>Mukund S Joshi</i>	i
Spinal Affections in Rheumatological Diseases <i>Pradeep Kumar Dave</i>	139
Cervical Cancer – Bench to Bedside <i>T Rajkumar</i>	144
Clinical Epidemiological Study of Oral Pre Cancer and Cancer in a Tertiary/Referral Hospital <i>Sadaksharam Jayachandran</i>	155
An Innovative 3 Dimensional Model of Middle Ear <i>Shilpi Gupta Dixit, Abhinav Dixit, Pushpa Potaliya, Surajit Ghatak</i>	166
Short Answer Open-Ended versus Multiple-Choice Questions: A Comparison of Objectivity <i>Bharti Bhandari, Bharati Mehta, Parul Sharma, Rimplejeet Kaur</i>	173

(i)

Editorial

Doctor as Teacher and Books and Journals as Educator

The word “Doctor” derives from Latin “*Docere*” which means “to teach” (in fact all words 'doctor', 'docile', 'docent', 'document' and 'doctrine' derive from the Latin word “*docere*” in one way or the other and describe the quality of a teacher). Unexpectedly the word shows up in the roots of the word 'docile' is easy to teach and also the word 'document', which originally the thing from which one took information that was to be taught. Therefore, it is the responsibility of all doctors (with medical qualifications) to pass on their knowledge skills for the good of the profession in the future. This could also be considered as a “duty of care” which ensures tomorrow's doctors are well trained and knowledgeable as possible, and helps to ensure best possible care for tomorrow's patients as well.

Within minutes of consulting a new patient, a doctor knows what caused the problem he/she has and also knows what you have to tell them and how to treat him/her. When we engage a patient in the process of listening and explaining to him/her with an attitude of compassion and empathy, it develops a bond of trust. With engaged patients, medical problems can be diagnosed swiftly and treated with higher success rate. Illness can be prevented and emergency department usage can be reduced. Care can be personalized to improve outcomes that matters to providers and patients as well. In the process, patient engagement can indeed perform miracles : it can combat voracious healthcare costs.

The attitude of doctors towards profession influences to a large extent a number of aspects of clinical competence. Their attitude towards the patient is particularly important as it determines the quality of communication. There is a reason to believe that a number of practising clinicians have not acquired the appropriate attitude to their patients and the skills in communicating that this entails inspite of specific undergraduate medical education programmes. This specially warrants more and different attention to this subject by medical colleges than is actually the case. This also requires introduction of syllabi and curricula which help in developing attitudes between doctor-centred, disease-oriented, patient-centred and problem-oriented basis of studying, teaching and evaluating individual attitudes of medical students.

Besides patient engagement, the other thing which matters in making a knowledgeable and competent health care provider is evidence-based medical

knowledge, just as being a good doctor is far more than merely being a good clinician. It must involve fostering of a critical awareness— a critical consciousness of self, others, and the world and a commitment to addressing issues to societal relevance in health care. One way of doing is fostering a habit of reading medical books and journals of one's interest with the aim to serve the society in a better way. It also involves not only reading but contributing to the current medical literature by one's own medical experiences and researches.

Now a look at the contents of the present issue of the Annals : spine-related disorders and deformities are among the most frequently encountered problems in clinical medicine. Near about 80% of the population, at some point in life suffer from low back pain that causes 1-2% of such population to become morbidly disabled. The need for care of these patients has led to an array of treatment options, including medications, manipulative care, interventional spine procedures, and a number of surgical approaches. There are several emerging interventional innovative spine procedures but the role that many of these play in spine care is unclear. Perhaps the best way to address the future is to examine the past.

Oral cancer has a tendency to be detected at late stage but an early detection of such cancer is an important aspect to reduce the burden of this devastating disease. The 5-year relative survival rates for cancer of oral cavity and pharynx are 83% for cancer that has not spread, 62% for cancer that has spread to nearby lymph nodes and 38% for cancer that has spread to distant parts. On the other hand, study of cervical cancer, the fourth-most common cause of cancer and death from cancer in women after the breast, lung and colorectal cancers. The 5-year survival rate for all women with cervical cancer is 68%. This paper attempts to show its multi-factorial causation, potential for prevention and successful treatment if diagnosed early. The study of its epidemiology through National Cancer Registry Programme (NCRP) and a more comprehensive and larger programme called National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS) are important keys to success to address common risk factors and treatment strategies for reducing the scourge of such diseases in the affected population. The reaching goal of health care delivery must be for achieving high value for patients, with value defined as the health outcomes achieved per expenditure made. This goal is what matters for patients and if value improves, patients, payers, providers, and suppliers can all benefit while the economic sustainability of the health care system increases. Value in health care remains largely unmeasured and misunderstood. Both scientific papers related to cervical cancer and oral cancer emphasize this point more relevantly. To add to the variety, the rest two articles are related to medical education. How innovations in teaching of complex topics of medical anatomy make the matter

(iii)

simple to understand by using physical models of middle ear, which as such seems to be difficult when accessed through the cadaveric study and text book reading, has been explained in one paper. Whereas the other paper compares the merits of students' evaluation through carefully designed short-answer questions with the multiple-choice questions in the area of same topic.

The Annals, the official publication of the National Academy of Medical Sciences is a platform which provides good opportunity to medical fraternity of specialists to not only read but also publish and share their experiences and researches to emphasize the role and current status of research in India for the young minds by its rich contents. The present issue is an example of uniformity in diversity as it contains articles with a blend of variety of medical issues by doctors who are “*docere*” in real sense of the term.

Dr. Mukund S Joshi
President, NAMS

Spinal Affections in Rheumatological Diseases

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ABSTRACT

A brief resume of management of rheumatoid arthritis in India is highlighted causes of deformity its radiological features and the goals of its management are discussed. Management included medical drug treatment, physical therapy and surgical treatment including synovectomy, osteotomies and joint replacement. Brief description of involvement of cervical spine in rheumatoid arthritis is also made.

The evolution of treatment of scoliosis starting from conservative to all stages of surgical treatment is also described. Surgical correction involved posterior instrumentation and fusion anterior release with or without instrumentation and fusion. Treatment of congenital and paralytic scoliosis is also discussed. Newer surgical modalities in treatment of paediatric scoliosis was also highlighted.

Keywords : Spine in rheumatoid arthritis medical treatment and surgical scoliosis correction, paralytic, congenital and in the paediatric age group.

Correspondence : Dr. P.K. Dave, A-8, Sector 26, Noida – 201301.

NAMS GOLDEN JUBILEE LECTURE delivered at North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong on April 9, 2011.

INTRODUCTION

Rheumatoid arthritis (RA) affects about 0.75% to 1% of the general population. The onset of disease is particularly in the younger population within the age group of 35 to 50 years. RA is a highly inflammatory and destructive polyarthropathy affecting both small and large joints of the body. The disease results in a substantial personal, social and economic loss. About 80% of the patients affected with RA are permanently disabled after 20 years with a reduced life expectancy. Fortunately RA in Indian patients tends to be less severe as compared to western population; both geographic and genetic variations have been implicated as the possible causes.

Early radiographic changes consist of soft tissue swelling only. Advanced changes result in juxta articular osteopenia with narrowing of joint spaces due to articular cartilage destruction and juxta articular erosions as well. Later on large cystic erosions, bony proliferation and gross joint destruction constitute the picture.

Goals of therapy is to alleviate pain, control disease activity, slow joint destruction and improve quality of life. There should always be a team approach in management of RA patients. Team should consist of rheumatologist as the team leader, orthopaedic surgeon, physical and an occupational therapist. Psychologist and a social worker also form an important part of the team.

NSAIDs (Nonsteroidal Anti-

inflammatory Drugs) are the initial drug treatment of choice. They reduce pain and swelling thus improving function. NSAIDs do not alter the course of the disease or prevent joint destruction. Corticosteroids in dose as low as 10 mg (PREDNISOLONE) help to control acute flare ups. They act as a bridge therapy between initiations of DMARDs (Disease-modifying antirheumatic drugs) therapy and its onset of action. However its long term treatment is associated with side effects. DMARDs form the mainstay of treatment for RA. DMARDs can be used in various combinations and regimens. DMARDs therapy should be initiated at the time of diagnosis and should not be delayed for more than 3 months to avoid irreversible joint and bone damage.

Various DMARDs are in use these days such as hydroxychloroquine, methotrexate and sulfasalazine. Newer DMARDs include leflunomide, etanercept (TNF-receptor fusion protein), Infliximab (Chimeric monoclonal antibody which binds to TNF) and adalimumab.

Radioactive synovectomy can be done using radioactive isotopes (Yttrium-90, Gold-198, Erbium-169, Rhenium-186, Phosphorus-32, Dysporium-165). Laser arthroscopic synovectomy and total synovectomy is performed in refractory cases. In late stages of disease, surgical intervention becomes mandatory to improve function and to improve quality of life. Synovectomy in acute stage of rheumatoid arthritis occasionally results in remission in other joints also. Joint

replacement, arthrodesis, correction of deformities especially hand and feet, repair of ruptured tissues such as rotator cuff constitute the surgical aspect of treatment of RA.

The final treatment of joints which are deformed and have got stiffness respond well to joint replacement surgery. Most common replacement is in the knees but the hip joint, elbow and finger joints also respond well in replacement surgery.

Rheumatoid arthritis in spine usually affects young individuals. Cervical spine is involved more often than the thoracic and lumbar spine. Atlanto axial involvement is often the common involvement; pain and muscle spasm in the cervical spine involvement are common manifestations. Neurological symptoms are not common. However, in cases where myelopathy supervenes difficulties in gait and hand function may be seen. Radiological diagnosis if taken in conjunction with other clinical symptoms and laboratory investigations, other modalities like magnetic resonance imaging can be helpful particularly for evidence of compression of spine.

Treatment in most cases is proper immobilization of cervical spine to alleviate pain and avoiding any neurological damage. Cervical spine isometric exercises and cervical collar are helpful. Surgical intervention is resorted to if there is neurological damage or severe pain.

Advanced spondylotic changes call for surgical fusion of unstable spine.

There are a large number of techniques of fusion of spine for stabilizing the spine and thus alleviating the pain. RA sometimes also affects spine especially cervical spine.

Scoliosis :

Besides rheumatoid arthritis, I had also been interested in the treatment of scoliosis which occurs due to various aetiological factors. The basic principle of treatment of scoliosis is to control the curve till the growth of the child stops at puberty. After that period the scoliotic curve also does not increase.

However, some surgeons control the curve till the age of ten and then fuse the spine. In India, since the children are not very tall we prefer to fuse the spine at a much later age say around fourteen or fifteen years of age.

There are many ways of controlling the curve, ultimately a properly done spinal fusion is the gold standard of scoliosis treatment. The technique of a properly done spinal fusion is a meticulous one involving a thorough decortication of lamina upto the transverse process, excision of face joints and placing autologous bone graft on the decorticated area.

During the early seventies (1), Paul Harrington devised a rod which could be placed over the decorticated area. The curve was distracted with an outrigger engaging two hooks placed in the laminar space at two ends of the curve. Decortication was performed and then

autologous graft placed over decorticated area. This was followed by immobilization period of 6-9 months. However, the follow-up of a large number of cases, complications of Harrington rod began to appear, the commonest being breaking of the rod at the junction of the shaft of the rod and the ratchet.

The Harrington rod went into disrepute. Around the same time an era of segmental instrumentation came into vogue. The principle of segmental instrumentation was correcting the curve at each vertebral level of the curve. This was devised by a Mexican surgeon called Luque (2). The technique required excision of spinous processes passing a double loop wire through the ligamentum flavum and the lamina and then passing it around the vertical rod of the implant. However, it was a fiddly operation. Shuffle Barger HL *et al.* (3) also reviewed 234 cases of idiopathic scoliosis treated by segmental instrumentation meticulous technique. There were complications like neurological damage. In such cases removal of the implant posed a major problem.

Some surgeons combined both the procedures called the Harri-Luque instrumentation procedure. This technique required the Harrington rod to be placed on the concavity of the curve which was distracted. The double loop wire was then passed in a similar manner around the lamina and was tied around the rod to secure it in place. There was some limited success for this operation. Here also it was realised that although this procedure corrected the curve and rotation

of the curve to some extent the rate of complication like neurological damage was quite high.

However, in our country, scoliosis in the early stages of childhood was not treated adequately due to the mistaken motion that correction out once the child had reached the age of maturity. Hence the patients reported to us when the curved spine had become rigid and was not correctible by posterior instrumentation.

A very significant observation in relation to the curve and the rotation was made by Zeilke from Germany. He felt that approaching a scoliotic curve anteriorly would not only correct the curve but also the rotation. His anterior approach involved loosening of the curve by excision of discs in the curve. The vertebral bodies in the curve were fixed by means of screws placed in its body which were fixed by means of a rod. The whole assembly was then rotated by means of a strong lever. The space created by removal of discs was filled by bone graft taken from the excised rib. Most significant advantage of this technique was the correction of rotation.

In some cases after performing a Zielke instrumentation, posterior instrumentation and fusion was carried out either at the same sitting or after a week. In some cases where it was not possible to use Zielke instrumentation a simpler technique was used. After doing the anterior release and wound closure halo-traction was applied to the patient with the head end raised and the body weight acting as a counter traction. This

device was kept on for three weeks. The patient was then taken for posterior spinal instrumentation and fusion.

Congenital Scoliosis :

This was due to imperfect segmentation or restrictive segmentation unilaterally leading to a concave bar which necessitated an immediate fusion. In some cases there was diastematomyelia. The bony spur was excised posteriorly and then an anterior fusion was carried out. Dubousset J (4), Katti E and Seringe R, carried out epiphysiodesis of the spine in young children with congenital deformity (5). Freedman, Leong and Lub *et al.* performed a one stage combined procedure, both anterior and posterior excision of the hemivertebra in the lower lumbar spine. However, a periodic radiological analysis is done; if the curve is increasing excision of hemivertebra is to be carried out. If not, it should be left alone and to be kept under observation.

Paralytic Scoliosis :

These deformities have a long C-curve which should be maintained in correction with a Milwaukee brace and then fused posteriorly. In some cases a child with paralytic scoliosis had severe collapsing spine and both the lower extremities affected with polio. The case was operated with posterior instrumentation and in the postoperative care a corset was given and with a lateral linge the lower limb orthosis were incorporated. It is a very satisfactory

outcome since the patient who had never walked now had a posterior gait albeit with a support.

Newer techniques for correction are being devised particularly in growing children where the device has to be distracted periodically as the child grows.

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Cervical Cancer – Bench to Bedside

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ABSTRACT

Cervical cancer is the second most common cancer in Indian women and 4th most common cancer in women world-wide. Over nearly two decades, we have carried out epidemiological and molecular studies in cervical cancer, with an intent to identify potential early diagnostic biomarkers, predictive and prognostic markers, develop newer therapies against cervical cancer and identify potential new targets for therapy.

Our studies had identified 14 high risk and 10 low risk human papilloma virus (HPV) in our cervical cancer patients for the first time; had identified life style related co-factors in the development of cervical cancer (paan chewing, parity, early age at first sexual intercourse and first childbirth, husband with two or more sexual partners). We have developed a p16 ELISA kit for cervical cancer screening for use at point of care like PHC's; identified a 7 gene signature which help identify patients who can be treated with radiotherapy alone; identified potential prognostic markers for use in the clinic; developed the country's first Dendritic cell vaccine therapy for cervical cancer and completed the phase 1 study; have identified newer potential therapeutic targets for treatment of cervical cancer.

Keywords: Cervical cancer; Human papilloma virus; p16 ELISA; Predictive and Prognostic markers; UBE2C; Dendritic Cell Vaccine for treatment.

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DR. R.V. RAJAM ORATION delivered during NAMSCON 2015 at the All India Institute of Medical Sciences, Patna.

INTRODUCTION :

Cervical cancer is the 2nd most common cancer in Indian women and 4th most common world-wide (1). High risk human papilloma viruses (HPV) are considered to be important in the genesis of these cancers (2). However, most of the women infected (>95%) will clear the infection but a Few can have HPV induced pre-cancerous changes which can worsen to invasive cancers, indicating that other factors are also important in the genesis of the cancer. Identifying additional life style related factors which increase or decrease the risk can help better control the disease development.

Cervical cancer is a disease of relatively slow progression, going through different grades of dysplasia before becoming invasive (3). The standard screening procedure for cervical cancer is the Pap smear. However, in a country as large as India and with a huge population load, it is near impossible to use PAP smear for screening, simply because we do not have enough Pathologists/Cytologists. Low cost techniques like Visual inspection after application of acetic acid (VIA) or Lugol's iodine (VILI) have lower sensitivity and specificity. HPV testing has the drawback of needing re-testing after a year to confirm persistence of infection, as a single test cannot confirm if it is a transient infection. There is, therefore, an urgent need for a simple, low cost and objective testing to identify the pre-cancerous lesions of the cervix at the Primary Health Centres itself.

The standard line of management of stage IIB and stage IIIB till the end of the 20th century was radical radiotherapy. The cure rates with radical radiotherapy was around 60% for stage IIB and around 40% in stage IIIB. The introduction of cisplatin based concurrent chemo-radiotherapy has helped improving the cure rates by nearly 10%. The question is, can we identify those patients who could be cured with the radical radiotherapy itself thereby avoiding the cost and toxicity of the chemotherapy.

In view of the stagnation of the cure rates newer approaches and newer therapeutic agents need to be identified. One promising approach is to use therapeutic immune based approaches such as Dendritic cell vaccine therapy in the treatment of cervical cancer. Additionally identification of newer therapeutic targets and development of drugs to those targets is essential to improve the cure rates in cervical cancer.

A. Epidemiological studies in cervical cancer :

International Agency for Research on Cancer (IARC, Lyon) funded the case control study on HPV in cervical cancer conducted from June 1998 to May 1999 in the Cancer Institute (WIA) (4). Inclusion criteria for case subjects were: (i) histologic confirmation of invasive cervical cancer (ICC) diagnosis; (ii) no previous cancer treatment; (iii) lack of physical or mental impairments that would have made the interview impossible; (iv) willingness to provide

informed consent. Healthy control women were either other patients in the Institute or visitors of patients other than women with cervical cancer and were age-matched to ICC cases within 5-year age groups. Exclusion criteria for control women included: (i) a diagnosis of anogenital tract cancers (i.e., cervix, vagina, vulva, anal canal), cancer of the breast, endometrium, ovary or colon, benign genital tumours and tobacco-related diseases (e.g., coronary heart disease, chronic bronchitis and cancer of the head and neck, lung and bladder); (ii) a history of hysterectomy or cervical conization; (iii) physical or mental problems and (iv) not willing to provide informed consent.

All the cases (n=205) and control (n=213) women underwent a gynaecologic examination and ectocervical & endocervical cell collection was done using appropriate spatulas and brushes. The cells were stored at -70°C and then shipped to IARC, Lyon. HPV detection was done using PCR followed by an Enzyme immunoassay containing probes which would detect high risk and low risk HPV subtypes.

After excluding inadequate samples, we had 191 ICC and 184 control women's samples with HPV data. High risk HPV was detected in 190/191 cases (178/179 squamous cell carcinoma; 12/12 adenocarcinoma) and in 40 of the 184 control women. Low risk HPV only was seen in 11 of the control women but not in ICC cases. HPV infection with any subtype was associated 498-fold increased ICC risk. HPV16 was the most

common subtype seen in cases and controls, followed by HPV18 and 33. Multiple subtype infection was seen in 17% of cases and 4% of controls.

This was the first study from the country to look at all the HR and LR HPV subtypes. It confirmed the strong association of HR-HPV subtypes with ICC. It also for the first time showed the incidence of HR-HPV infection in control women to be as high as 22%. The study also identified several risk factors including paan chewing with and without tobacco (OR 2.3) with a dose dependent effect; parity; women with husbands who had extramarital affairs; age at first intercourse <15 years compared to ≥ 21 years was associated with OR 2.2; age at first child birth (<17 years compared to ≥ 19 years was associated with OR 2.2); more than one sexual partner; all of which increased the risk. High vegetable and fruits intake was associated with a decreased risk for ICC (OR 0.5) (5). The data from the study was included in an International Collaboration of Epidemiological studies of cervical cancer co-ordinated by IARC, Lyon. This reanalysis of data involving 25 epidemiological studies with more than 16000 ICC and more than 30,000 controls showed:

1. Reproductive factors (6) :

- a. The risk for developing invasive cervical cancer increases with parity (≥ 7 full term pregnancy compared with 1–2).
- b. Early age at first full term pregnancy

(<17 years versus ≥ 25 years) was associated with increased risk for invasive cervical cancer and for CIN3/CIS lesions.

2. *Tobacco smoking (7) :*

- a. Tobacco smoking (current smokers and past smokers) had an increased risk for squamous cell carcinoma (SCC) of cervix. The RR in current smokers was 1.6 (95% CI: 1.48 – 1.73; $p < 0.001$) and in past smokers was 1.12 (95% CI: 1.01 – 1.25).
- b. The risk in current smokers for the development of SCC of the cervix, increased with increasing number of cigarettes smoked and on the younger age at which they started smoking ($p < 0.001$).
- c. Tobacco smoking was not associated with an increased risk for Adenocarcinoma of the cervix.

3. *Hormonal contraceptives (8) :*

- a. Individuals using combined oral contraceptives for 5 or more years had a RR of 1.9 (95% CI: 1.69 – 2.13) for the development of invasive cervical cancer.
- b. A similar risk was also seen for CIN3/CIS.
- c. Injectable progestagen-only contraceptives showed a slightly raised risk for invasive cervical cancer, when used for 5 or more years (RR 1.22 [95% CI: 1.01 – 1.46] $p = 0.03$).
- d. The risk of cervical cancer declines once the drugs are stopped and by 10

years or more, the risk is similar to that of a never user.

4. *Sexual behaviour (9) :*

- a. A lady with many sexual partners (≥ 6) has more than two fold risk for development of invasive cervical cancer and for CIN3/CIS, after conditioning on age, study and age at first intercourse.
- b. The age at first intercourse is also a risk determinant, with ≤ 14 years of age at first intercourse having a greater than 2 fold risk, when compared with age at first intercourse of ≥ 25 , and after conditioning for age, study, number of sexual partners and reproductive factors.

5. *Education (10) :*

- a. Low education level was found to be associated with cervical cancer but not with HPV infection.

B. **Molecular studies in cervical cancer :**

Microarray studies were carried out on normal cervical tissues ($n = 5$), different grades of dysplasia (CIN1 & 2 – $n = 4$; CIN3/CIS $n = 4$) and ICC ($n = 28$). Differentially expressed genes were then validated using quantitative Real Time PCR (qRT-PCR). Some of the genes were then validated at the protein level using Immunohistochemistry (IHC) (11).

1. *p16 ELISA :*

Our qRT-PCR data identified p16 as being highly expressed in high grade CIN3/CIS and in ICC compared to normal and low grade CIN1/CIN2. IHC showed the protein to be overexpressed in tumours and in high grade CINs. We then proceeded to develop a sandwich ELISA for detection of p16 using commercially available antibodies. Concurrently we started raising monoclonal antibodies to p16 using recombinant p16 protein which we had expressed and purified from bacterial cells.

The Sandwich ELISA using commercial antibodies was validated using recombinant p16. Once we had the monoclonal antibodies raised and characterized by us, we used a combination of the monoclonal antibodies in the sandwich ELISA and were able to detect reliably 1pg. We then evaluated the ELISA using HeLa cells, and were able to detect upto 500 cells reliably. One of the problem we faced was assessing the adequacy of the cervical scrape sample. In PAP smear, the Pathologists can assess whether the sample is adequate or not for interpreting and can order for a fresh sample if found inadequate. In an ELISA, this was not possible and hence we developed and added another ELISA for cytokeratin level. Cytokeratin is expressed in almost all epithelial cells and an antibody against pan-cytokeratin can identify the epithelial content. By running the p16 and cytokeratin ELISA in parallel, we were able to show the adequacy of the sample and also determine the levels of

p16 expression. This was a major advance over an existing ELISA kit for p16 developed and marketed in Germany. We have done the preliminary assessment of the functioning of the ELISA using well annotated clinical samples from Nargis Dutt Memorial Cancer Hospital, Barshi, wherein a cervical cancer screening program has been going on for more than a decade. Patent has been applied for the p16 kit [Application number 475/CHE/2014, filed on 03-02-2014]. Further validation is being planned by using blinded samples from Barshi which will be followed by independent validation in 3 major centres in India involving at least 1000 samples. We are in the process of transferring the Technology to a Govt. of India subsidiary for commercialization of the kit.

2. *Predictive markers for radiation response in cervical cancer :*

As mentioned earlier, the addition of concurrent chemotherapy with radical radiation improves the cure rate by around 10%. However, we do not have a means of identifying who would fail treatment, so that chemotherapy could be reserved for them thereby minimizing toxicity and cost of the chemotherapy. To this end we had carried out gene expression studies using microarray as described in (12) which was then validated using qRT-PCR.

Using 24 samples from patients who had undergone therapy with more than 3 years follow-up, we developed a scoring method based on the qRT-PCR data. The cut-off was set at 40% of the potential total

score possible. A 7 gene signature score was found to identify patients likely to fail treatment. At the cut-off score set, all the failed samples were identified as high risk. The sensitivity, specificity, PPV and NPV were 0.64, 1.0, 1.0, 0.67, respectively.

This needs further validation using a larger sample size, in samples collected from patients who had undergone radical radiotherapy only. We are hoping to collaborate with other centres which would have frozen tumour samples available of patients treated with radiotherapy only.

3. Prognostic markers for cervical cancer :

At the Institute, most of the cervical cancer cases are stage IIB and IIIB (nearly 80%) and of high grade (80%). Since stage and grade of the tumours are strong prognostic indicators, this meant that most of our patients were high risk group and additional markers are required to better sub-stratify them.

Our department had evaluated several proteins for their potential as prognostic markers, overexpression of BCL2 was found to be associated with poor response to treatment with Radical radiotherapy and more patients failed treatment after achieving a complete response, as well (Table 1 – BCL2). This was independent of the stage of disease (13). C-myc oncoprotein overexpression was also likewise associated with poor prognosis independent of the stage (14).

4. Identification of molecular targets in cervical cancer :

Based on our gene expression studies (microarray and qRT-PCR) we identified several potential targets for treatment in cervical cancer, including UBE2C, MELK, ISG15, STAT1, MMP3, MMP1 (11).

UBE2C which is a Ubiquitin conjugating enzyme E2C, is expressed at high levels in cervical tumours and high grade dysplasia but at low levels or is absent in normal tissues and low grade dysplasia. Using a functionally inactivated dominant-negative mutant of UBE2C (C114S), we showed that the mutant protein alters the tumorigenicity (soft agar cloning assay) and sensitises cancer cells (cervical cancer cell lines) to radiation (Clonogenic assay) (15).

We are now involved in *in-silico* modelling and docking of compounds to the active site including C114. Compounds showing UBE2C blocking activity will be taken forward for further evaluation.

C. Development of dendritic cell vaccine therapy for cervical cancer :

Immune perturbation is one of the critical factor in the development of cancer. Every day in a normal individual there are millions of cells undergoing proliferation which is essential to maintain normal physiological functions. Some of the cells undergoing proliferation will have error in DNA sequence. The first

line of defence in this is the DNA repair mechanism which can correct the errors and if the cell fails to correct the error and tries to enter another cell division, apoptosis is triggered, so that the abnormal cell does not result in clonal proliferation. In addition, several environmental and dietary factors can damage the cellular DNA and again the DNA repair mechanisms ensure the DNA integrity is maintained. However, in spite of well-regulated DNA repair process, sometimes the error can be propagated to daughter cells. At this level, the immune system comes into play with its continuous surveillance, detecting these abnormal cells and destroying them. In some situations, the immune system is also compromised and the developing tumour cells can alter its MHC protein expression and secrete factors which can result in tolerance to the developing tumour. There are several ways to break the immune tolerance, one of which is to use primed dendritic cells to overcome the resistance.

Dendritic cells (DC) are the most potent antigen presenting cells and can help initiate a strong immune response. In the tumour microenvironment, the dendritic cells are either inactive or can be inhibitory to the immune response due to tumour / stroma derived factors such as IDO (Indoleamine deoxygenase). We and others have shown that DCs can be generated from peripheral blood derived monocytes and these can then be matured into primed dendritic cells and then injected back into the patients to generate a robust immune response.

1. Generation and characterization of mature primed Dendritic cells for DC vaccine :

Under funding from Dept. of Biotechnology, Government of India, we first standardized the protocol for generation of DC's and then functionally characterized them (16). Briefly, we obtained peripheral blood mononuclear cells from patients and then plated them in plastic petridishes. Monocytes adhere to the plate while other cells float up and are removed and used for functional assays. The monocytes are then grown in the presence of IL4 and GM-CSF (100ng/ml each) in therapeutic grade serum free AIM-V medium for 7 days. The floating immature DCs were transferred on the 7th day to fresh plate containing AIM-V medium and then exposed to tumour antigens derived either from patient's own tumour lysate or mRNA from the tumour for 4 hours. IL-1 β and TNF- α are added at 100ng/ml and incubated for another 3 days. The mature primed cells were then characterized using FACS and functional assays.

Mature primed DC's were HLA-DP, DQ, DR +++; CD86++; CD14 negative. In contrast, immature DC's were HLA-DP, DQ, DR +++; CD86+; CD14 negative, indicating that they are less likely to be good antigen presenter due to lower levels of co-stimulatory molecule CD86. The tumour lysate primed DC's were more effective in functional assays compared to mRNA primed DC's particularly when primed in a ratio of 3 tumour cell : 1 DC.

2. A Phase 1 clinical trial to evaluate the toxicity of DC vaccine in recurrent and/or metastatic HPV positive cervical cancers :

This was a part of the DBT funded study. The study was a 3 arm study recruiting cervical cancer patients who had relapsed or had progressive disease after initial radical radiotherapy. Arm 1 patients received saline; Arm 2 received mature unprimed DC's; Arm 3 patients received mature tumour lysate (patient's own tumour) primed DC's. The inclusion and exclusion criteria have been published (16). Arm 1 was dropped after recruitment of 9 patients, as the DBT review committee found a satisfactory difference between patients receiving the DC's (primed or unprimed) compared to those

receiving saline. 5 additional patients were recruited (3 in Arm 2 and 2 in Arm 3). Patients were given 3 doses every 14 days, of the appropriate DC vaccine at a maximum dose of 1×10^6 mature DCs per injection.

The DC vaccine was well tolerated with most of the patients having no side effects. Itching at the site of injection (1 patient), grade 1 fever possibly due to urinary tract infection (2 patients) and one patient had elevated serum Alkaline phosphatase. The Delayed Type Hypersensitivity (DTH) response was evaluated in 11 of the 14 patients recruited, with 2/4 Arm 2 and 2/4 Arm 3 patients tested being positive. In one of the Arm 3 patient who had locally persistent residual disease and a solitary lung

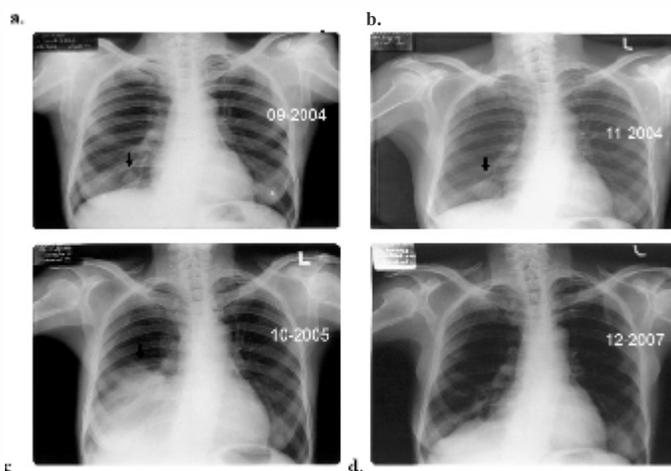


Fig. 1: Progress in the metastatic lung lesion in one of the patient.
Fig. 1a. Lung metastatic lesion detected at patient enrolment (indicated by black arrow). **Fig. 1b and c** show progression of lesion after vaccination (1c. Was taken a year after vaccination). **Fig. 1d.** Shows complete regression of lesion three years after vaccination and 1.5 years after cisplatin chemotherapy. The patient is disease free 9 years after the chemotherapy in 2006.

metastasis after radical radiotherapy, her local disease resolved within 6 months after her last dose. Her lung lesion progressed and she was advised symptomatic treatment only at her last follow-up in 2005 at which time the lesion was pushing her chest wall. In December 2007, when we were updating our follow-up information telephonically, she was found to be alive and well. She was then reviewed at the Institute and was found to be free of disease locally and at the metastatic site (Fig.1). She continues to be free of disease 9 years since receiving cisplatin. While cisplatin is known to produce complete response in metastatic sites, the disease relapses within 18 months to 2 years. That this patient is free of disease for more than 9 years suggests that the DC vaccine could have contributed to the sustained disease free status by triggering the memory T-cells when the tumour antigens were released due to the chemotherapy administered. The same patient had the strongest proliferative response as well as a strong DTH response, indicating that her immune system had been stimulated well.

Based on our data, we have been now funded by the Department of Science and Technology, Government of India for conducting a Phase 2 study. This will be a 3 arm study in untreated stage IIIB cervical cancer patients, with Arm 1 patients receiving standard therapy of concurrent chemo-radiation; Arm 2 patients receiving standard therapy of concurrent chemo-radiation plus DC vaccine primed with patient's own tumour lysate; Arm 3 patients receiving standard

therapy of concurrent chemo-radiation plus DC vaccine primed with SPAG9 recombinant protein (developed by Prof. Anil Suri, National Institute of Immunology). DCGI clearance was obtained in Feb 2015 and hope to start the study by August 2015.

Conclusion :

Work summarises our research in cervical cancer covering almost all aspects of the disease. There are several firsts in the country highlighted here – the first Epidemiological study to identify 14 HR HPV and 10 LR HPV subtypes in cervical cancer patients and healthy controls; first to identify a predictive marker for identifying patients who can be treated with radical radiotherapy alone; first to develop and conduct a phase 1 Dendritic cell vaccine clinical trial; first to develop a low cost ELISA for cervical cancer screening. Ours is an on-going endeavour to help control the disease.

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Clinical Epidemiological Study of Oral Pre-cancer and Cancer in a Tertiary/Referral Hospital

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ABSTRACT

Aim: To study the prevalence of oral cancer in patients reported to the Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College and Hospital.

Materials and Methods: After selecting the patients with the clinical criteria the history of the habits, duration in months and frequency per day, duration of the symptoms, oral mucosal site involvement, lymph node involvement, associated with lesions were recorded in a structured proforma. Incisional biopsy under Local anaesthesia and histological examination was performed. The results obtained were analysed statistically.

Results: 200 patients were diagnosed with oral cancer, 49% were male and 51% were females. In that 51(25%) were associated with premalignant lesions, 94 had only one habit, 74 had a combination of habits, 40% were histopathologically moderately differentiated followed by 33% poorly differentiated and 27% well differentiated. And patients with stage III (31%) and IV (43%) were reported predominantly than stage I (12%) and II (14%).

Conclusion: Early diagnosis and intervention prevent the progression of oral cancer.

Keywords : Tobacco, awareness, oral cancer, epidemiology.

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INTRODUCTION

Oral carcinoma is a global health problem with increasing prevalence and mortality rates. It is the sixth most common cancer in the world (1). Worldwide, the annual incidence exceeds 3,000,000 new cases (2). Oral cancer accounts for 2% cancer death in males and 1% in females. Majority of oral cancers involve tongue, oropharynx and floor of the mouth. The lips, gingiva, dorsum of the tongue and palate are less common sites (3). Oral cancer is a disease of increasing age. Approximately 95% of cases occur in people older than 40 years (1). The age related incidence suggests that time dependent factors results in initiation and progression of genetic events that results in malignant change. The incidence of oral cancer is clearly age related which may reflect declining immune surveillance with age, time for accumulation of genetic changes and duration of exposure to initiators and promoters.

Tobacco and alcohol are acknowledged with factors for oral cancers. In parts of Asia, for example India where the use of tobacco, betel nut or lime to form a quid is widespread, the incidence of oral cancer is high. The use of smokeless tobacco products (chewing tobacco and snuff) is of increasing concern due to increase in their use at young age (4, 5, 6).

Benign hyperkeratosis and epithelial dysplasia have been documented after short term use and it is

likely that chronic use will be associated with an increase in incidence of malignant lesions (7).

All forms of alcohol including hard liquor, wine and beer have been implicated in etiology of oral cancer. The combined effect of alcohol and tobacco result in synergistic effect on the development of oral cancer (6). The mechanism may include dehydrating effects of alcohol on the mucosa, increasing mucosal permeability and the effect of carcinogens contained in alcohol/tobacco. In lip cancer, sun exposure and tendency to burn, pipe smoking and alcohol are identified risk factors.

Oral cancer is a result of a multistage process from normal to dysplastic lesions and ultimately to carcinoma. Dysplastic lesions have been categorized as mild, moderate or severe based on histologic criteria. Carcinoma *in situ* is a lesion in which abnormal cells involve the entire epithelium without invasion through the basement membrane (8). The presence and severity of dysplasia is thought to have an impact on the malignant risk of potentially malignant disorders (7).

Oral cancer is initially asymptomatic and symptoms develop after progression of disease. Discomfort is the most common symptom that leads the patient to seek care and is present at the time of diagnosis in up to 85% of the patients. Patients also may present with an awareness of a mass in the mouth or neck.

Dysphagia, odynophagia, otalgia, limited movement and bleeding occur less frequently. Lymphatic spread of oral carcinoma usually involves the submandibular and digastric nodes, the upper deep cervical nodes and finally the remaining nodes along the cervical chain (9).

Imaging including routine radiology, computed tomography, nuclear scintigraphy, magnetic resonance imaging and ultrasonography can provide evidence of bone involvement and can indicate the extent of some soft tissue lesions.

The principle objective of treatment is to cure cancer patients. The choice of treatment depends on such factors as cell type and degree of differentiation. Surgery/radiation are used with curative intent in the treatment of oral cancer. Chemotherapy is an adjuvant to principle therapeutic modalities of radiation and surgery.

Materials and method:

The study was conducted at the Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College and Hospital, Chennai, after obtaining the ethical clearance. The study population was screened from the patients visiting the Department of Oral Medicine and Radiology TNGDC&H. After selecting the patients with the positive history of betel quid, tobacco, alcohol use, pain, swelling, ulceration, growth, white/red patches, numbness,

difficulty in swallowing and chewing, socio-demographic-economic characteristics, past history as well as informed consent were obtained from each patient after explaining the complete detail about the study. Complete clinical examination (intra and extra oral examination) by using diagnostic instruments was performed. Laboratory investigations including routine blood (CBC, Hb%, ESR, Peripheral smear), urine analysis (urine glucose, protein and deposits) and ICTC for HIV screening was done. The history of habits, especially with reference to the duration in months and frequency per day, duration of the symptoms, oral mucosal site involvement, lymph node involvement, associated with lesions were recorded in a structured proforma specially designed for the study. The results were analysed statistically.

The parameters used in the establishment of the diagnosis are positive history of the use of betel quid, tobacco and alcohol. Besides symptoms and signs of pain, swelling, ulceration, growth on oral mucosal sites along with the involvement of lymph nodes and the associated potentially malignant disorders were recorded in a structured proforma designed for the study.

Radiological examinations were carried to evaluate bone involvement. Patients with diffuse and multifocal lesions were subjected to toluidine blue staining. The patients were then subjected to incisional biopsy under Local anaesthesia and histological examination

was performed.

After the histopathological result, the patients were sent to the Department of Oncology for further management. Necessary treatment was given to patients with oral precancer and cancer.

Results:

200 patients were diagnosed with oral cancer. Their ages ranged from 30-80 years (36%). The age of 72 patients were between 30-50 years, 75 patients were between 50-60 years (37%) and 53

patients were more than 60 years (27%).

Among the 200 patients, 98 patients were male (49%) and 102 patients were female (51%). Regarding the distribution of habits in patients included in the study, 32 patients had no habits, 75 chewed quid, 26 chewed pan parag, 45 were smokers and 22 were alcoholic. Among the patients who had the history of habits, 94 had only one habit, 74 had a combination of habits [Chewing + alcohol + smoking (23), Chewing + alcohol (19), Chewing + smoking (32)] (Table 1).

Table 1: Distribution of Risk Habits

Habits	No of patients(n=200)	Percentage
No habit	32	16%
Quid	75	38%
Pan Parag	26	13%
Smoking	45	22%
Alcohol	22	11%
Only one habit	94	47%
Combination of habits	74	37%
1.Chewing + alcohol + smoking	23	11.5%
2.Chewing + alcohol	19	9.5%
3.Chewing + smoking	32	16%

Regarding the oral hygiene practise of the patients included in the study, we have found that 70 were using brush to cleanse the tooth, 91 were using fingers and 39 were using stick. The frequency of habit among them was 149 were brushing once daily, 25 twice daily and 26 don't brush regularly.

Out of 200 patients, on careful clinical examination, 51 were found to have associated with premalignant lesions (Fig-1a,1b,1c,1d) [Oral submucous

fibrosis (31), leukoplakia (14), lichen planus (6)] and 149 had no premalignant lesion. 71 lesions (36%) were present on Buccal Mucosa, 31 lesions (16%) were on Tongue, 28 lesions (14%) were on alveolar mucosa, 23 were on the floor of the mouth(11%), 13 were on the Palatal Mucosa (6%), 13 were on the Retromolar trigone (6%), lip (6%) and gingiva (5%). Buccal Mucosa was clearly the predominately affected site among the 200 patients (Table 2).

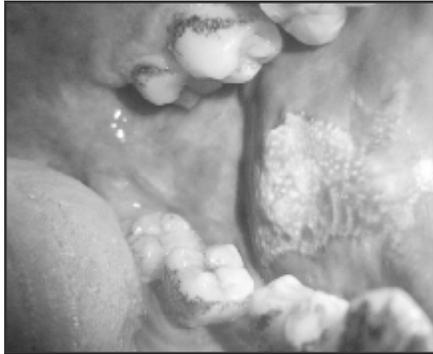


Fig. 1a: Speckled leukoplakia



Fig. 1b: Leukoplakia

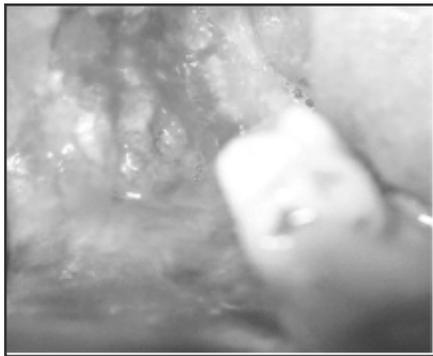


Fig. 1c: Erosive Oral lichen planus

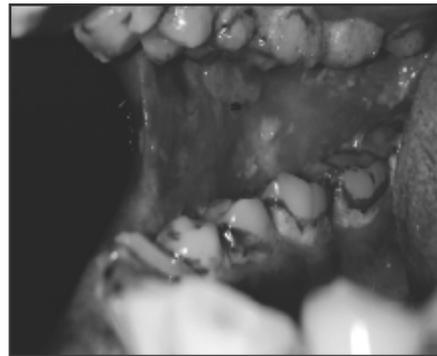


Fig. 1d: Oral submucous fibrosis

Fig. 1: Clinical pictures of potentially malignant disorders.

Table 2: Distribution of Lesions and Sites

Associated pre malignancy	No of patients(n=200)	Percentage
Associated	51	25%
1. Oral submucous fibrosis	31	15%
2. leukoplakia	14	7%
3. lichen planus	6	3%
Not associated	149	75%
Site	No of patients(n=200)	Percentage
Buccal mucosa	71	36%
Tongue	31	16%
Alveolar Mucosa	28	14%
Floor of the mouth	23	11%
Palate	13	6%
Retro molar region	13	6%
Lip	11	6%
Gingiva	10	5%

On through clinical examination, we have found that, 128 had involvement of submandibular lymph nodes, 32 involved the upper deep cervical and 40 had no node involvement. The

submandibular lymph node showed predominant involvement than the other nodes. Regional node involvement was found to be as N0 (40), N1 (62), N2a (47), N2b (23), N2c (16), N3 (12) (Table 3).

Table 3: Lymph Node involvement and Staging of Tumor

Lymph nodes	No of patients(n=200)	Percentage
Sub mandibular	128	64%
Upper deep cervical	32	16%
Regional node involvement	No of patients(n=200)	Percentage
N0	40	20%
N1	62	31%
N2a	47	23.5%
N2b	23	11.5%
N2c	16	8%
N3	12	6%
Staging	No of patients(n=200)	Percentage
Stage I	25	12%
Stage II	28	14%
Stage III	61	31%
Stage IV	86	43%

25 were diagnosed stage I, 28 as stage II, 61 as stage III and 86 as stage IV (Table 3). The patients in the stage III and IV were out numbering the patients in stage I and II. Being a tertiary care and a referral hospital, most of the reported were referred at the stage II and IV for the treatment to this hospital.

After histopathological confirmation, among the 200 patients, 65 cases were histopathologically poorly differentiated, 55 were well differentiated (Fig-2a,2b) and 80 were moderately differentiated figure (Fig-3a, 3b) (Table 4).

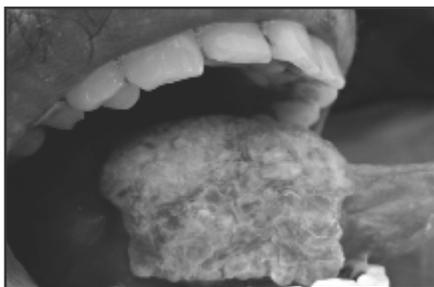


Fig. 2a: Carcinoma of tongue TNM stage III

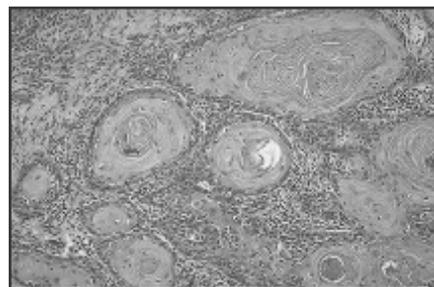


Fig. 2b: Histopathological photo

Fig. 2: Well differentiated squamous cell carcinoma.



Fig. 3a: Carcinoma of lip

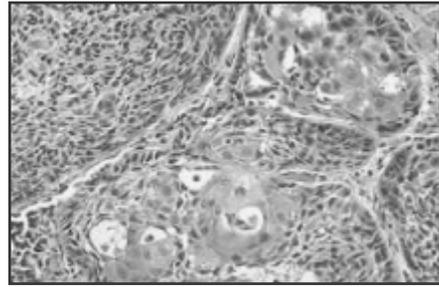


Fig. 3b: Histopathological photo

Fig. 3: Moderately differentiated squamous cell carcinoma.

Table 4: Distribution of Histopathological Grading of Squamous cell carcinoma

Histopathology	No of patients (n=200)	Percentage
Poorly differentiated	65	33%
Moderately differentiated	80	40%
Well differentiated	55	27%

Among the 200 patients who were study population, 158(79%) were native of Tamil Nadu and 42(21%) were from other states.

Discussion:

Oral carcinoma is a global health problem with increasing prevalence and mortality rates. Among these, the majority are squamous cell carcinoma. 64% of the total study population were from 50-70 years of age group and 36% of the population were from 30-50 years of age group. In the aspect of age, present study was consistent with study by Burungale *et al.* (10), suggesting that incidence of malignancy increases with age. But it is also found that the percentages of patients in younger age groups were also considerably affected. The age related

incidence suggests that there dependent factors result in initiation and progression of genetic event that result in malignant change. The incidence of oral cancer is age related which may reflect declining immune surveillance with age.

In our data, 25 were diagnosed stage I, 28 as stage II, 61 as stage III and 86 as stage IV (Table 3). The patients in the stage III and IV outnumbers the patients in stage I and II. Being a tertiary care and a referral hospital, most of the reported were referred at the stage II and IV for the treatment to this hospital. Our results correlates with studies by Khandekar *et al.* (11) and Singh *et al.* (12) that the reported cancer cases were in the advanced stages i.e. stage III and IV of TNM classification and majority of them were squamous cell carcinoma.

The most important etiological factors are tobacco, excess consumption of alcohol and betel quid usage, these factors act separately or synergistically. Attributable risk of oral cancer due to both tobacco and alcohol is estimated to be more than 80% (13).

Observation in this study is similar to the study conducted Burungale *et al.* (10) who reported that tobacco chewing, tobacco smoking and alcohol consumption habits shows the synergistic effect in development of oral premalignant and malignant conditions.

A diet deficient in antioxidants is a further factor that predisposes towards the development of oral cancer (13).

Gabriel *et al.* (14) in 2006 in his study to determine the effects of smoking in the antioxidant level in serum, found that chronic smoking lowers the concentration of dietary antioxidants in serum. So from his observation he suggested that smoking as the risk factor for oral cancer.

Reactive oxygen species are highly reactive molecules that have been implicated in the etiology of potentially malignant disorders. The protective mechanism exerted by the antioxidants is by preventing the production of free radicals and repairing the damage. When the level of free radicals exceeds the antioxidant level disease will result (15).

Babu S *et al.* (16) in 1996 from his study revealed that habitual chewing of

pan masala is associated with earlier presentation of potentially malignant conditions.

In this study, cases showed poor oral hygiene which is similar to the study performed by Anirudh Shukla (17) who reported that in 29.41 % of the cases had poor oral hygiene.

In this study, among the premalignant disorders oral submucous fibrosis accounts for highest prevalence followed by leukoplakia and least being lichen planus which is similar to the studies conducted by Anirudh Shukla (17). Buccal mucosa was the commonest site among both oral premalignant and malignant conditions which is consistent with studies by Anirudh Shukla (17) and Burungale *et al.* (10).

Finding out the source and planning for health awareness activities for the prevention are the major role of the epidemiological studies. Epidemiological studies will be helpful in planning future health care awareness activities, tobacco cessation counselling needed towards prevention of oral cancer. This epidemiological study will be helpful to the patients as it will reduce the morbidity, reduce the incidence of invasive oral cancer, improve the prognosis of individual patients and also helps in identification of high risk group and opportunities for intervention (18).

After the diagnosis of oral cancer, the survival rate of the patients are 50-55%, even less in patients when diagnosed

at the stage III and stage IV. Prevention of oral cancer and its mortality depends upon the early detection of the lesion. For this the dental professionals have to update their knowledge regarding the oral cancer and its prevention and early diagnosis. And it is also emphasized on them, the importance of thorough multiple oral examination and obtaining the complete history from the patient (19).

Since there are enormous evidences to support the relation between the oral diseases and oral habits, controlling and preventing the tobacco usage is now gaining greater significance. In tobacco cessation counselling, in addition to asking and advising the patients regarding the ill effects of habits, steps should be taken for the intervention of the habit (i.e.) 5As' protocol should be followed, asking about the smoking status, advising the benefits of quitting, assessing the motivation to quit, assisting in the quitting attempt and arranging for supportive follow-up (20).

Conclusion:

Creating awareness about the evil effect of chewing and/or smoking form of tobacco and about the early precancerous lesions and conditions, self- examination of the mouth is essential for preventing the occurrence of oral cancer.

Early diagnosis and intervention prevent the progression of oral cancer. In general, the early signs and warnings of oral cancer should be displayed in dental hospitals for patient education. Dental

surgeons play a vital role in the prevention of oral cancer by educating the patients on various bad effects of tobacco chewing, snuff and alcohol use. The dental surgeons should also have a thorough knowledge about the diagnosis of various precancerous lesions and conditions, investigations and the treatment modalities for quick intervention. They should also know the referral protocol if they diagnose frank malignancy.

Tobacco cessation counselling centres should be initiated in dental hospitals for counselling the patients.

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An Innovative 3 Dimensional Model of Middle Ear

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ABSTRACT

Background: Physical models are particularly useful in demonstrating complex topics in anatomy or those ones that are difficult to access when seen in the textbook or cadaver. One such topic is middle ear. Aim of the present study was to introduce a multicolored cardboard model of middle ear to provide ease in understanding of its anatomical structure.

Methods: The participants were 2nd semester medical undergraduate class of students. They were exposed to a cuboidal multicolored model (made from cardboard box) with 6 walls that could be opened to see the details of structures related to them. Student feedback was taken through a structured Questionnaire based on Likert Scale (5 to 1).

Results: More than 80% of students felt that this model was a good tool for visualizing complex anatomy of middle ear in small groups and it reduced the time needed for self-study. This model provided multifaceted feedback with active participation from students. A low fidelity middle ear model proved to be a practical low cost tool for use in both didactic and small group teaching.

Conclusion: Low fidelity models continue to have a place in anatomy and can be integrated in the current curriculum.

Keywords: Middle ear, 3 dimensional, teaching methodologies, gross anatomy education.

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INTRODUCTION

Since historic times, teaching and learning anatomy has been an integral part of medical education. The course content of Anatomy is vast and requires in-depth knowledge. The study of anatomy is generally related to identifying various structures along with their spatial relationships with respect to each other. The primary goal of study of human gross anatomy as well as physiology is anatomical reasoning with anatomical and physiological explanations of normal and abnormal functioning of the body, clinical signs and pathogenesis of various diseases as well as of procedures for clinical examination and surgeries.

A strong foundation of understanding anatomy requires appreciation of complex 3D spatial relationships and conceptual 3D visualization skills. There has been a continuing debate about the best way of teaching anatomy. For centuries, the classical way of anatomy education was cadaveric dissection, which has been a gold standard due to its engagement of multiple senses of students (1). There are alternative methods like computer aided learning with construction of human body in virtual 3 dimensional space generated by digital computers and low fidelity models which show spatial relationships between structures of human body (2,3).

The morphology of the middle ear is difficult to appreciate during human dissection because of its complex shape and intricately arranged structures in 3D

configuration.

The aim of the present study was to introduce a multicolored cardboard model of middle ear to improve the concept of 3D relationship of various structures in it.

The students were encouraged to participate in the practical session and were allowed to manipulate the model with their hands. Student feedback was taken through a structured questionnaire based on Likert scale (from 5 to 1).

Materials and Methods:

The study involved 2nd Semester medical students (n=78). The students were divided into random groups and exposed to a 3D model of middle ear under the supervision of facilitators.

A cuboidal cardboard box was converted into a multicolored model with 6 faces corresponding to roof, floor, medial, lateral, anterior and posterior (Fig. 1,2). The walls could be opened to see the details of structures related to them (Fig. 3). Anatomical color code was followed i.e. arteries were in red, veins in blue, nerves in yellow and muscles in brown. The legends of the model were separately printed as a small manual. The students were encouraged to actively participate in the demonstration of the model.

The contents of the middle ear i.e. the ear ossicles were not demonstrated in the model.

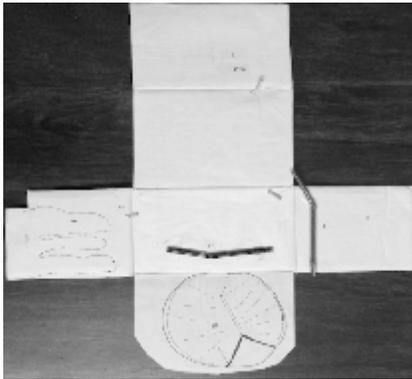


Fig. 1: Model of middle ear opened from outer aspect



Fig. 2: Model of middle ear opened from inner aspect

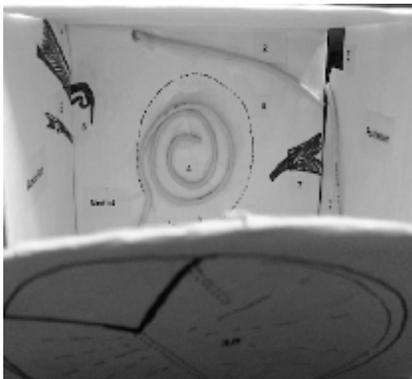


Fig. 3: Model of middle ear with closed walls

At the end of the session, the students were asked to record advantages of this external representation of middle ear under the following headings:

1. Dimensions
2. Number of structures included in the model
3. Spatial relationships between structures
4. Size of structures in comparison to normal size
5. Shape and details of color, pattern of structures

A student feedback was taken through a structured questionnaire and rated on a score of 5-1 based on Likert scale (Table 1) was taken at the end of the session.

Results:

The physical model of middle ear was well perceived by the students and was assessed in the following aspects by the authors:

1. Dimensionality: The model was 3 dimensional with a close resemblance to the actual middle ear having 6 walls. This was better understood by the students as compared to the computer generated virtual 2D model with just visual clues to indicate depth.

2. Number of structures: 18 out of 20 structures were represented in the model that was in close resemblance to the actual structure.

3. The spatial relationships between

Table1: Student feedback questionnaire with responses (in %)

S. No.	Questions	Strongly Agree (5)	Agree (4)	Neutral (3)	Disagree (2)	Strongly Disagree (1)
1.	I prefer to use this model in a group session.	47.4	44.9	7.7	0	0
2.	I prefer learning anatomy of middle ear by using this 3D model	65.4	28.2	2.6	2.6	1.3
3.	This 3D model demonstrates the middle ear anatomy in a way that is easier to visualize	47.4	41.0	7.7	3.8	0
4.	If I am learning the anatomy of middle ear I want to have this resource available to me	29.5	51.3	15.4	0	0
5.	It is a useful tool to students	50.0	44.9	5.1	14.1	0
6.	This physical model is better as a tool than any 3D software	34.6	26.9	21.8	0	2.6
7.	Helps in understanding/visualizing the anatomy of middle ear written in text books	52.6	42.3	5.1	0	0
8.	Small group learning is better than didactic lectures	53.8	30.8	15.4	0	0
9.	It reduced the time needed for self-study	33.3	50.0	12.8	0	3.8
10.	It had positive impact on my attitude towards learning	39.7	42.3	16.7	0	1.3

various structures in the model were clearly indicated which also included the relation of various structures with roof, floor, anterior, posterior, medial and lateral walls of middle ear cavity.

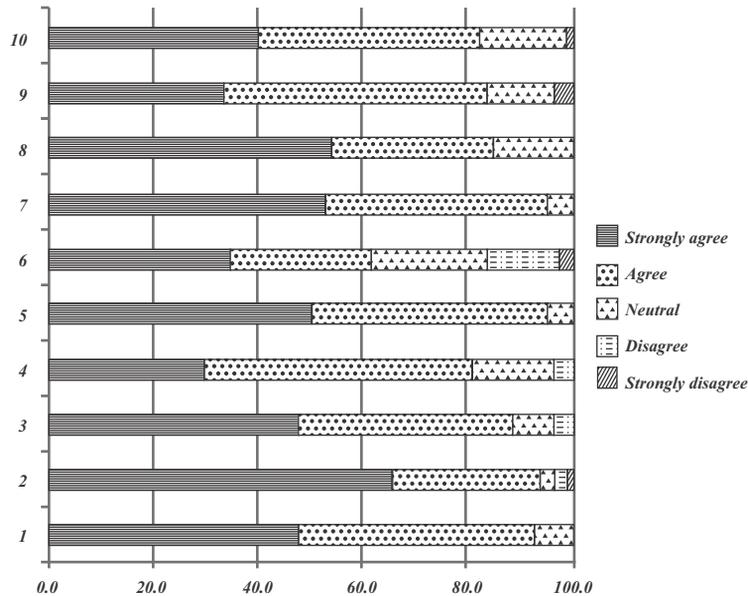
4. Absolute and relative size of structures: The size of structures were amplified as the middle ear cavity is very complex and cannot be comprehended in its absolute size.

5. The color and pattern of various structures as well as blood vessels was maintained closed to normal as much as possible.

A student feedback was taken through a structured questionnaire (Table 1). The feedback was expressed in percentage for each question (Chart 1).

Discussion:

More than 80% of students felt that the 3D model was a good and useful learning tool for demonstration of middle ear anatomy and helped in understanding/visualizing the anatomy of middle ear in textbooks. They also felt that it had a positive impact on their attitude towards learning. A large number of students also felt that small group learning

Chart 1: Student feedback response (in %)

was better than didactic lectures and that these kind of models reduced time required for self-study (Table 1, Chart 1).

Anatomy is a vast field and an essential foundation for the study of medicine in diagnosis and therapy (1). The study of anatomy mainly involves identification of structures and forming concepts through 3D visualization skills. Dissection and prosections are generally considered to be the gold standard of anatomy education (1). Various advantages of using dissection as a learning tool include conceptualization of multidimensional aspects of human body, tactile manipulation of tissues, acquiring practical skills for dissection, appreciation of anatomical variations, ethical and moral issues arising from obtaining and contact with cadavers.

However, there has been a decline in teaching through dissection due to decrease in the availability of cadavers and also moral and ethical issues surrounding their use. Medical institutions across the globe are introducing various alternative methods of teaching anatomy (1,4,5). 2 D representations like 2D images, textbooks, chalk drawings, cause an increase in the cognitive overload on students (6).

Interest in the development and use of new educational tools has grown due to increase in the demand of new products for teaching. Anatomy model is a construct that is similar to the structure of any part of human body and can be used in learning and teaching students. It can be physical or digital (virtual 3D computer

image). Physical models can be used to supplement current teaching methods and are particularly useful in demonstrating complex topics or those ones that are difficult to access when seen in the textbook or cadaver (7). One such topic is middle ear. Classical textbooks illustrate its morphology using drawings and pictures with different viewing angles and are difficult to comprehend. Physical models are good 3 dimensional external representations of human body. We assessed various aspects of the physical model of middle ear in a way that was similar to the study done by Chan and Cheng (8).

Studies have reported that physical models had visible visuospatial advantages over textbooks as well as 3D computer models both objectively and subjectively (6). Khot *et al.* in their study came to a conclusion that a group of students who used 3D plastic model did better than the groups using either 2D photographs or 3D computer based virtual images (9).

Although the model of middle ear made by the authors was low fidelity one, these models have several advantages over others in education. They serve as good memory aids as they can be easily remembered because they simplify complex spatial relationships of regions of the body, which are difficult to comprehend. Another advantage is reduction in cognitive overload by reducing the amount of information needed by them to attain their desired educational goals. These models arouse

student's enthusiasm and participation.

Krontiris & Litowitz have shown that hand held “manipulatives” improve critical thinking of undergraduate students (10). These models require minimal resources to make and reproduce by using inexpensive and easily available materials. These low fidelity models require proper instructions by the teacher to establish correspondence of the model to the structures of the body.

Thus, low fidelity models that are external representations of various structures of the body, which may not exactly correspond to these structures and require proper instructions for study by students, they still have numerous advantages over other alternative methods of education. Student manipulation of these models was encouraged, as they were easily reproducible even if damaged which is in contrast to expensive 3D virtual images and other life like physical models.

Limitations of the study:

The present study has few limitations. The student group on which the study was done was small in number and they were given the model after the didactic lecture on middle ear was taken.

Conclusion:

A low fidelity middle ear model proved to be a practical low cost tool for use in didactic and small group teaching. These models continue to have a place in

anatomy and can be integrated in the current curriculum as by making these models, the students get a better spatial orientation and understanding of the body.

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Short Answer Open-Ended versus Multiple-Choice Questions: A Comparison of Objectivity

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ABSTRACT

Objectives: We designed our study with the hypothesis that open ended Short Answer type Questions (SAQs), no matter how carefully framed, cannot be as objective as Multiple Choice type Questions (MCQs).

Methods: The study was conducted on 1st year MBBS students (n=99) studying at AIIMS, Jodhpur. A written test on 'Blood & Immunity' was conducted containing same questions in two formats; twelve MCQs (type E) in section A and 12 SAQs in section B. Maximum marks for all questions in both sections were equal. All the answers of section B were evaluated separately by two different examiners to reduce the subjectivity and a model answer sheet for both the sections was prepared and provided to both the examiners.

Results: The difference in the scores in Section B SAQs that were evaluated by two different examiners was not statistically significant. Mean of the marks awarded by the two examiners was taken as the final score of each student in section B. The difference in the scores by the students in the two sections was also non-significant (p=0.14). A significant correlation (r=0.99, p<0.0001) was found in SAQ and MCQ scores. Bland-Altman analysis also showed no proportion of bias and the two methods of scoring were in agreement with each other.

Conclusion: The results suggest that meticulously-framed open-ended short answer type questions can be as objective as multiple choice type questions.

Keywords: Multiple choice questions, medical education, assessment, open-ended questions.

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INTRODUCTION

Over the last few decades in India, there has been substantial re-evaluation in the undergraduate medical curriculum, especially on the teaching and assessment methodology. Assessment is a means of measuring knowledge and competence, has a pivotal role in stimulating learning as well as providing feedback to students and teachers(1). Written assessment is an integral part of medical education. Subjective assessment in theory is gradually giving way to objectivity; longer essay-type questions (LAQs) are being replaced by Short Answer Questions (SAQs) and Multiple Choice Questions (MCQs) (2). There have been much debate with respect to the type of written assessment to be administered to the students in order to test higher order cognition(3).

An assessment has to be reliable and valid, free from bias and manipulations (1, 2). Reliability is the degree to which an assessment tool produces stable and consistent results. Validity refers to how well a test measures what it is purported to measure (4). Open-ended format in the form of long-essay type, mini-essay type and short answer type questions is still preferred format for summative assessment. It is well documented that open ended questions have greater validity and they test higher order cognition level of knowledge (3, 5,6). On the other hand, closed-ended or

multiple choice format is shown to be reliable and efficient, objective, unbiased and make linguistic skills redundant. However MCQs can provide the unprepared students an opportunity to score if they guess right. One of the disadvantages of open ended questions is its low objectivity and reliability (7, 8).

Physiology as a discipline, creates a framework for understanding the normal functioning of the human body. It is a concept based subject and therefore has a scope for testing higher order cognitive skills with conceptual questions which, though open ended, have a precise answer. We designed our study with the hypothesis that open ended SAQs, no matter how carefully framed, cannot be as objective as MCQs.

Methods:

This Cross-sectional study was conducted on 1st year MBBS students (n=99) of All India Institute of Medical Sciences, Jodhpur in the department of Physiology, in 2014. A class test from 'Blood and Immune System' was declared about 2 weeks prior to the commencement of the study.

The following format of the test was decided. The students were not told about the type/format of the questions (Fig.1).

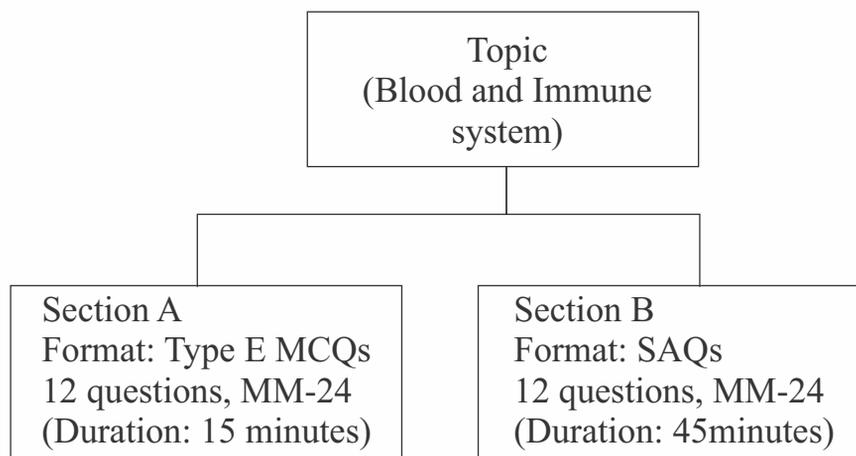


Fig. 1: Algorithm of topic and questions in Section A and B.

Both the sections comprised same questions but in different formats; MCQs and SAQs. Nevertheless, the questions were prepared by two different examiners. Marks for all questions in both sections were equal. Section B paper was distributed after collecting section A answer sheets. All the answers of section B were evaluated separately by two different examiners to minimize the level of subjectivity. A model answer sheet for both sections was prepared and provided to both the examiners. One of the examiners was the one who had taught the topic to these students during their routine teaching sessions.

There was no negative marking in

either section of the question paper.

Table 1 shows the questions in both the formats.

Section A consisted of Assertion-Reason (Type-E) multiple choice questions with following 5 options.

- A. Both A and R are true and R is the correct explanation of A.
- B. Both A and R are true but R is NOT the correct explanation of A.
- C. A is true but R is false.
- D. A is false but R is true.
- E. Both A and R are false.

Section B composed same concept based questions in SAQ format (explain why?)

Table 1 :Questions on identical subtopics in both the formats

Q.No.	Section A (MCQ format) Assertion-Reason	Section B (SAQ format) Explain why?
1	A- Globulin is the first plasma protein to appear in urine in renal diseases. R- Globulins are the smallest protein molecules in blood.	Albumin is the first plasma protein to appear in urine in renal diseases.
2	A- Jaundice is more common in the neonate than in the fetus. R- The fetus has a higher capacity to conjugate bilirubin than the neonate.	Jaundice appears in neonates but not in fetus.
3	A- ABO incompatibility in mother and fetus causes erythroblastosis fetalis. R- Fetal IgG can cross the placental barrier.	ABO incompatibility does not occur in mother and fetus.
4	A- Oxalate is the preferred anticoagulant during dialysis. R- Oxalate is metabolised in the body through the Krebs cycle.	Heparin is the preferred anticoagulant for dialysis.
5	A- Hypocalcemia impairs blood clotting. R- Calcium ion is essential for blood coagulation.	Persons with hypocalcemia never show clotting abnormalities.
6	A- The bleeding time is prolonged in obstructive jaundice. R- Obstructive jaundice is associated with poor absorption of vitamin K.	Clotting time but not bleeding time is prolonged in Obstructive jaundice.
7	A- Hypoproteinemia is associated with edema. R- Significant amount of plasma proteins are lost in the exudate.	Hypoproteinemia leads to generalised edema.
8	A- The hemolytic disease of the new- born is severe when a “B negative” mother bears an A positive fetus in the previous pregnancy. R- A “B negative” mother bearing an A positive fetus produces anti- B antibodies in the late third trimester.	The hemolytic disease of the new-born is less severe if the mother is B- and the previous baby was A+.
9	A-The secondary immune response is rapid and pronounced. R-B and T lymphocytes undergo blast transformation when exposed to antigens.	The secondary immune response is rapid and pronounced.
10	A-The mother well tolerates the fetus. R-The mother and fetus have same genetic makeup.	Fetus is a ‘transplant’ in the mother, yet it is well tolerated.
11	A- Decrease in helper T-cells decreases humoral immunity. R- Helper T- cells are essential for Tc- cell activity.	Decrease in helper T cells (as in AIDS) decreases, not only cellular, but also humoral immunity.
12	A- Immunity normally does not develop against ‘self’ antigens. R- Specific immunosuppression abolishes the response to ‘self’ antigens.	Immunity normally does not develop against self-antigens.

Question on identical subtopics in both the formats :

Statistical analysis was done using statistical packages; SPSS version 21 and GraphPad Prism version 6. Data on students' performance is expressed in percent Mean \pm SD. Unpaired t-test was applied to check inter-examiner bias. The mean and standard deviation, median and interquartile range of marks was calculated and scores in the 2 methods were compared using Wilcoxon Signed Rank test. Regression analysis was performed to see the association of the two scores. Spearman's correlation coefficient (r) was calculated to see the correlation between students' performance on short answer questions and the MCQs. Bland Altman analysis of differences and averages between SAQ and MCQ scores

was done (9). Mean bias and limits of agreement (mean bias \pm 1.96 times SD) were computed.

Results:

Mean marks awarded by examiner-1 and examiner-2 in all 12 questions in section B (open ended questions) were 14.44 ± 2.61 and 14.69 ± 2.82 , respectively, the difference was not statistically significant. Mean of the marks awarded by the two examiners was taken as the final score of each student in section B. **Table 2** depicts the percent marks (mean & median) scored by the students in section A and B. The difference in the scores was non-significant ($p=0.14$). A significant correlation ($r=0.99$, $p<0.0001$) was found in SAQ and MCQ scores (Fig.2, Table 2).

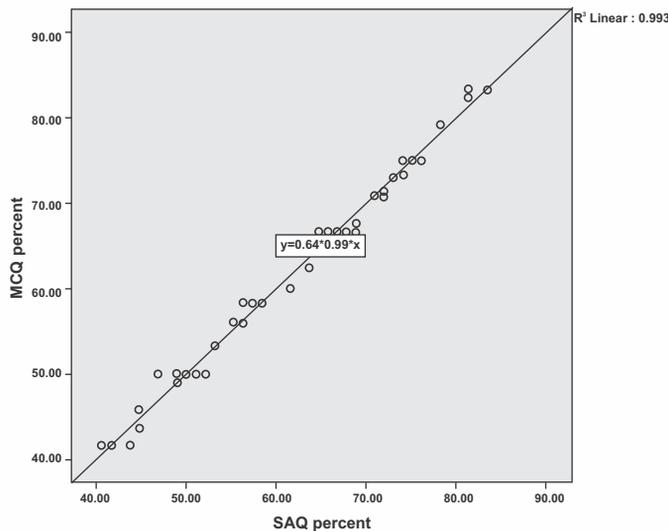


Fig. 2 : Scatter plot of the marks obtained in MCQ versus SAQ. Also shown is the linear best-fit line (Spearman $r = 0.99$, $p<0.0001$).

Table 2 : Marks awarded to students in section A and B.

No. of students	Section A - MCQ score (%)	Section B -SAQ score (%)	MCQ Vs SAQ score	
99	Mean: 60.92 ±11.23 (95%CI-58.68-63.16) Median: 41.67 (33.33-50)	Mean: 60.74 ±11.28 (95% CI-58.49-62.99) Median: 42.7(31.3-55.2)	Wilcoxon Signed Rank Test p=0.14 (ns)	Spearman's correlation r=0.99, p<0.0001

There was no significant difference in the marks scored by the students in the 2 sections. Significant correlation was observed in the 2 scores.

Figure 3 shows the Bland Altman Plot for the differences and averages between marks scored in SAQ and MCQ,

it is showing considerable agreement between the two methods of assessment (non-significant mean difference of 0.058), regression test showed non-significant results suggesting no proportion of bias ($t=-0.48, p=0.63$).

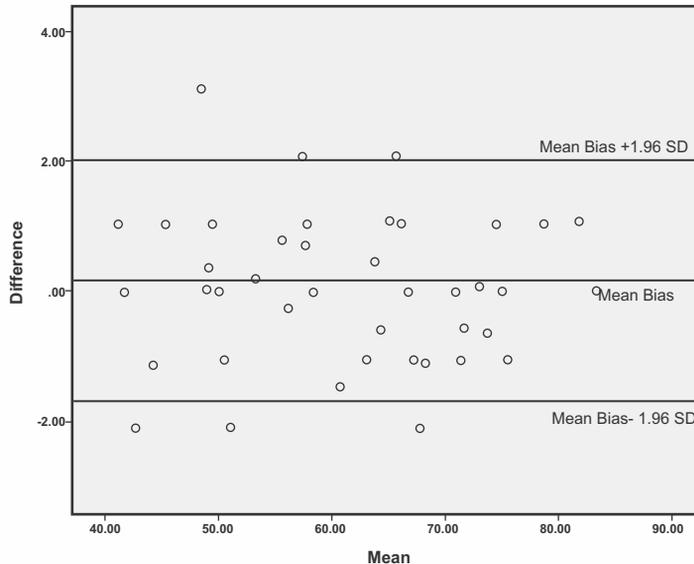


Fig.3 :Bland Altman Plot for the differences and averages between marks scored in SAQ and MCQ depicting considerable agreement between the two methods of assessment

Discussion:

Our study was designed with the hypothesis that small answer type open ended questions cannot be as objective as MCQs. In our study, we assessed the students by both open ended and closed ended questions on the same sub-topics. Contrary to our hypothesis, it was found that there was not much difference in the average scores obtained by the students, giving the impression that both the format are comparable in efficacy. Significant positive correlation was found between students' performance on MCQs and SAQs, emphasizing the fact that students who are bright, performed equally good in both the format. These findings were comparable to the findings by Dagogo J Pepple *et al* (10) who compared MCQs scoring with long essay questions. Similarly positive correlation between student performance on MCQ and short essay questions was observed by Mujeeb *et al* in Pharmacology. However, the correlation was not seen in the scores of the students who either failed or scored a distinction in the subject (11). We didn't correlate the marks in the two format on the basis of students' level of performance.

The Bland Altman plot for the measurement of agreement investigates any possible relationship between measurement error and true value. Bland Altman/Tukey mean-difference plot of the marks obtained by the two methods are showing agreement between the two methods.

A written assessment method

should be reliable, valid, cost effective and acceptable (1). There always have been a debate on type of questions most suited for a reliable assessment. Open ended questions are more pliable, requiring creativity, spontaneity—but they have lower reliability (1,3). Answering open ended questions is much more time consuming than answering multiple choice questions, hence they are less suitable for broad sampling. They are also expensive to produce and to score. Since the students have to frame the answers spontaneously, open ended questions are believed to be suitable to test the ability to solve medical problems(4,5,11). 'Subjected to examiners bias or lack of inter-examiner reliability' is probably the most recognisable disadvantage of such questions(7, 8). But in our study we have shown that if meticulously framed, open ended questions can be as objective as MCQs, free from other pitfalls of open ended questions as well.

Multiple choice questions are well known, and there is extensive experience worldwide in constructing them. Their main advantage is the high reliability per hour of testing—mainly because they are quick to answer—so a broad domain can be covered, free from examiners bias (1,3). However a common prevailing misconception about MCQs is that they are not suitable for testing the ability to solve medical problems (12). The reason behind this assumption is that all a student has to do in a multiple choice question is recognise the correct answer and the belief that MCQs test just the factual recall (13).

This was disproved by Palmer EJ and Devitt (14) who showed that the percentage of questions testing factual recall is same in MCQs as that of modified essay questions (MEQs) (14). Recently Moeen-uz-Zafar & Badr Aljarallah concluded in their study that a well-constructed MCQ is superior to MEQ in testing higher cognitive skills (15). If constructed well, multiple choice questions can test much more than simple facts as shown in the MCQs framed by us (assertion-reasoning type). This finding was supported by Hift who debated that MCQ format is better than open ended question format and suggested phasing out of open ended question format in summative assessment (16). Even if corrected for random guessing component, MCQs may overestimate some group of students and underestimate others (17). This was disproved in our study where the score in the two methods were comparable.

Research has repeatedly shown significant differences in the scores of the students with variation in the question's format (9, 16-18). However, others have proved that the question's format is of limited importance and that it is the content of the question that determines almost totally what the question tests (19,20). Every format has its advantages and disadvantages and a combination of different format is thus essential in assessing the students' performance (21). We too agree that though a well-designed testing format does not affect the performance of the students but assessment programme should include

different type of questions appropriate for the content being tested. At different stage during the course covering the subject curriculum.

Conclusion:

It is a well-known fact that MCQs are the most objective method of assessment testing higher order cognitive skills and several topics can be simultaneously covered through these questions. However, cheating and guessing component are the common drawbacks associated with this format. In this preliminary study, our hypothesis that open ended short answer type questions cannot be as objective as multiple choice type questions was proven wrong. The results suggest that meticulously-framed open-ended short answer type questions can be as objective as multiple choice questions (MCQs). Further they have short precise answers, so multiple topics can be covered and chances of guessing the answers are negligible.

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Conflict of interests:

None to be declared.

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