A brief introduction along with the aims and objectives of this study is must before we proceed to the detailed description of this study. Also rationale of conducting this study is reported in the end.
1.1 INTRODUCTION

1.1a Non communicable diseases and Cancer

Non communicable diseases (NCDs) were reported as major cause of death worldwide. According to World Health Organization report, in year 2008 more than 36 million deaths occurred due to NCDs. Most of the deaths were due to cardiovascular diseases (48%), cancer (21%), chronic respiratory diseases (12%) and diabetes (3%). Smoking and lack of physical activity was reported as major risk factors. Increased blood pressure, body mass index, blood sugar and blood cholesterol adds additional risk for NCDs. Similar trends of NCDs were reported in India. Globally incidence of cancer was 12.7 million in 2008, which will increase to 21.4 million by 2030. Mortality due to cancer was around 7.6 million in 2008, and majority of deaths (70%) happened in low and middle income countries. A recently published study reported about 5.56 Lakh cancer related deaths in India. Head and neck cancer (HNC) was the major cause of cancer related deaths in males (23%).

1.1b Head and neck cancer

Head and neck cancer (HNC) is most common in several regions of the world where people consume excessive tobacco and alcohol. HNC is fifth most common cancer globally and most prevalent cancer in Southern Asia. Incidence of HNC was reported more than half of a million per year in the world. HNC was eighth leading cause of cancer death worldwide in 2000. Among HNC, oral cavity is the most common region for developing cancer in Indian subcontinent and Southeast Asian countries. This is mainly due to their cultural habits of chewing betel quid and tobacco. In India, about one third of all cancers are HNC, about 23% in males and 6% in females. India has the world's highest reported incidence of Head and neck cancer in women. Most of patients (60-80%) report at the advanced stage of their disease, due to
lack of awareness about HNC. Squamous cell carcinoma represents more than 90% of all HNC.\textsuperscript{7} In our center, which is a tertiary care hospital in South India cancer registry records from 1975-2011 showed incidence of HNC was around 25%.

Advanced stage HNC poses major therapeutic challenge to clinicians because of their poor prognosis. Treatments options include surgery, radiation therapy, chemotherapy or a combination. Patients with locally advanced unresectable HNC are frequently treated with concurrent chemoradiotherapy (CCRT).\textsuperscript{8-10} The rationale behind the use of CCRT is that chemotherapeutic agents possess radiation sensitizing properties besides their own anticancer effect. Also, effective chemotherapy can control micro-metastasis outside the lesions treated with radiotherapy\textsuperscript{11}. Studies proved that more aggressive therapeutic regimens lead to improvement in overall survival, disease-free survival, loco-regional control of the disease, or a decrease in distant metastasis with CCRT compared to radiotherapy alone.\textsuperscript{8-11}

\textbf{1.1c Oral Mucositis}

These aggressive treatment regimens related improved outcomes came along with increased treatment related morbidities such as severe grades Oral Mucositis (OM) (grades >2), skin reactions and Xerostomia. Pain associated with OM significantly impairs the patient’s ability of mastication, deglutition and phonation. Swallowing difficulty related to OM can also hamper the nutrition of the patient. Severe grades OM increase the risk of developing infections and septicemia. Overall OM significantly impairs quality of life of HNC patients in all the domains including physical, emotional, functional, and social well-being.\textsuperscript{12,13}

Mucositis associated symptoms arising during CCRT for HNC include “oropharyngeal soreness”; difficulty swallowing; pain; lost or altered taste (Dysgeusia); excessive secretions that may lead to gagging, nausea, and vomiting; loss of appetite; fatigue; weight loss; and aspiration.
The problem of excessive viscid mucus in the oropharynx was rarely reported, but it is one of the most burdensome symptoms for many patients with higher grades of OM.\textsuperscript{12-14} Morbidities associated with severe OM sometimes may require unplanned treatment interruptions, leading to failure of delivering planned chemotherapy and radiotherapy. Interruption in therapy allow healing of normal tissues, but also allow tumor regeneration resulting in poorer disease control hence the cancer treatment delivered rendered useless.\textsuperscript{15} Pain from mucosal injury is often severe, requiring aggressive narcotic pain management and invasive forms of nutritional support that adds significantly to the cost of a treatment program.\textsuperscript{14}

The incidence of OM varies considerably depending on the radiotherapy/chemotherapy/combined modalities regimen used. Overall incidence of all grades of oro-pharyngeal mucositis with various treatment regimens was reported as 80\% (range 3-98\%). While overall incidence of severe grades (grades >2) mucositis was about 39\%. Among patients treated with CCRT it was 43\% (range 31-86\%) and with altered fractionation schedules it was 57\% (range 34-78\%). Unplanned treatment interruptions were required for 11\% patients because of severe grades OM. Especially radiation to head and neck region for HNC, the incidence of severe mucositis varied from 50-98\% in some trials.\textsuperscript{14}

Many treatment modalities were tried for the prevention and treatment of OM such as prostaglandin E2, vitamin E, cryotherapy, chlorhexidine digluconate, benzydamine hydrochloride, placental extracts, amifostine and palifermin. Despite some positive studies none hold promising results against OM.\textsuperscript{16} Till date use of general oral care, oral hygiene, good nutrition, topical mucosal coating agents (sucralfate, magnesium hydroxide), topical anesthetics (lidocaine, capsaicin) and systemic analgesics are recommended for the symptomatic management of OM.\textsuperscript{17}
1.1d Low-level laser therapy

Low-level laser therapy (LLLT) was introduced to medicine in 1967 by Professor Endre Mester (A Hungarian scientist). He published the research regarding therapeutic effects of low intensity Ruby laser in wound healing and hair growth.\textsuperscript{18-20} He coined the term \textit{Laser bio-stimulation}, based on his research findings using of low power laser.\textsuperscript{18-20} Role of LLLT to improve wound healing and pain relief has been already established.\textsuperscript{21,22} LLLT also proved to be useful in acute pain conditions like Rheumatoid arthritis, osteoarthritis and other orthopedic ailments.\textsuperscript{23-25}

Since early 1990s LLLT is being studied as a physical modality for the prevention and treatment of OM and its associated pain in patients receiving chemo-/radiotherapy for HNC/Whole body irradiation for Hematopoietic stem cell Transplant (HSCT).\textsuperscript{26-32} Few trials reported the beneficial effects of LLLT in preventing and decreasing the severity of oral mucositis.\textsuperscript{26-32}

Several mechanisms were explained related to therapeutic effects of LLLT against OM. In vitro and in vivo research, it was observed that LLLT reduced the oxidative stress (i.e. reactive oxygen species)\textsuperscript{33} and also enhanced the immune system response at local region. These are important steps for controlling the pathogenesis of OM.\textsuperscript{34-37} LLLT enhances enzymes activity that can improve cell functions. LLLT acts on the cell membrane and mitochondria which can increase ATP production resulting in the optimal cell functions and hence healthier cells.\textsuperscript{38} Also, laser helps in increasing the protein synthesis within the cells\textsuperscript{39}. LLLT can speed up delayed bone adhesion, regenerate damaged tissue, stimulate angiogenesis and enhance immunological processes.\textsuperscript{34,36,40} Laser can convert fibroblast into myofibroblast which has more stability and tensile strength.\textsuperscript{37} That can prevents the oral mucosa against an early damage with the CCRT.
Also, analgesic effects of LLLT may be because of modification of nerve conduction via releasing the endorphins and enkephalins in the nervous system.41

1.2 NEED AND RATIONALE BEHIND CONDUCTING THIS STUDY

There was limited evidence regarding therapeutic effects of prophylactic LLLT in the prevention and treatment of CCRT induced OM in HNC patients. Hence, this study was carried out to evaluate the effects of LLLT for the prevention and treatment of CCRT induced OM and its associated morbidities.

Despite being highest incidence of HNC in Asian region to our knowledge, this study seems to be the largest sample triple blinded randomized controlled trial in Asian Countries mainly Southern Asia, which evaluated the therapeutic effects of LLLT in the prevention and treatment of CCRT induced oral mucositis in HNC patients. Also, our study seems to be the largest study to date which investigated the effects of LLLT on the subjective outcomes after CCRT induced OM. In addition, there was a need to substantiate the evidence of LLLT against cancer therapy induced OM in HNC patients. So this study contributed the qualitative and quantitative evidence about the therapeutic effects of LLLT against CCRT induced OM in HNC patients.
1.3 AIMS

To evaluate the therapeutic effects of Low Level Helium Neon (He-Ne) Laser Therapy in the prevention and treatment of concurrent chemoradiotherapy induced oral mucositis in Head and Neck cancer patients.

1.4 OBJECTIVES

1.4a Primary Objectives

1. To evaluate the oral mucositis in patients undergoing concurrent chemoradiotherapy and to compare the differences between laser and control groups.

2. To determine the pain intensity associated with oral mucositis in patients undergoing concurrent chemoradiotherapy and to compare the differences between the laser and control group.

1.4b Secondary Objectives

3. To determine the need of supplement analgesics to reduce the pain intensity associated with oral mucositis in patients undergoing concurrent chemoradiotherapy and to compare the differences between the laser and control group.

4. To determine the degree of dysphagia in patients undergoing concurrent chemoradiotherapy and to compare the differences between laser and control groups.

5. To study the impact of mucositis on the nutritional status of the patients, measured in terms of weight loss over the course of treatment.

6. To determine the change in patient reported measures of oral mucositis in patients undergoing concurrent chemoradiotherapy and to compare the differences between the laser and control group.
7. To determine the cancer treatment break associated with oral mucositis in patients undergoing concurrent chemoradiotherapy and to compare the differences between the laser and control group.

8. To study the impact of oral mucositis on quality of life in patients undergoing concurrent chemoradiotherapy and to compare the differences between the laser and control group.