A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms

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Certificate

This is to certify that the dissertation entitled "**A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms**" is a bonafide record of the original work done by **Dr. Jeba Karunya** towards the partial fulfilment for the award of **Doctor of Medicine** in **Radiotherapy** of The Tamil Nadu, Dr. M.G.R Medical University, Chennai conducted in April 2014.

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Contents

1. AIMS

1.1) Primary objectives:

1. To assess the feasibility and toxicity of hyperthermia along with radiation in patients with locally advanced non metastatic head and neck cancers

2. To assess the palliation of distressing symptoms in locally advanced head and neck cancers treated with palliative intent

3. To assess the duration of treatment in comparison with the standard of care, which is usually six weeks

1.2) Secondary objective:

To assess the efficacy of this modality in terms of disease response as weekly clinical assessment, at the end of treatment and at three months.

2. INTRODUCTION

Head and neck cancers are the sixth most common cancers worldwide (1). They are responsible for significant morbidity and mortality rates, more in developing countries. The major risk factors are smoking, tobacco consumption, human papilloma virus (HPV) infection, Epstein barr virus (EBV) infection. Most of the incidence of these cancers in various parts of the country is related to the risk factors prevalent in those regions, indicating the need for cancer education and screening campaigns. Most of the Indian patients present with locally advanced malignancies to the hospitals. The standard treatment option is multimodality regimen with surgery, radiotherapy and chemotherapy. Surgery in most cases is not possible due to inoperability, lack of technical facilities and associated comorbidities.

Radiotherapy has been the standard non-surgical treatment modality for head and neck cancers. Radiotherapy has evolved from once daily conventional fractionation to accelerated fractionation and hyper fractionation (2–4). These newer strategies led to a 7 % to 10 % improvement in local control relative to once daily regimens.

Hyper fractionation had demonstrated 8 % absolute improvement in 5 year survival (5). However, the most effective radiotherapy regimens have resulted in local control of 50% to 70 % and disease free survival of 30 % to 40 % in these patients. Later on it was found that chemotherapy when added to radiotherapy acted as a radio sensitizer, and had led to increased local control and improved disease free survival and overall survival. The commoner chemotherapeutic agents used in head and neck cancer are Cisplatin, Carboplatin, 5 Flourouracil, Docetaxel, and Methotrexate. Many randomized trials have shown that combined chemo radiation is superior to radiotherapy alone in the treatment of locally advanced, non-metastatic head and neck cancers. Meta- analysis of radiotherapy and concurrent chemotherapy (MACH

NC) demonstrated that the use of radiotherapy and concurrent chemotherapy resulted in 19 % reduction in the risk of death and an overall improvement of 6.5 % overall survival (6). Chemo irradiation has also proven to be successful in organ preservation (7). Randomized comparisons of concurrent chemo irradiation versus induction chemotherapy followed by radiotherapy alone are few but confirm that the former strategy is superior.

Radiotherapy and concurrent chemotherapy is the recommended and most commonly practiced treatment modality in locally advanced head and neck cancer due to the radio sensitization concept and the proven benefit in local control, disease free survival and overall survival.

But concurrent chemotherapy has its own acute toxicities and might delay the total duration of radiotherapy which is of prime concern. The most commonly used drug Cisplatin causes nephrotoxicity, hematological abnormalities and electrolyte disturbances. Majority of our patients are not fit for administration of chemotherapy due to poor general condition, low creatinine clearance, associated comorbid illnesses and lack of finances to procure chemotherapy drugs and also manage the toxicities. It is often found that many of these patients are unable to complete the planned radiotherapy within the recommended duration because of chemotherapy related toxicities. In view of this, patients might not benefit from the addition of chemotherapy. There is definitely a need for an alternative modality in the treatment of this subset of patients who are unfit or unable to undergo chemotherapy along with radiotherapy. Most of these patients end up being treated with radiotherapy alone which might not be effective due to advanced nature of disease and the presence of hypoxic clone of cells. Hyperthermia is known to be beneficial in these hypoxic tumours as they act mainly by direct cytotoxicity and DNA damage. Due to unorganized and poorly formed vasculature, the heat from the tumour is poorly disseminated which leads to additional

cytotoxicity. There are various randomized controlled trials which prove the benefit of hyperthermia when used along with radiotherapy.

Therefore we have conducted a pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms.

2.11 EPIDEMIOLOGY:

Head and neck cancers account for more than 5,55,000 cases annually worldwide (8). In the United States, they account for about 3 % to 5 %, with an estimated 53,000 Americans developing head and neck cancer annually and 11,500 dying from the disease (9). Males are more commonly affected than females, the ratio being 4:1. They account for 23 % of all cancers in males and 6 % in females. The incidence rate in males exceeds 20 per 100,000 in the countries of Hong Kong, Indian subcontinent, France, Spain, Brazil, central and Eastern Europe, Italy and among African Americans in the Unites States. In the Indian subcontinent, incidence of cancers of oral cavity is more due to the prevalent habits and addictions. The incidence of nasopharyngeal cancers is more in the country of Hong Kong, and laryngeal, pharyngeal cancers are more common in other populations (10).

The incidence of laryngeal cancer, but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African American men (11).

2.12 HEAD AND NECK CANCER IN INDIA:

Head and neck cancers in India have a distinct demographic profile, different risk factors and are emerging as a major public health burden. Highest priority should be given to head and neck cancers in India and management guidelines should be formulated according to the limited resources in the country and social status of the patients. Overall 57.5 % of global head and neck cancers occur in Asia especially in India. Head and neck cancers contribute to 60 % of all cancers in males except in Dibrugarh in Assam (49.6%). Tongue and mouth cancers contribute to more than one third except in Dibrugarh where hypopharynx is more common. In females head and neck cancers contribute to 11 to 16 % of all cancers and mouth cancers are more common in them. Nearly 80,000 oral cancers, 40,000 cases of pharyngeal cancers and 29,000 cases occur each year in India.

2.13 EVALUATION OF HEAD AND NECK CANCERS:

Initial evaluation starts with a good history and clinical examination. An indirect laryngoscopy, nasopharyngolaryngoscopy should be done to define the extent of the primary as well as to rule out any synchronous lesions. Biopsy from the lesion is mandatory prior to treatment. Chest x ray is mandatory in all patients. Routine bloods should be done and to assess the general condition of the patient.

Computed tomography scan (CT) with intravenous contrast is more useful for appropriate staging, precise delineation of the tumour, infiltration of the surrounding structures, and to detect nodal metastases. It helps in deciding regarding operability.

Magnetic resonance imaging (MRI) is more informative in proper soft tissue resolution, to rule out base of skull infiltration, invasion of cartilages and detection of early lesions.

In patients diagnosed to have nasopharyngeal cancers bone scan is done as a part of workup to rule out skeletal metastases.

In head and neck cancer PET CT is an emerging diagnostic tool. It has a detection rate between 88 % and 98% for head and neck primary tumours and has a higher sensitivity than CT or MRI(12). It has been found to alter the TNM staging in 15 % to 36 % of patients compared to CT/MRI staging. Because of the greater sensitivity for detection of metastatic lesions this may be used for staging and detection of synchronous second primaries in appropriately selected patients who have more than 10 % risk for distant metastases. These include patients with bilateral nodes, level 4 nodes, more than 4 lymph nodes, nodes larger than 6 cm in and recurrent tumours (13). But due to the false positive rates of 20 % and because of the relatively small number of patients in the studies, the PET findings need to be correlated with histopathological confirmation (14). PET CT is a very useful tool in the workup of unknown primary and also has been a very useful

tool for follow up in post radiotherapy patients especially when they are planned for salvage surgeries.

2.14 TREATMENT STRATEGIES:

Locally advanced head and neck cancers (stage III, stage IV A, stage IV B) constitute about 50 % of the cases which pose a clinical challenge and require aggressive treatment. Surgery, chemotherapy and radiotherapy are the various treatment modalities in head and neck malignancies.

a) SURGERY: Surgery is the single modality treatment in early oral cancers. Function preserving surgeries are performed in selected cases of oropharyngeal cancers and hypo pharyngeal cancers. Surgery is done first in locally advanced laryngeal cancers if they are not planned for organ preservation. In most of the cases surgery is not possible due to extensive disease, inoperability of the disease condition, and poor general condition of the patient and associated comorbidities.

b) CHEMO IRRADIATION:

Post-operative adjuvant chemo irradiation improved loco regional control and disease free survival in patients who had high risk features such as extra capsular extension and positive surgical margin (15,16). Chemo radiation is emerging as the standard of care in locally advanced head and neck cancers. The meta analyses of chemo radiation reported by Pignon et al confirmed the benefit of chemo radiotherapy to be around 6 % (17). Induction chemotherapy followed by radiation showed similar survival rates and organ preservation in various trials (18–20). The modest benefit of chemo radiotherapy is achieved with considerable morbidity. Chemo irradiation and induction chemotherapy will add to the morbidity in those patients with co morbidities, poor general condition, and poor renal function and also might not be possible to

administer this subset of patients. The intent of treatment often becomes palliative when these patients are treated with radiotherapy alone. There are different palliative radiotherapy treatment regimens described for locally advanced head and neck cancers such as 30 Gy in 10 fractions, 20 Gy in 5 fractions (21), 40 in 16 fractions (22), Quad shot regimen (14 Gy in 4 fractions) (23), etc depending on the institutional experience on toxicity rates and feasibility.

Hyperthermia is an alternative modality which can be tried as this modality is proven to be beneficial in these locally advanced tumours where there is hypoxia and radio resistant clone of cells. Hyperthermia improves the effectiveness of radiotherapy and acts as a radiosensitizer (24).

2.2) HYPERTHERMIA:

Hyperthermia is defined as heating the tissues beyond the physiological temperature (42 degree Celsius to 45 degree Celsius).

2.21) HISTORY:

Hyperthermia is an ancient treatment described in literature which is as old as medicine. The first paper on hyperthermia was published in 1886. In 1898, Westermark, a Swedish gynecologist, published a paper describing marked regression of large tumours of the uterine cervix after local hyperthermia. Interest in hyperthermia flourished in the 1970s and 1980s. The first international congress on hyperthermic oncology was held in Washington in 1975. A Hyperthermia group was formed in 1981 in the United States and the European hyperthermia institute was formed in 1983. Hyperthermia research started in 1978 and the Japanese society of hyper thermic oncology was established in 1984.

2.22. RATIONALE:

The factors limiting the efficacy of loco regional control of cancerous cells are well known. These include the presence of hypoxic cells in the tumour mass, acidic environment, cells in the

radio resistant phase of the cell cycle (S and G1) and the potentially radio resistant type of cancer cells. It has been proved that hyperthermia at 42 – 45 degree Celsius is lethal to the radioresistant hypoxic cells, cells at low pH and the radioresistant S phase cells. Hyperthermia causes direct cytotoxicity and radio sensitization.

2.23) MECHANISM OF ACTION:

The predominant molecular target for hyperthermic cell killing appears to be protein (25) . Protein denaturing and cell membrane damage is the most direct effect of hyperthermia toxicity (26). Protein starts to denature when the temperature is greater than 40° C which leads to alterations in multi molecular structures (e.g. cytoskeleton and membrane) and enzyme activity. Nucleic acid damage is more likely to happen during the S phase of the cell cycle when the DNA is being synthesized and in the M phase of the cell cycle when chromosomes are dividing. As a result cells die when they undergo mitosis. The newly synthesized DNA is vulnerable to heat stress, the double stranded DNA might be incorrectly joined or contain aberrant base pairs under heat stress. At the same time mutations can occur due to damaged DNA repair mechanisms under hyperthermia. Hyperthermia can decrease the DNA replication process through damage of key enzymes (27). Hyperthermia can also damage the cell membranes which is a key concept in thermal chemo sensitization, as altered membrane may increase the permeability of drug uptake (28). Hyperthermia affects many key functions of the cytoskeleton which is heat sensitive. Heat stress can also lead to depolymerisation and inactivation of microtubule proteins and fragmentation of the mitotic spindle which will result in cytokinesis disruption (29–31).

2.24 HEAT SHOCK PROTEINS (HSP):

If cells are exposed to heat, proteins of a defined molecular weight (mainly 70 or 90 k Daltons) are produced. The appearance of these heat shock proteins tends to coincide with the development of thermo tolerance and their disappearance coincides with the decay of thermo

tolerance. HSP are molecular chaperones (32). The function of a chaperone is to correctly assemble other macromolecules such as proteins and nucleosomes. When proteins and nucleosomes are synthesized chaperones attach to them and help them to fold to three dimensional conformations and perform their normal biological function. Chaperones themselves are not components of these macro molecules. When folding is complete the chaperones disassociate from the proteins. Hyperthermia can severely affect protein folding. Under heat stress, newly formed protein polypeptide chains tend to aggregate and lose their biological function. HSP are actively involved in the protection of cells against heat damage. These heat shock protein localize to the cytoskeleton and help reinforce structural proteins and enhance their tertiary configuration following treatment with heat (33,34). HSP also helps resist DNA fragmentation upon heating and decreases cell apoptosis (35). The expression of HSP is temperature dependent. Moderate hyperthermia stimulates HSP synthesis. In general it is widely accepted that HSP inhibits hyperthermic cell death, especially apoptosis (36–38).

2.25 THERMOTOLERANCE:

Cancer cells may confer thermotolerance as a result of continuous heat exposure or after pre hyperthermia treatment. Tumour tissues that develop thermotolerance are less susceptible to heat induced cytotoxicity. The development of thermotolerance depends on the temperature. Moderate hyperthermia has more chances to induce thermotolerance and 43 °Celsius seems to be a critical temperature (39). Thermotolerance can develop rapidly by cooling down to 37° Celsius between two shock treatments. Thermotolerance is reversible if the cells are returned to normal temperature (28). However thermotolerance takes much slower than its induction and it is usually in 3 to 5 days in most cells (40,41). The development of thermotolerance is mainly due to the appearance of heat shock proteins(HSP expression) (33)(42).

2.26 HYPERTHERMIA INDUCED APOPTOSIS AND NECROSIS:

Generally cells are committed to death through two distinct pathways: apoptosis and necrosis. Necrotic cell death is passive and involves lysis of the damaged cell and the release of its cellular contents to the surrounding environment (43). Necrosis is a traumatic cell death and occurs when the injury to the cell is acute in nature followed by inflammatory response. Apoptosis, in contrast, is an active and programmed cell death which involves condensation of the nuclear chromatin, shrinkage of the cytoplasm, blebbing of the membrane, nuclear fragmentation and finally the formation of apoptotic bodies (44). Hyperthermia is capable of causing both necrosis and apoptosis depending on the temperature. It was found that hyperthermia causes apoptosis at lower temperatures and necrosis at higher temperatures.

2.27 HEAT AND TUMOR VASCULATURE:

Additive toxicity in the tumour due to heat is due to the combination of inability of the blood vessels to undergo vasodilatation to the maximum extent and lesser dissipation of heat.

Preferential heating and damage of tumor can be expected only if heat is preferentially delivered to the tumor or if heat dissipation by blood flow is slower in the tumors than in the surrounding normal tissues (45). Tumour cells are found next to the endothelial cells along the thin walled tumour capillaries (46,47), which has sluggish blood flow (48,49). As a result of sluggish blood flow and the decreased density of functional capillaries, the total blood flow per unit weight of tumours, particularly in larger tumours is smaller than that in most normal tissues (57,58). Consequently although blood flow may be greater in tumours compared with normal tissues at physiologic temperatures, the capacity of tumour blood flow to increase during heating appears to be rather limited in comparison with normal tissues due to inadequate vasodilatation (poorly formed vasculature and lack of proper nervous receptors). It is a well-known fact that heat induces a prompt increase in blood flow accompanied by dilatation of vessels and an increase in

permeability of the vascular wall in normal tissues (52). Because the tumour blood vessels are unable to undergo vasodilatation to the maximum extent there is lesser dissipation of heat leading to temperature difference which is responsible for cytotoxicity.

2.28 METHODS OF HYPERTHERMIA:

In clinical applications, hyperthermia can be divided into three types: Local, regional and whole body hyperthermia.

1) Local hyperthermia**:** Local hyperthermia is usually applied to a tumour while the surrounding normal tissue is not heated (53). Local hyperthermia can be applied by external or interstitial methods.

a) External local hyperthermia:

External local hyperthermia is usually performed with superficial applicators such as radiofrequency, microwave or ultrasound. Although the penetration depth can be tuned by the size or the frequency of the applicator, the therapeutic depth of this type of hyperthermia is not more than 3 – 4 cm. Tumour temperatures are increased and surrounding tissues are heated not to exceed tolerance levels (54). Usually patients with chest wall recurrences, malignant melanoma lesions and lymph nodes of head and neck tumours are treated with external local hyperthermia.

b) Intraluminal local hyperthermia:

Intraluminal or endocavitary methods can be used to treat tumors within or near body cavities. Endocavitary antennas are inserted in the natural openings of hollow organs. These cavities include gastrointestinal (esophagus, rectum), gynaecological (vagina, cervix and uterus), genitourinary (prostate, bladder) and pulmonary (trachea, bronchus). Localized treatment is

possible with various possible electrodes according to the size of the lesion and the size of the lumen. Sugimachi etal (55–57), Kitamura etal (58) and Saeki etal (59) have used intraluminal hyperthermia in addition to radiotherapy and chemotherapy to treat locally advanced esophageal cancers.

c) Interstitial local hyperthermia: In order to treat deep seated tumours where external local hyperthermia is unreachable such as brain tumours, interstitial local hyperthermia can be applied (60). There are several types of applicators for delivering energy by this method. Interstitial heating enables more heating of the malignant cells than the normal tissues when compared to other techniques. In this technique there is better control of heat distribution. Problems are difficulty of repeated invasiveness and limited sites of access. Interstitial thermo radiotherapy was tested against radiotherapy alone in a prospective randomized study and did not show any additional benefit in spite of the efforts taken to deliver it (61).

2) Regional hyperthermia:

When a tumour is locally advanced or deep seated such as those in the abdomen and pelvis regional hyperthermia can be used. Unlike local hyperthermia in regional hyperthermia it is hard to avoid a temperature increase in normal tissues. Therefore it requires that heat dissipation in normal tissues is faster than in the tumour usually due to blood flow. Most clinical trials have used regional hyperthermia as an adjuvant to chemotherapy or radiotherapy, mostly in the pelvis when locally advanced or recurrent tumors are present (62).

a) Deep regional hyperthermia by external applicators:

Treatments of deep seated tumours are difficult with electromagnetic (EM) energy since it can be absorbed by human tissue very quickly. Therefore in order to deliver energy to the tumour while avoiding overheating adjacent normal tissue applicator arrays are used. Annular phased array systems delivering electromagnetic energy and radiofrequency capacitive heating apparatus are examples of regional heating devices.

b) Regional perfusion hyperthermia:

Regional perfusion is a technique where heated fluids are used to perfuse cancerous tissue. It is usually used to treat cancers in the arms and legs like melanoma or soft tissue sarcoma where the cancer is in advanced stage or non resectable. When regional hyperthermia is applied to limbs and without a cytotoxic agent the temperature can be increased to around 43° C for as long as 2 hours. However if a cytotoxic drug is applied simultaneously the temperature must be lower to avoid toxicities. Clinically regional perfusion hyperthermia combined with chemotherapy has shown much higher response rate than treating cancer with systemic chemotherapy. The success is due to well controlled heat application and more drug concentrations possible. This success is due to both the homogeneous and well-controlled heat application and the much higher (more than tenfold) drug concentrations possible with this technique (62). However the procedure is more risky.

3) Whole body hyperthermia (WBH):

Whole body hyperthermia has been investigated since 1970's as an adjuvant modality to chemotherapy or radiotherapy in metastatic disease. The temperature of WBH is usually limited

to 42 ° C because temperature higher than that can cause irreversible damage to brain and liver tissue. But this temperature can be maintained for hours.

The application of WBH can be divided into three major types: thermal conduction, extracorporeal induction and radiant or electromagnetic induction.

Thermal conduction can be achieved by immersion in heated fluids, heated air, heated blanket or using thermal chambers (similar to incubator).

In extracorporeal induction blood is first pumped out of the patient's body heated to 42°C and then put back into the body.

Since the whole body temperature will be elevated it can be applied to patients only in good clinical condition, otherwise significant adverse effects will occur due to doubling of basal metabolic rate when compared to 37 degree Celsius.

2.29) HYPERTHERMIA HEATING SYSTEMS:

Hyperthermia has been achieved by external energy sources. Especially diathermic heating devices have become a new research focus in the treatment of cancer due to their targeting capability which eventually leads to accurate targeting capability and small side effects to healthy tissues (28). Most clinically used hyperthermia systems are diathermic, which means the heating of the body tissues due to their resistance to the passage of high frequency ultrasound waves, electromagnetic radiation and electric current.

1) Ultrasound:

The ultrasound induced hyperthermia effect is caused by tissue absorption of ultrasound waves at the frequency of 2 - 20 M Hz. Theoretically, ultrasound has the best combination of short

wavelengths among all the diathermic devices and therefore low attenuation coefficient which allows for deep penetration in the human body with the ability to focus power into small regions. With newly designed ultrasound hyperthermia delivery systems equipped with multiple applicators we have achieved improved heating uniformity and controlled depth of penetration. However in application, ultrasound has limited utility by the fact that it is incapable of penetrating air and bone (63,64).

2) Electromagnetic fields:

Electromagnetic field can cause temperature increase in biological tissues. According to the frequency EM field can be in the radiofrequency (RF) or micro wave range. Frequency between 300 MHz and 300 G Hz are assigned to microwave. The most commonly used frequencies for microwave hyperthermia are 433, 915 and 2450 MHz. Frequencies higher than 2450 MHz have no value due to their limited penetrations. Radiofrequency by definition occupies the band between 3 KHz and 300 GHz.

In hyperthermia applications it generally means frequencies below microwave range usually between 10 – 120 MHz. The radiofrequency frequencies of 13.56 and 27.12 have been widely used in hyperthermia.

a) Radiofrequency: RF fields in the range of 10 – 120 MHz are used for treatment. A closed loop circuit is made which has a generator, a dispersive electrode (ground), patent and the needle electrode. The dispersive electrode and the needle electrode are active and the patient acts as a resistor. Due to the resistance of the tumor tissue the ionic agitation within the tumor tissue creates heating within the body. This can be tightly controlled through modulation of the amount of radiofrequency energy deposited.

b) Microwave:

Microwave hyperthermia uses single wave guide microwave antennas at 434,915, 2450 MHz. The system has an antenna and non-contact temperature sensor which senses the temperature of the tissue and provides feedback that adjusts the microwave power increasing the tissue temperature.

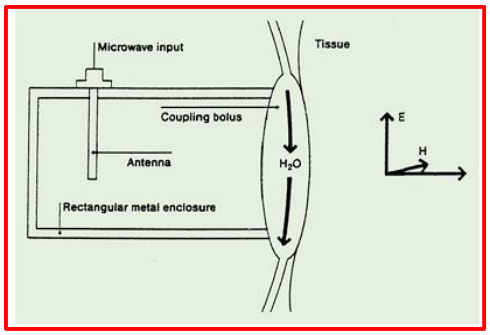


Fig 1: Schematic diagram of the microwave waveguide

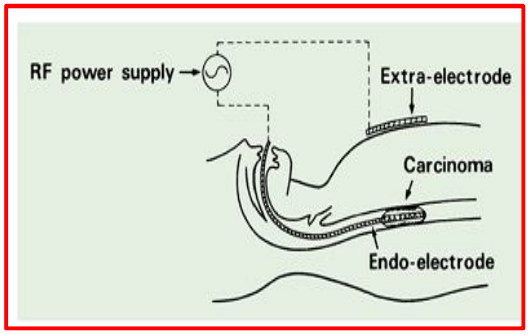


Fig 2: Capacitive heating approach for heating tumors in the esophagus

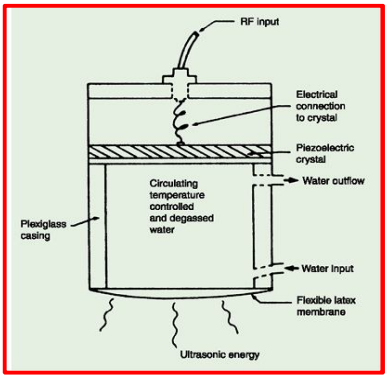


Fig 3: schematic diagram of single transducer ultrasound applicator for use in superficial tumours

Courtesy (Fig 1,2 &3): Perez and Brady's principles and practice of Radiation Oncology, 5th edition.

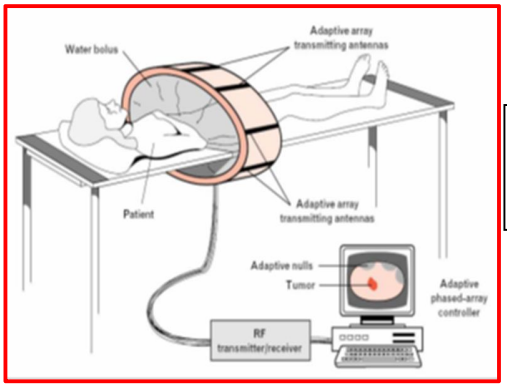


Figure 4: Hyperthermia with radiofrequency radiative device.

Courtesy: Thermal therapy – hyperthermia techniques – *Critical reviews in Biomedical Engineering 34(6): 491 – 542 (2006)*

2.30) HYPERTHERMIA AND OTHER MODALITIES:

Hyperthermia is used along with radiotherapy and chemotherapy, also used in increasing the perfusion of nano particle drugs, monoclonal antibodies and drug carrying polymers.

2.31) THERMAL DOSIMETRY:

Treatment outcome of hyperthermia is highly dose dependant. The temperature of hyperthermia treatment and the exposure duration at that temperature could make a great difference in tumour growth. After examining numerous survival curves of different cell lines upon treatment, the threshold temperature for thermal damage was found. This threshold temperature is also called a breakpoint (65,66)

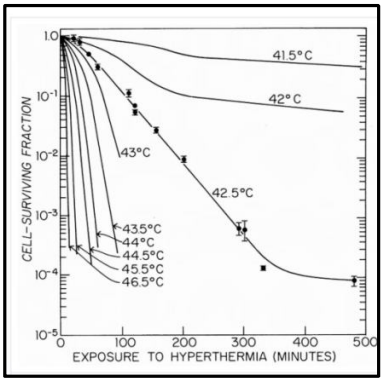


Fig 5: Arrhenius plot Courtesy: Textbook of radiobiology for the radiobiologist Eric. Hall

The Arrhenius plot could be used to estimate the energy needed to inactivate the cells. The Arrhenius plot is typically biphasic which also suggests the existence of a breakpoint. The plot is steeper below the breakpoint than above it. The calculated inactivation energy is around 120 – 150 k cal /mole which is consistent with the heat energy required to inactivate proteins and enzymes (67). Arrhenius plot is done by plotting the log of the slope of cell survival curves versus temperature. Above the breakpoint, a change in temperature of 1^0 C will double the rate of cell killing. The rate of cell killing will drop by a rate of 4 to 8 for every drop in temperature of 1^0 C. The change in slope below the breakpoint is due to the development of thermotolerance during heating.

2.32) CUMULATIVE EQUIVALENT MINUTES (CEM 43)

It has been demonstrated that hyperthermia cytotoxicity is dependent on both temperature and time, so that some time – integrated descriptor is the best concept of thermal dose. The quantity that has emerged as the most widely used measure of thermal dose is CEM43 degree Celsius CT 90, the number of cumulative equivalent minutes at 43 degree Celsius exceeded by 90 % of the monitored points within the tumour. Jones et al in his study (68) concluded that hyperthermia with a thermal dose more than 10 CEM 43°C provides a benefit in local control when compared to a thermal dose of < 1 CEM 43 ° C.

2.33) TEMPERATURE MEASUREMENT:

Invasive thermometry was used initially in most of the clinical trials. Nowadays noninvasive thermometry is being studied. .Magnetic resonance imaging is more promising for monitoring and control of deep hyperthermia. The patient is taken into the MRI scanner during hyperthermia and proton resonance frequency shifts are measured as a means to determine temperature. MR thermal imaging has clearly demonstrated its usefulness for monitoring clinical hyperthermia (69).

2.34) REVIEW OF CLINICAL TRIALS:

1. Hyperthermia in addition to radiotherapy has shown local control and survival benefit. Vanderzee etal (70) performed a prospective randomized control multicenter trial (1990 – 96). The number of patients enrolled were 358 , who were diagnosed to have locally advanced pelvic tumours comprising of bladder cancer, rectal cancer, cervical cancers and were randomly assigned between radiotherapy versus radiotherapy and hyperthermia.

Hyperthermia was prescribed once weekly, 1 – 4 hours after radiotherapy to a total of five treatments. Treatment was continued till the measured temperature had reached 42° C and persisted for 60 minutes the maximum time not exceeding 90 minutes. In all these patients

comprising of pelvic tumours, the complete response rate was 39 % in the control group and 55 % in the study group who received radiotherapy and hyperthermia. The local control rates were more in the study group. The 3 year overall survival was 27 % in the study group and 51% in the combined group. Among all the pelvic tumours, this combined treatment was found to be more beneficial in cervical cancers with the complete response rate was 83% versus 57%. Subcutaneous burns were observed in 20 patients, skin burns in 5 patients and deeper burns were noted in 2 of the patients. The acute and late radiation toxicities were similar between the two treatment groups.

2.The Cochrane review (71) had reviewed six randomized controlled trials between 1987 and 2009 for analysis (Chen 1997; Datta 1987; Harima 2001; Sharma 1991; van derZee 2000; Vasanthan 2005). All these trials have randomized locally advanced cervix cancer patients between radiotherapy and radiotherapy with hyperthermia. Combined treatment showed significant better outcome. The complete response rate was higher in the combined group (relative risk (RR) 0.56; 95% confidence interval (CI) 0.39 to 0.79; $p < 0.001$), with reduced local recurrence rates (hazard ratio (HR) 0.48; 95% CI 0.37 to 0.63; $p < 0.001$) and an improved overall survival (HR 0.67; 95% CI 0.45 to 0.99; $p= 0.05$) and a significantly better overall survival (OS) following the combined treatment (HR 0.67; 95% CI 0.45 to 0.99; $p= 0.05$). There was no significant difference in the treatment related acute or late toxicities between the two treatment groups.

3. A Cochrane review done on treatment with hyperthermia and radiotherapy had also demonstrated the benefit in rectal cancers (72). Six randomized controlled trials published between 1990 and 2007 were included in this review. Among them, four were single centre (Berdov 1990; Berdov 1996; Kakehi 1990; Trotter 1996) and the remaining two (van der Zee

2000;You 1993) were multi centre trials. The total number of patients were 520, 258 in the control arm and 262 in the combined arm. The overall survival was better in the combined group (HR 2.06;95% CI 1.33-3.17; p=.001), at 2 years which did not persist at 3,4 and 5 years. A higher complete response rate was reported in the combined group. (RR 2.81; 95% CI 1.22-6.45; p =0.01). Toxicity was reported only from two studies which had no differences between the two groups. Late toxicity was not reported.

4. Huigol etal, in a randomized study demonstrated benefit of hyperthermia and radiotherapy over radiotherapy alone in locally advanced head and neck cancers. Fifty six patients were randomized into two groups, one receiving radiotherapy and the other receiving radiotherapy and hyperthermia. All the patients received 66 – 70 Gy. Patients in the study group received additional hyperthermia which was delivered once a week on the same day of the week for five to seven sessions , with a radiofrequency machine operating at 8.2 MHz. All the patients received precooling for ten minutes followed by hyperthermia for 30 minutes. Except for the thermal burns in the combined group, acute and late effects were comparable in both. Complete response was seen in 42.4 % of patients in the study arm and 78.6 % in the patients in the combined arm.

5. Amichetti et al (73) in a phase 2 trial with 15 patients had tested microwave hyperthermia in cancers of unknown primary with N2 – N3 neck metastatic neck nodes. These 15 patients were treated with a median dose of 70 Gy and with hyperthermia with minimum temperature of 42.5 degree Celsius and at a frequency of 280 – 300 MHz. Hyperthermia was delivered twice a week 20 – 25 minutes after radiation. Complete response was observed in nine patients (60%) and 4(26 %) patients achieved a partial response and there was no response in the remaining patients. The overall response rates noted in the patients was 86.5 %. The acute toxicities noted were

mild with dry desquamation. The reported cases of late skin toxicities were mild with 2 cases of soft tissue fibrosis. Distant metastases was seen in 5 patients in (1 patient with liver metastases, 2 patients with lung and one patient with bone metastases). Nodal recurrence was noted 2 patients, in one patient within the irradiated field after a duration of 20 months and in the other patient outside the irradiated field after a duration of 25 months. Two patients died of non neoplastic unrelated causes (1 of cirrhosis and 1 of heart failure).

6. Hyperthermia along with radiotherapy had increased local control in head and neck cancer patients with fixed, N3 neck nodes. Valdagni (74) et al had randomized 44 patients having head and cancers with N3 neck nodes to radical radiotherapy and radiotherapy with hyperthermia. The dose of radiotherapy was 64 – 70 Gy, in both the arms and hyperthermia was twice a week in the combined arm alone. There was significant difference in the response rate in the combined arm ($p = 0.0152$). The complete response rates were 82.3 % (14/17) in the combined arm and 36.8% (7/19) in the radiotherapy only arm. The acute toxicities were similar in both the groups. Only one skin burn was observed in the combined arm. One patient in the combined arm died due to carotid rupture. The report of long term follow up of this randomized trial was published in 1993(75). The local control continued to be significant even after five years with a p value of 0.0164. Complete response was seen in 9/22 patients in the radiotherapy alone arm and 15/18 patients in the combined arm. The 5 year survival was more in the combined arm (53.3 % Vs 0%). Late toxicity occurred in the form of bone necrosis in two patients who had mandibular bone fixation in the combined arm.

7. Hyperthermia as a combined modality has shown better control in those patients with advanced disease when compared to those patients having early cancers. Datta et al in a

randomized clinical study (76) had treated the study group with hyperthermia and radiotherapy and the control group with radiotherapy alone. The patients received 60 – 75 Gy fraction with conventional fractionation. Hyperthermia was carried out with radiofrequency waves at 27.12 MHz using a diathermy machine twice a week until a temperature of 42.5 – 43 degree Celsius, was reached with a gap of 72 hours between two sittings. The patients received radiotherapy immediately following hyperthermia. The complete response in stage 3 disease was 20 % in the control group and 58 % in the study group. In stage 4 patients, 38% had complete response in the study group versus 7 % in the control group. Pain was well controlled in the study group patients (79 % versus 50%) when compared to control group. It was noticed that regression rates were better in those lesions with larger dimensions. The acute toxicity rates were almost similar. Erythema and facial edema were seen in three out of thirty three patients in the study group.

8.Martine Franckena (77) in a review article on hyperthermia and radiotherapy had concluded that hyperthermia when added to radiotherapy definitely improves local control and offers survival benefit in locally advanced cervical cancers. It was also insisted in this article that modern technology and the appropriate methodology should be used in clinical practice in terms of delivery devices, temperature measurements and quality assurance.

9. There are studies which did not show much benefit with hyperthermia. In a multi institutional, prospective randomized study which had two groups of patients of locally advanced carcinoma cervix treated with radiotherapy versus radiotherapy and hyperthermia (78), all patients received external beam radiotherapy and brachytherapy. The study group received five sessions of hyperthermia with a radiofrequency capacitive device. There was no significant difference

between the two arms in terms of local control and survival .The acute toxicity was more in the study group (18.2% Vs 3.6%) with no difference in the late toxicity.

10. Hyperthermia along with chemoradiotherapy has also demonstrated benefit in head and neck cancers. Huilgol etal (79) treated 40 patients with chemoradiation along with hyperthermia. All patients received 70 Gy in conventional fractionation with weekly chemotherapy of Cisplatin (50 mg) or paclitaxel (60 mg**).** They all received hyperthermia on a radiofrequency machine at 8.2 MHz for thirty minutes at 41° C to 43 ° C with pre cooling of 10 minutes to 5 °C. There were no enhanced mucosal or thermal toxicities when documented to their earlier experience with chemo irradiation. The overall survival was 75.69 % at 1 year and 63.08 % at 2 years.

11. Hyperthermia has also been tested and proven to be beneficial in patients with recurrent superficial breast tumors who were already treated with radiotherapy. Vernon etal (80) had combined five phase 3 trials (1988 -1991) which had 306 patients who were randomized between hyperthermia and hyperthermia with radiotherapy. The overall local response was better in the combined arm (59%) when compared to the radiotherapy arm alone (41%).

3. METHODS AND MATERIALS

3.11. TITLE OF RESEARCH PROJECT:

A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms.

3.12. TYPE OF STUDY:This study was a single arm prospective study. The study was conducted after approval by the Institutional Review Board (Ethics committee) on 04.01.2013. The study included patients who fulfilled the inclusion criteria and were registered in the department of radiotherapy unit 2, Christian Medical college between January 2012 to August 2013. All patients were informed about the treatment protocol and written informed consent was obtained from the patients to participate in the study.

3.13 TARGET SAMPLE SIZE AND RATIONALE: Since it is a pilot study the sample size was conveniently selected to be 20 patients to assess the feasibility.

3.14. FUNDING: This study was funded by the FLUID research grant.

3.15. OBJECTIVES OF THE STUDY:

a) Primary objectives:

1. To assess the feasibility and toxicity of hyperthermia along with radiation in patients with locally advanced non metastatic head and neck cancers

2. To assess the palliation of distressing symptoms in locally advanced head and neck cancers treated with palliative intent

b) Secondary Objectives:

1. To assess the efficacy of this modality in terms of disease response as weekly clinical assessment, at the end of treatment and at three months

3.16. INTERVENTION AND COMPARATOR AGENT – The interventions are radiotherapy and Hyperthermia in a single group of patients. Comparator agents do not exist in this study

This cohort was compared with age and stage matched control of 40 patients treated with palliative radiotherapy regimens. Comparison was done between the patients treated with hyperthermia in this study, ten patients treated with 66 Gy in 33 fractions (conventional fractionation along with concurrent chemotherapy), data from the study published on 33 patients who were treated with 40 Gy in 10 fractions and data from the study done on 10 patients treated with 6/7 fractionation. The toxicity profile, tolerability, response rates, local control and time to progression (local/systemic) were compared.

3.17. PRETREATMENT WORKUP:

All the patients were evaluated by physical examination and required laboratory investigations, radiological investigations which included complete blood picture, liver function tests, creatinine, chest x ray, baseline CT head and neck.

Flexible naso pharyngo Laryngoscopy (NPL scopy) was done for assessment of the extent of the primary disease and staging before initiation of treatment. Biopsy from the tumour or FNAC from the nodes were done. ECG and ECHO for baseline evaluation of cardiac function were done. All patients had routine dental assessment and clearance before initiation of radiotherapy. All the patients had dietary consultation before and during the treatment.

3.18 .KEY CRITERIA:

The patients who were diagnosed to have inoperable locally advanced head and neck cancers (stage IV A and IV B) who were unfit for chemotherapy and decided for palliative treatment were screened for inclusion into the trial

a. Inclusion criteria:

a) Performance status - </ = 2

b) More than 18 years of age and not more than 75

c) Non metastatic histologically or cytologically proven squamous cell carcinoma of the following sites:

1. Oral cavity
2. Larynx
3. Hypopharynx
4. Carcinoma unknown primary with neck nodes

d) Inoperable disease – intent of treatment being palliative

e) Not fit for chemotherapy due to poor general condition or renal condition

b. Exclusion criteria:

a) Metastatic disease

b) Patients undergoing altered fractionation schedules (400 TD/6 fractions per week)

c) Patients who had prior treatment with chemotherapy

d) History of cardio logical interventions viz. CABG, PTCA, temporary or permanent pacing

e) Unstable angina

f) acute myocardial infarction within last 6 months

g) Any implanted device insitu

h) Patients with leprosy or syringomelia or syringobulbia or any other medical or surgical condition in which there is impaired pain perception

i) Heart rate > 90 bpm

j) Hypertension : Diastolic > 100 mm Hg and /or systolic < 90 mm Hg

K) Hypotension : Diastolic < 50 mm Hg and / or systolic < 90 mm Hg

l) Severe cerebrovascular disease: multiple cerebrovascular accidents (CVA) or a CVA < 6 months before treatment

3.19. SCHEMATIC DIAGRAM OF THE PROTOCOL:

Screening of the patient

Assesment + clinical + NPL scopy + EORTC QOL H & N assessment (self administered questionnaire for baseline quality of life) + imaging (CT scan) (Dental clearance and dietary consultation)

Radiotherapy as per protocol – Cobalt 60 beam/ 66 Gy to the CTV primary 5 days a week once daily with a TD of 200 cGy per fraction

Hyperthermia once in a week on a particular day – 30 minutes before radiotherapy

Weekly clincal assesment of the radiation reactions

End of RT assessment – Clinical + NPL scopy + EORTC H & N assessment (self administered questionnaire)

Assesment at the end of six weeks after radiotherapy clinically, with NPL scopy and EORTC QOL H & N assessment (self administered questionnaire)

Three months from the date of completion of radiotherapy – assessment – clinical, NPL scopy, EORTC QOL H&N assessment (self administered questionnaire) and imaging (CT scan)

3.20. OUTCOMES:

a) Primary outcomes:

1. To assess the feasibility, clinical utility of hyperthermia concurrently with palliative radiotherapy for head and neck cancers. Feasibility was assessed in terms of technical issues, the amount of break(discontinuation) in treatment due to toxicity and total duration required to complete the complete course of radiotherapy

2.To assess the tolerability of use of hyperthermia concurrently with palliative radiotherapy for head and neck malignancy in terms of incidence and severity of radiation related toxicities like dermatological toxicity, mucositis, hematological toxicity graded by common toxicity criteria

b) Secondary Outcomes:

1. To assess the efficacy in terms of disease response at the end of radiotherapy by clinical examination at the end of six weeks and at three months by CT scan with RECIST criteria

2.To assess the improvement of quality of life at the end of radiotherapy and at 6 weeks and 3 months from the completion of radiotherapy by EORTC(H&N) QOL assessment questionnaire

3.21 TREATMENT:

a) RADIOTHERAPY:

Simulation was done with the patient in supine position with immobilization with a thermoplastic mask. Then planning was done in the simulator. Radiotherapy was delivered with cobalt 60 photons. Three field technique with two parallel opposed fields and 1 anterior neck field was used. The two parallel opposed fields were designed so as to fit the primary and the nodes with a margin. Anterior field was used to treat the nodes. Spine shielding was done at 40 Gy and the posterior neck was treated with electrons. Boost plan was done at 50 Gy in which the

borders of the photon field were shrinked and the remaining dose was delivered. After planning the radiotherapy charts were sent for calculation which was carried out in the treatment planning system and then treatment was initiated. The distribution and the dosimetry were reviewed by a senior consultant and a medical physicist.

Radiotherapy dose:

Phase I : Total dose of 50 Gy (2 Gy per fraction) was delivered through the lateral portal which encompassed the primary and the nodes with a margin and the possible sites of microscopic spread.

Phase II: Field size reduction was done at 50 Gy and 16 Gy was delivered to the radiotherapy portal encompassing the primary and the significant nodes with a margin.

The areas not needed to be treated were shielded by manual lead wires, which were represented on the simulator film and reproduced in the treatment machine.

Change of match was done at every 22 Gy.

Spine shielding was done at 40 Gy and the posterior neck was treated with electrons.

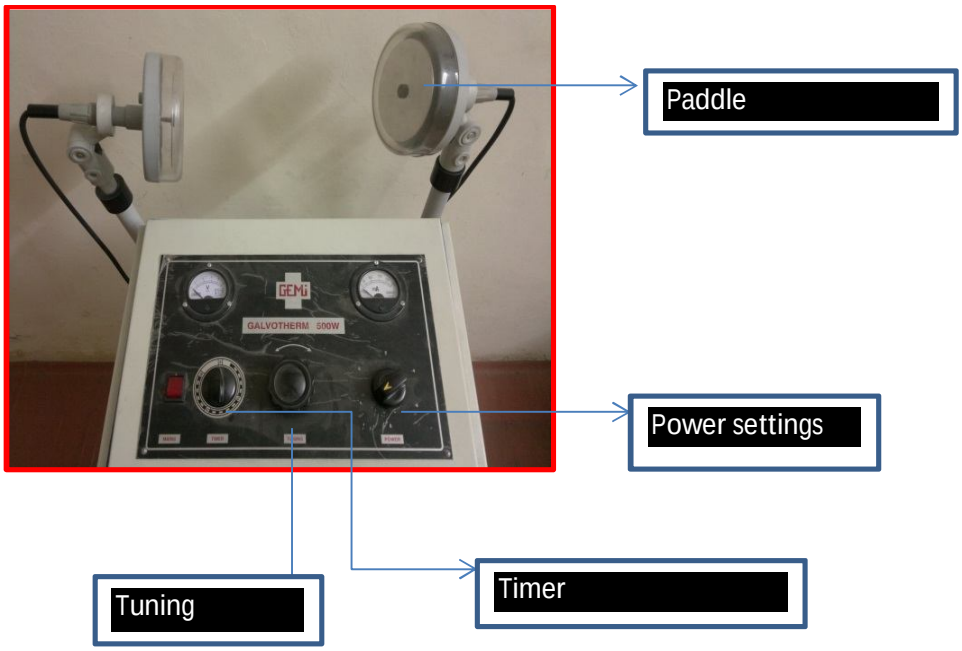
b) HYPERTHERMIA:

The patients were treated with hyperthermia once a week for 30 minutes just before radiotherapy on the same particular day. Hyperthermia was delivered by galvotherm 500 W machine (Gemi manufacturers). Patients were seated in a chair with the paddles focused towards the region of treatment. The paddles were kept as close to the patient's body but not in contact with the surface. The active paddle was kept on the side of the neck which required more temperature and the passive paddle on the opposite side. After positioning the patient the power button was

Pic 1 : Hyperthermia machine and paddles

Pic 2 : Contactless infrared thermometer

Fig 3: Picture showing hyperthermia settings



switched on and the frequency and the current was adjusted and treatment was started after the timer was set at 30 minutes. Temperature was monitored by an infrared thermometer every 10 minutes for 30 minutes and was noted down in the record. Care was taken that the temperature did not exceed 102ºF. The frequency was at 27 MHz and the current was set at 4 mA. After completion of hyperthermia the patient was treated with radiotherapy. Six sittings were delivered once a week throughout the treatment.

3.22. WEEKLY ASSESMENT AND FOLLOW UP:

Patients were assessed weekly for tolerance of treatment and acute toxicity documented by RTOG and CTCAE criteria. Radiation dermatitis and mucositis was graded according to the RTOG criteria (Appendix 6). Hematological parameters (Haemoglobin, Total counts, differential counts and platelets) were monitored and were graded according to the CTCAE criteria(Appendix 7) if there was any abnormality. The nodal size was measured and recorded every week. Neck separation was also measured and noted and repeat calculation was done if there was any gross variation.

All patients underwent an End RT assessment with bloods, NPL scopy, chest xray were done. All patients were followed for six weeks and then after three months. Each visit bloods, ENT examination and chest x ray were done. Additionally a CT scan was done after three months for disease response assessment.

3.23) RESPONSE ASSESMENT:

Response assessment was done by RECIST criteria (Appendix 8)

Date of enrolment: The first patient was enrolled in January 2013(08/01/2013) and the tenth patient in August 2013(23/08/2013).

3.24) TRIAL BENEFITS: The study patients were covered under the institutional insurance scheme for the costs of any trial related complications and hospitalization.

3.25) STATISTICAL ANALYSES: For the primary outcome (Categorical variable) descriptive statistics are applied and frequency distributions are plotted. As per CTCAE criteria, toxicity was graded (Categorical variable) and descriptive statistics are applied and frequency distributions are plotted.

European Organization for research and treatment of cancer Quality of life (EORTC H QOL H & N)(Appendix 9) quality of life tool which is a validated and accepted QOL tool for head and neck cancer was administered before starting radiotherapy and at the completion of radiotherapy and at follow up. Mean value before and after treatment was compared and test of significance was done (paired t –test)

Response was compared with CT scans based on pre and post treatment tumor volume (Wilcoxan sign test).

Survival analysis was done by Kaplan meier survival analysis.

4. RESULTS

A total of ten patients were included in the study during the period of January 2013 to August 2013. All the patients were planned for hyperthermia and radiotherapy as per the study protocol. Six patients underwent treatment as per the protocol and among the remaining four, one patient discontinued treatment and the rest of them died due to complications while on treatment. The data of these patients who completed the planned treatment was analyzed for response and toxicity during follow up. The demographic characteristics and evaluation of toxicity during therapy was done for all ten patients.

4.1 PATIENT CHARACTERISITICS:

4.11 AGE and SEX: Mean age of the patients (n = 10) was 57.4 years and range was 33 – 71 years. Majority of the patients were in the age group of 61 to 70 years.

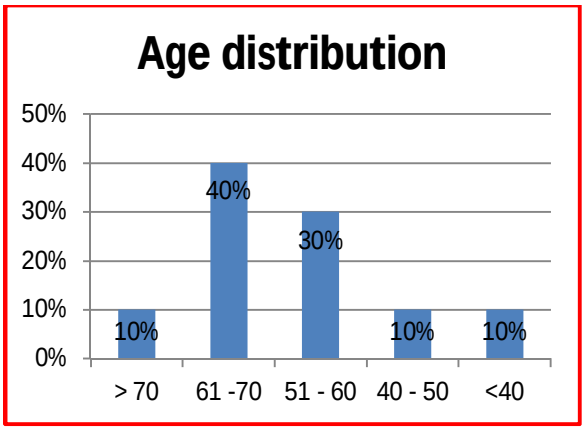


Fig 5: Age distribution of patients and corresponding percentage values

All the patients were male patients.

4.12 SOCIOECONOMIC STATUS:

Kuppuswamy's classification was used for the stratification of socioeconomic classification (81). Among the ten patients, one belonged to upper middle class, four to lower middle class, one to upper lower class and four to lower class.

4.13 PERFORMANCE STATUS:

Five patients had a performance score of ECOG 1 and the remaining five patients had a performance score of ECOG 2.

4.14 SITE OF TUMOUR:

The most commonest site of tumour was pyriform sinus followed by tongue.

4.15 PRESENTING SYMPTOMS:

The commonest presenting symptom was neck swelling (30 %). The other presenting symptoms were pain (26%) which included throat pain, pain in the region of neck swelling, painful ulcerative lesions and referred pain in the ear, dysphagia (20 %) , hoarseness of voice (12 %) of and tongue ulcer (12 %).

4.16 ADDICTIONS:

Among the 10 patients, 7 patients were addicted to smoking, 4 patients to tobacco consumption in the form of leaves and along with betel nut and 2 patients to alcohol consumption. Two patients were addicted to a combination of smoking and tobacco and 2 patients to a combination of tobacco and alcohol consumption.

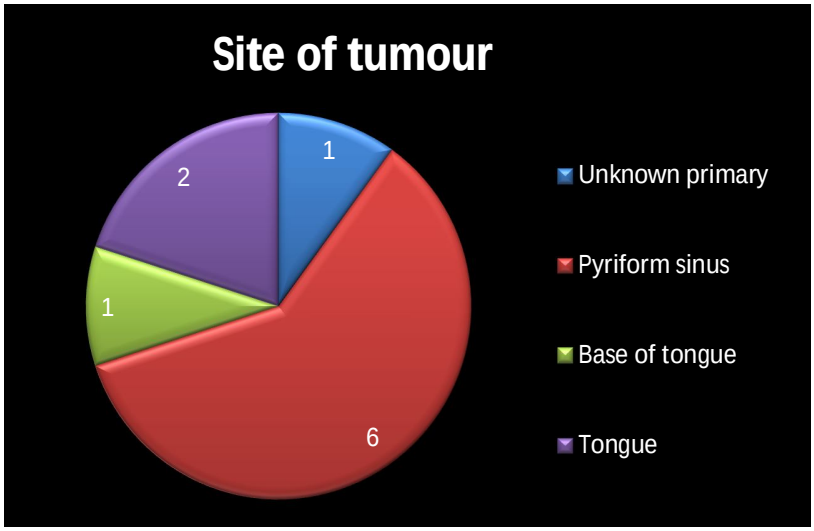


Fig 6 – Graphical representation of distribution of the site of tumour

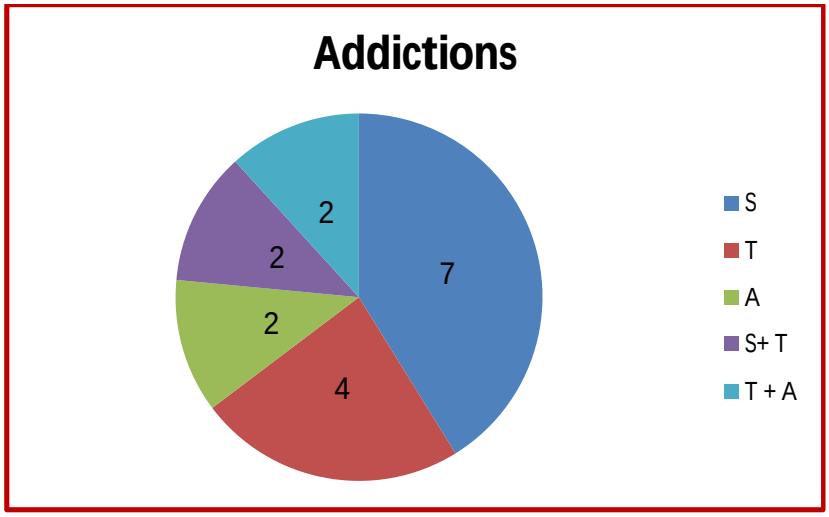


Fig 7 : No of patients addicted to smoking, alcohol consumption and tobacco chewing

Abbreviations: S = smoking, T = Tobacco chewing, A = alcohol consumption, S + T = smoking and tobacco consumption, T + A = Tobacco chewing and alcohol consumption

4.2 TUMOUR CHARACTERISTICS:

4.21 T STAGE :

Among the 10 patients, 3 patients (30 %) had T4b stage with infiltration of the pre vertebral and retropharyngeal spaces and encasement of the carotid vessels, among which two patients had primary arising from the hypopharynx and one from lateral border of the tongue.

Three patients (30 %) had T4a stage, 2 patients with hypopharyngeal primaries with the tumour infiltrating the cartilages and the other patient had a tongue primary infiltrating the intrinsic muscles.

One patient (10%) had T3 stage with primary in the base of the tongue and 2 patients (20 %) had T 2 stage with primary arising from the pyriform sinus.

Table 1 : Distribution of T stage and their percentage

T stage	No of patients	Percent(%)
Tx	1	10
T2	2	20
T3	1	10
T4a	3	30
T4b	3	30

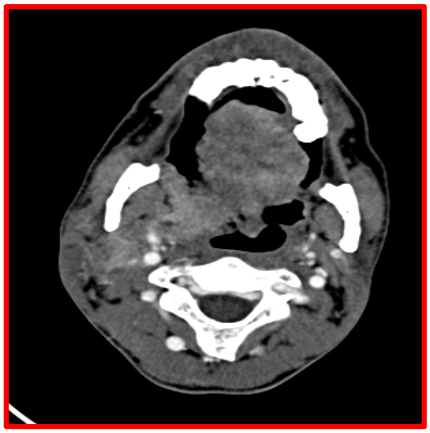


Fig 8: 45 year old gentleman case of locally advanced carcinoma Tongue. The tumour is seen encasing the right carotid vessel

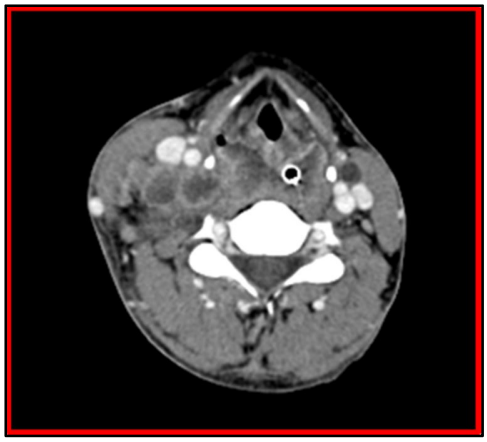


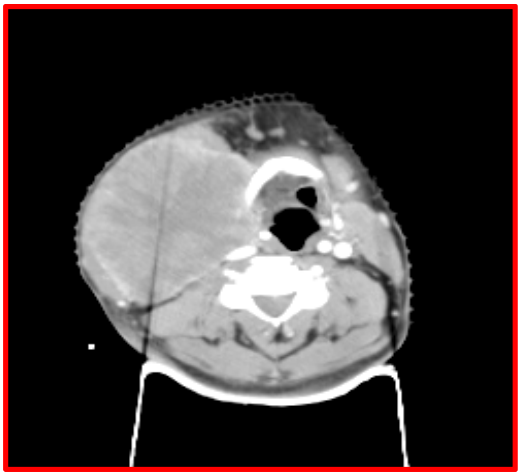
Fig 9 : 33 year old gentleman, case of locally advanced hypopharynx. The growth is seen infiltrating the pre vertebral space.

4.22 N STAGE

N2b nodal status was present in 6 patients (60 %) of patients and N3 nodal status was present in 3 patients (30 %). The remaining one patient (10%) had N2c nodal status.

Table 2: Distribution of N stage and their percentage

N STAGE	No of patients	Percent(%)
N1	0	0
N2a	0	0
N2b	6	60
N2c	1	10
N3	3	30



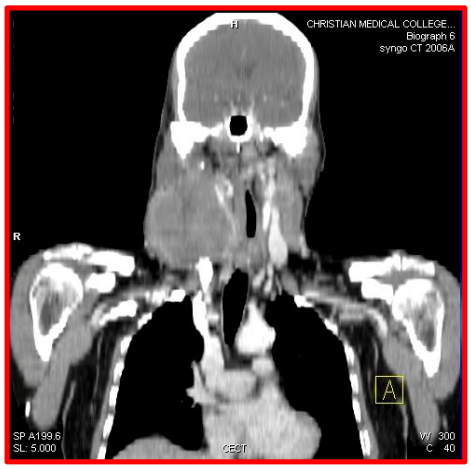


Fig 10: A 62 year old gentleman diagnosed t have Unknown primary with a N3 neck node measuring about 9 x 8 x 10 cm in dimensions involving Level 1b, 2 , 3 ,4 levels on right side

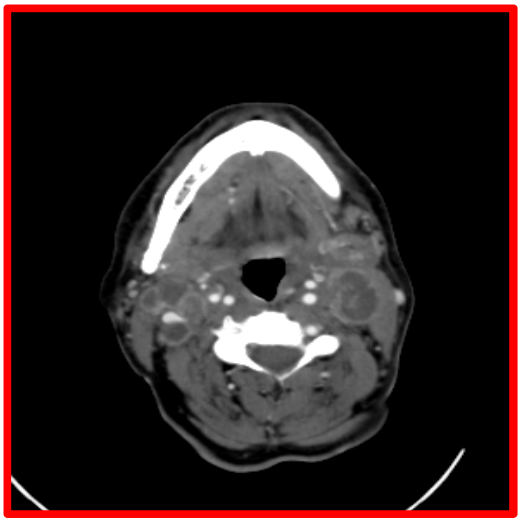


Fig 11: A 71 year old gentleman diagnosed to have locally advanced carcinoma Tongue. Figure shows bilateral necrotic nodes involving predominantly level 2 and 3

4.23 STAGE GROUPING

Table 3: Stage grouping of the patients

STAGE	FREQUENCY	PERCENT(%)
Stage 4a	4	40
Stage 4b	6	60

4.24 HISTOLOGY:

The histology was as poorly differentiated squamous cell carcinoma in 5 patients, moderately differentiated squamous cell carcinoma in 4 patients and well differentiated squamous cell carcinoma in 1 patient.

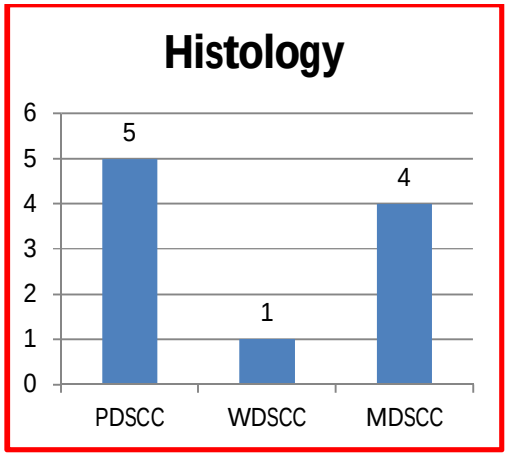


Fig 12 : Pictorial representation of different histologies. *Abbreviations*: PDSCC – poorly differentiated squamous cell carcinoma, WDSCC – well differentiated squamous cell carcinoma, MDSCC – moderately differentiated squamous cell carcinoma

4.3 TREATMENT CHARACTERISTICS:

The treatment planned for the patients was radiotherapy, five days a week along with six once weekly hyperthermia treatment. The radiotherapy dose planned was 66 Gy in 33 fractions with conventional technique using Cobalt 60 machine.

Table 4: Combined treatment details of the patients:

Pt No	RT Dose(Gy)	Hyperthermia	Duration of treatment	Reason of deviation from treatment
1	66	6	9 weeks	Nil
2	14	2	7 days	Death*
3	66	6	6 1/2weeks	Nil
4	66	6	6 1/2 weeks	Nil
5	6	1	3 days	Discontinued *
6	66	6	61/2 weeks	Nil
7	56	5	8 weeks	Death*
8	36	1	4 weeks	Death*
9	66	6	9 weeks	Nil
10	66	6	8 weeks	Nil

Discontinuation and Death* = details are explained below in section 4.35 & 4.43

4.31 RADIATION THERAPY:

Among the 10 patients 60 % (6 patients) received the planned dose of 66 Gy of radiation . One patient discontinued treatment after 8 Gy (4 fractions) due to personal reasons. The remaining 3 patients could not continue the planned treatment due to life threatening complications which lead to death . Among the three who died, one patient received 56 Gy, the second and the third patients received 36 Gy and 14 Gy respectively.

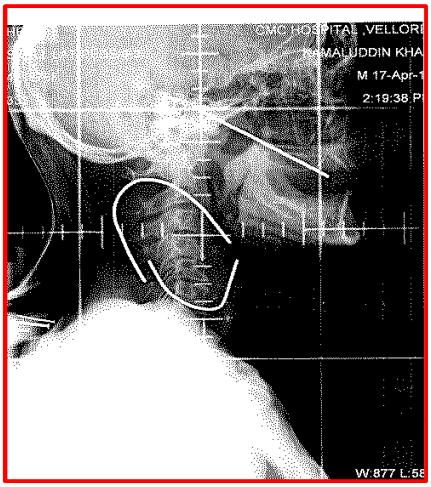


Fig 13: Simulator film of a 70 year old gentleman who was diagnosed to have Carcinoma hypopharynx T2N2bM0. The node was outlined with lead wire during simulation.

4.32 HYPERTHERMIA TREATMENT:

Among the 10 patients, 6 patients(60 %) received the planned six sittings of hyperthermia, 1 patient (10 %) received 5 sittings, 1 patient(10 %) received 4 sittings and 2 patients(20 %) received only 1sitting of hyperthermia

4.33 MEAN TEMPERATURE READINGS:

The mean temperature reading measured with the contactless infrared thermometer in patients was 101.4 ° F. Three readings were measured during each treatment of hyperthermia and the mean of those readings was taken. The mean temperature was 101° F in seven patients and 102° F in three patients.

4.34 DURATION IN WEEKS AND TREATMENT COMPLETION:

Among the 10 patients 3 (30 %) completed the treatment within the planned duration of 6 ½ weeks, 3 (30%) had delay in treatment (2 completed in 9 weeks and 1 in 8 weeks) and 4 (40%) did not complete the planned treatment. (refer table 4).

4.35 TREATMENT BREAKS AND REASONS AND DISCONTINUATION:

Three patients completed treatment within 6 ½ without any breaks, 1 patient had 3 fractions and discontinued treatment due to social reasons and 2 patients died after undergoing 7 and 18 fractions of radiotherapy. Among the remaining four patients, 1 patient had one break of 9 days due to grade 3 dermatitis, the other 3 had two breaks each due to grade 3 mucositis, grade 4 mucositis, grade 3 dermatitis or tumour bleed. The longest duration of break in radiotherapy was 20 days in a patient who had two breaks, one for 15 days and the second for 5 days.

Table 5 : Duration and reasons of treatment breaks

Pt No	No of breaks	Duration of each break in days	Reason	Comment
1	2	7 each	Gr 3 & Gr 4 mucositis	-
2	-	-	-	Death after 14 Gy
3	Nil	Nil	Nil	-
4	Nil	Nil	Nil	-
5	-	-	-	Discontinued after 6 Gy 3 fractions(social reasons)
6	Nil	Nil	Nil	-
7	2	2 & 6	Tumour bleed and grade 3 mucositis	Death at 56 Gy
8	-	-	-	Death at 36 Gy
9	2	14 & 5	Grade 3 mucositis & Grade 3 dermatitis	-
10	1	9	Grade 3 dermatitis	-

The major reason for treatment break was Grade 3 mucositis (42%), followed by grade 3 dermatitis (28%). The other reasons were Grade 4 mucositis (14%) and tumour bleed (14%).

4.4 TREATMENT ASSOCIATED MORBIDITIES:

4.41 NON HAEMATOLOGICAL TOXICITY:

Weekly assesment was done for all patients to monitor the toxicities. CTCAE criteria were used to grade toxicities like cough, throat pain, dysphagia, anorexia, fatigue. RTOG scale was used to assess dermatitis and mucositis. Pain was assessed with Universal pain assessment tool.

a) DERMATITIS:

Table 6: Table representing the number of patients who had various grades of dermatitis during treatment

Weeks of treatment	Grade 1 dermatitis	Grade 2 dermatitis	Grade 3 dermatitis	Grade 4 dermatitis
First week	1			
second	4	2		
Third	6	3		
Fourth	2	6	1	
fifth	2	5	1	
Sixth		6	1	
Seventh		6		

Three patients had grade 3 dermatitis which occurred in the fourth, fifth and sixth weeks leading to treatment breaks.

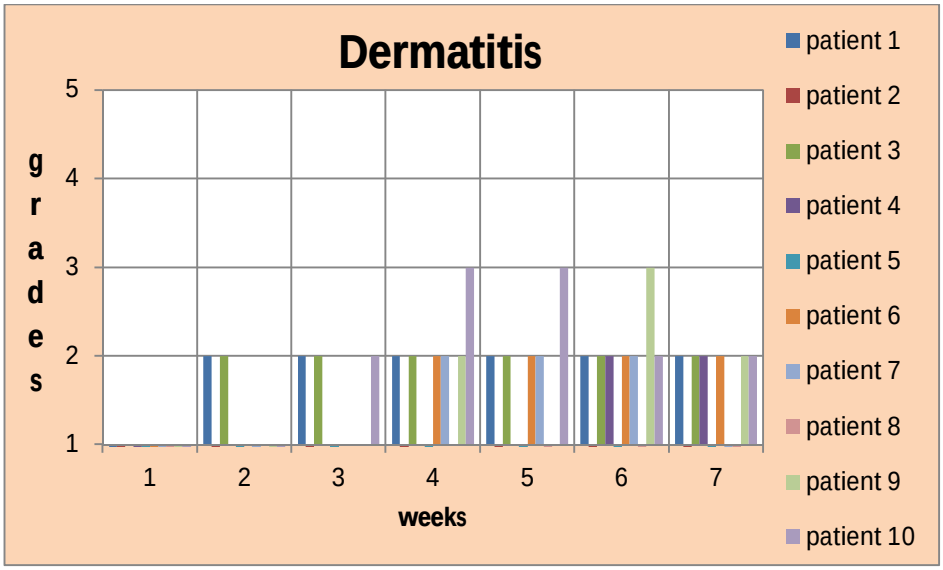


Fig 14 – Graphical representation of dermatitis in patients during treatment in weeks

b) MUCOSITIS:

Table 7 : Table representing the number of patients who had various grades of mucositis during treatment

Weeks in treatment	Grade 1	Grade 2	Grade 3	Grade 4
First week	2	3		
Second week	4	1		
Third week	4	3	1	
Fourth week	3	2	2	1
Fifth week	2	5		
Sixth week		5		1
Seventh week		5		

Two patients had grade 3 mucositis in the third and fourth week. Two patients had grade 4 mucositis in the fourth and sixth week.

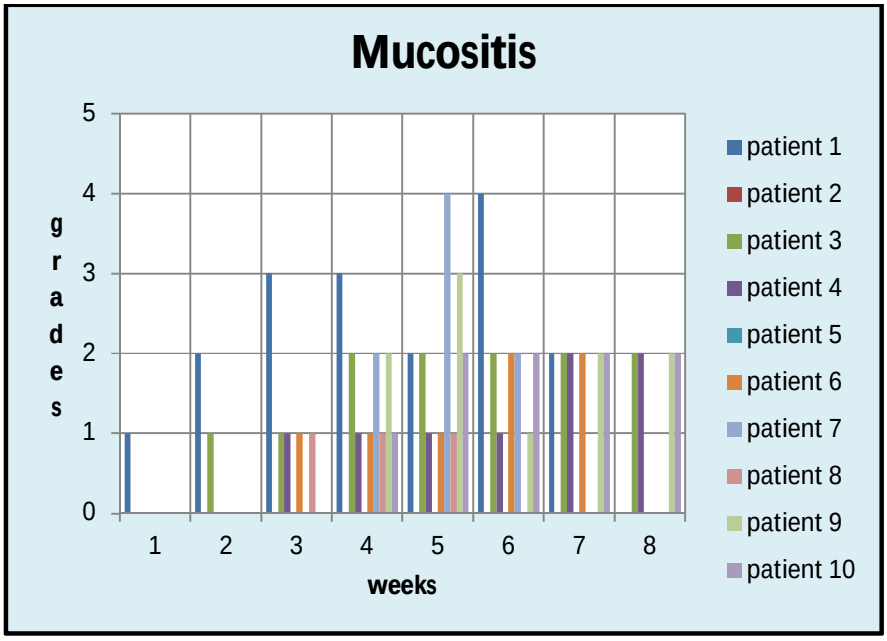


Fig 15: Graphical representation of all grades of mucositis in patients during treatment.

C) PAIN ASSESSMENT:

Pain was assessed every week according to the pain score and analgesics were administered and adjusted according to the WHO step ladder pattern.

Table 8: Table representing the different pain scores during treatment

Weeks in treatment	Pain score Mild	Pain score Moderate (interfere with tasks)	Pain score moderate (interfere with concentration)	Pain score moderate (interfere with basic needs)	Pain severe (needs bed rest)
First week	8	2			
Second week	9				
Third week	4	4			
Fourth week	3		2	2	
Fifth week	2	4		1	
Sixth week	1	4		1	
Seventh week	2	3			

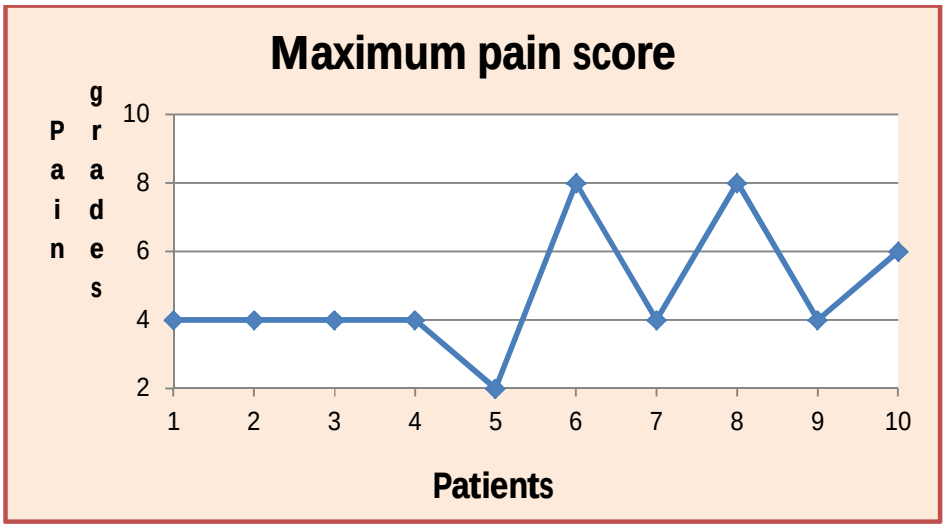


Fig 16: Graphical representation of the maximum pain scores experienced by all the patients

Mild pain (score2) was experienced by 55 % of the patients, 32 % of patients had moderate pain interfering with tasks(score 4), 3.8 % of patients had moderate pain interfering with concentration (score 6), 7.6 % of patients had moderate pain interfering with basic needs(score 8). Pain was well controlled with combination of NSAIDs, weak opioids (Tramadol) and adjuvant analgesics (amitriptyline).

D) THROAT PAIN:

Grade 3 throat pain occurred in the fifth, sixth and seventh weeks. None of the patients had grade 4 throat pain .

Table 9 : Table representing the number of patients who had various grades of throat pain during the treatment

Weeks in treatment	Grade 1 Throat pain	Grade 2 throat pain	Grade 3 throat pain	Grade 4 throat pain
First week	2	3		
Second week	4	4		
Third week	2	5	1	
Fourth week	1	4	2	
Fifth week	1	5	1	
Sixth week		3	3	
Seventh week		3	3	

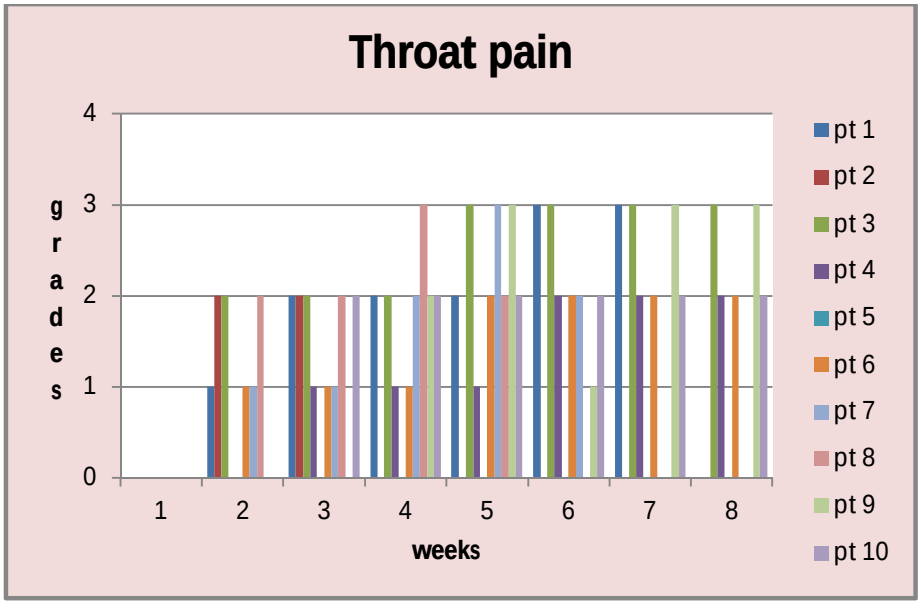


Fig 17: Graphical representation of all grades of throat pain in patients during treatment

E) DYSPHAGIA:

Majority of the patients (65 %) had grade 2 dysphagia. Grade 3 dysphagia occurred in 17% of the patients during the fourth, fifth, sixth and seventh week and all these patients needed ryles tube insertion for feeding purpose.

Table 10: **Table representing the number of patients who had various grades of dysphagia during treatment**

Weeks in treatment	Grade 1	Grade 2	Grade 3	Grade 4
1st week	1	3		
2nd week	3	4		
3rd week	1	5		
4th week	1	4	2	
5th week	1	4	1	
6th week		4	2	
7th week		2	2	

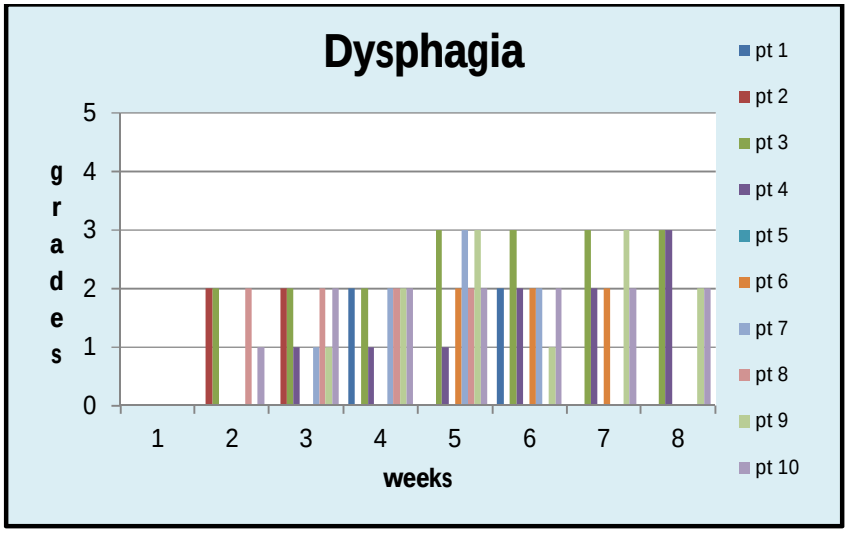


Fig 18: Graphical representation of all grades of dysphagia in patients during treatment starting from week 1 to week

g) COUGH:

Grade 3 cough was experienced in fourth, fifth, sixth and seventh weeks.

Table 11: Table representing the number of patients who had various grades of cough during the treatment

Weeks in treatment	Grade 1 cough	Grade 2 cough	Grade 3 cough
First week	3	1	
Second week		2	
Third week		5	
Fourth week	1	3	2
Fifth week	1	3	2
Sixth week	1	4	1
Seventh week		3	1

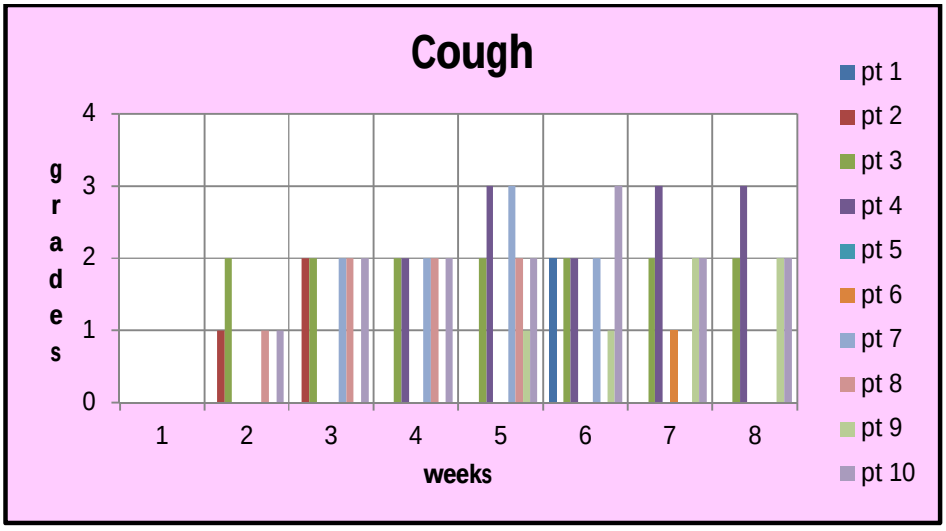


Fig 19: Graphical representation of all grades of cough in patients during treatment starting from week 1 to week 7

H. ANOREXIA AND FATIGUE:

One patient experienced grade 3 anorexia in the sixth week of treatment. Majority of the patients had grade 2 fatigue in the last two weeks of treatment.

I) NAUSEA AND VOMITING:

Only 2 patients had grade 3 nausea, the remaining had grade 2 nausea. None of the patients had grade 3 vomiting.

J) RYLES TUBE PLACEMENT:

During the treatment 50 % of the patients had ryles tube placement. Two patients had before treatment and the remaining during treatment. Two patients refused ryles tube feeding in spite of requirement.

4.42)HAEMATOLOGICAL TOXICITY:

Hemoglobin was monitored once a week during treatment. One patient had grade 1(9.9 gm%) anemia for which he was started on hematinics after which his hemoglobin level had improved (10.5 gm%). Three patients received one unit of blood transfusion each. Among them, two patients had grade 2 anemia (8.8% gm%, 9.5 gm%) which had improved to grade 1(10.6 gm%, 11.8 gm%) after blood transfusion. The third patient had grade 3 anemia (7.9 gm%) which had improved to grade 2 anemia (9.5% gm%) after blood transfusion .

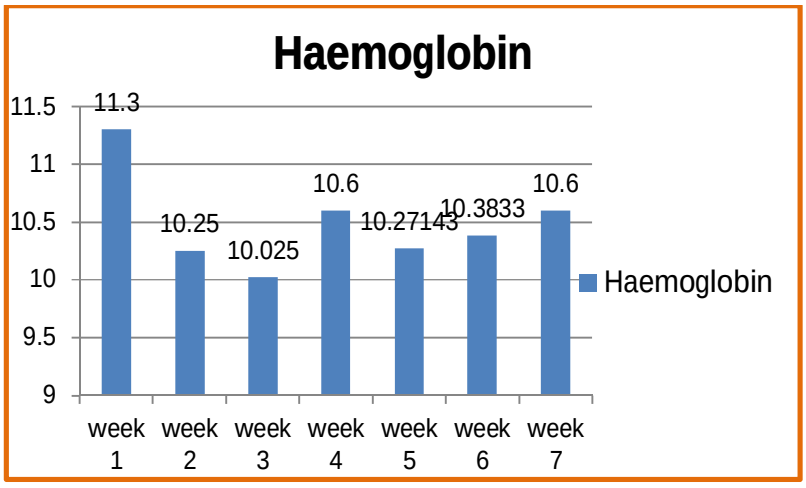


Fig 20: Mean haemoglobin values of all the patients represented from week 1 to week 7

Total white blood cell counts, their differentials and platelet counts were monitored each week. None of the patients had low total counts , differential count and low platelet counts.

4.43) DEATH:

Three patients died after initiation of treatment.

PATIENT 1:

The first patient died after completion of 14 Gy. He was diagnosed to have carcinoma hypopharynx stage T4aN2cM0. He had stridor after 7 fractions ,underwent an emergency tracheostomy and was hospitalized. After discharge from ward, he presented to subsequent OPD with complaints of fever, cough and generalized weakness. He was diagnosed to have right lower zone pneumonia and was admitted and treated with antibiotics. His general condition did not improve, and he had progressive disease. In view of this he was advised supportive care at home. He died later at home which was informed by the relatives.

PATIENT 2:

This patient died after completion of 36 Gy. He was diagnosed to have carcinoma hypopharynx stage e T4bN3M0. He had sudden onset of breathlessness and died suddenly at home which was informed by the relatives.

PATIENT 3:

This patient died after completion of 56 Gy. He was diagnosed to have carcinoma tongue T4bN2bM0. He presented with complaints of cough, breathlessness and chest x ray showed multiple bilateral reticular opacities. He was diagnosed to have bilateral pneumonia, was hospitalized and was treated with antibiotics and other supportive measures. His general condition did not improve and he died of respiratory failure.

4.5 RESPONSE EVALUATION AT SIX WEEKS:

The data of six patients was available for response evaluation at the end of six weeks.

4.51 NODAL RESPONSE: The clinically palpable nodes were measured each week during treatment and during follow up. During the first follow up there was 56.25% reduction in nodal size in the first patient, 33 % reduction in the second patient , 75 % reduction in the third patient and more than 85 % of reduction in the remaining three patients. The mean reduction in the nodal size was 70 % at first follow up.

4.52 RESPONSE OF THE PRIMARY LESION:

The primary site was assessed by clinical examination or NPL scopy at the end of six weeks. One patient was a case of unknown primary, among the remaining five patients, 2 patients did not have disease at the primary site, 2 patients had residual disease and 1 patient had progression of the disease. Overall, four patients had disease regression and two patients had progressive disease, one at the primary site and the second had lung metastases even though there was regression at the nodal site

4.53 DISTANT METASTASES:

One patient had distant metastases (lung) at first follow up (6 weeks).

Table 12 : Response assessment at six weeks:

Patients	Primary	Node	Distant	Comments
Pt 1	Unknown primary	85 % reduction in size	No metastases	Disease regression
Pt 2	Residual present	56 % reduction in size	Lung metastases	Disease progression
Pt 3	No disease	33 % reduction in size	No metastases	Disease regression
Pt 4	No disease	85 % reduction in size	No metastases	Disease regression
Pt 5	Progressive disease	87.5 % reduction	No metastases	Disease progression
Pt 6	Residual present	76 % reduction	No metastases	Disease regression

4.6 RESPONSE EVALUATION AT THREE MONTHS:

One patient died eight weeks after treatment and five patients had come for follow up at three months. Four patients had disease progression and one patient had complete response.

Table 13: Response assessment at three months:

Patients	Primary site	Nodal size in comparison with first follow up	Distant	Comment
Pt 1	Unknown primary	Increase in size	Lung metastases	PD
Pt 2	Residual present	Same size	Lung and liver metastases	PD
Pt 3	Residual present(not seen at first follow up	Same size	No metastases	PD
Pt 4	No disease	No clinically palpable nodes	No metastases	CR
Pt 5	Progressive disease	Same size	No metastases	PD

Abbreviations: CR: complete response, PD: progressive disease

CT scans done post treatment showed decrease in the nodal size which was statistically significant.

Table 14: Comparison of pre-treatment and post treatment CT scans

Pt .No	**CT pre RT Primary(cm)**	**CT post RT primary(cm)**	**CT pre RT node(cm)**	**CT post RT node(cm)**
1	-	-	76	26
2	6	0	12	0
3	28	46.4	10.44	1.92
4	10.5	5	8.7	5.28
5	5.06	5.5	33.12	32

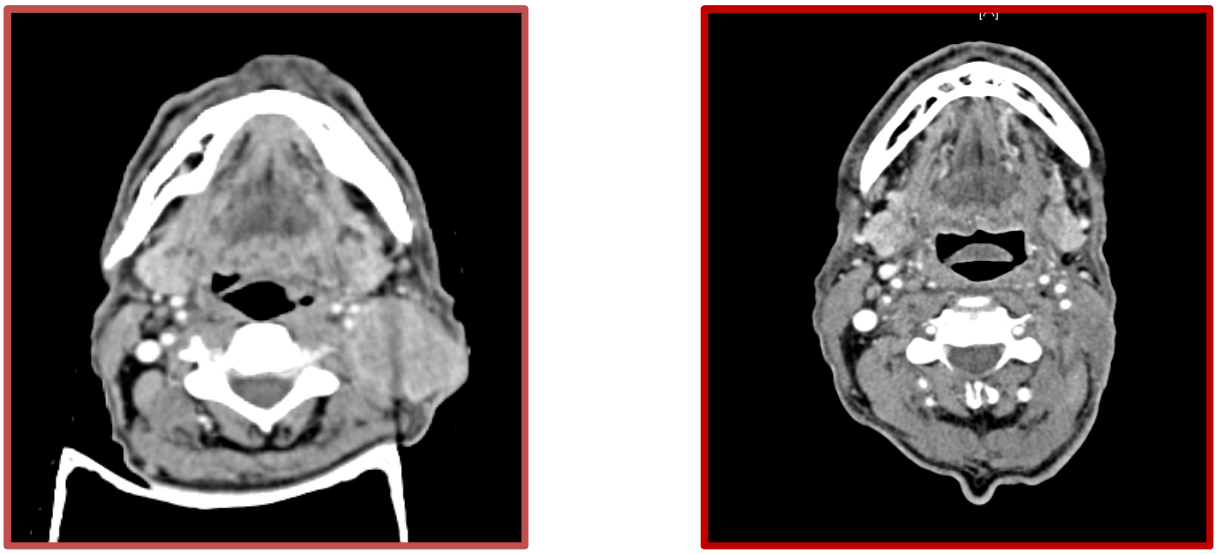


Fig 21: 70 year old gentleman diagnosed to have carcinoma pyriform sinus and left sided left sided level 2 neck node measuring 3 x 3.9 cm. Post treatment the patient has complete response with minimal thickening at the left sided pyriform sinus and no significant lymphadenopathy

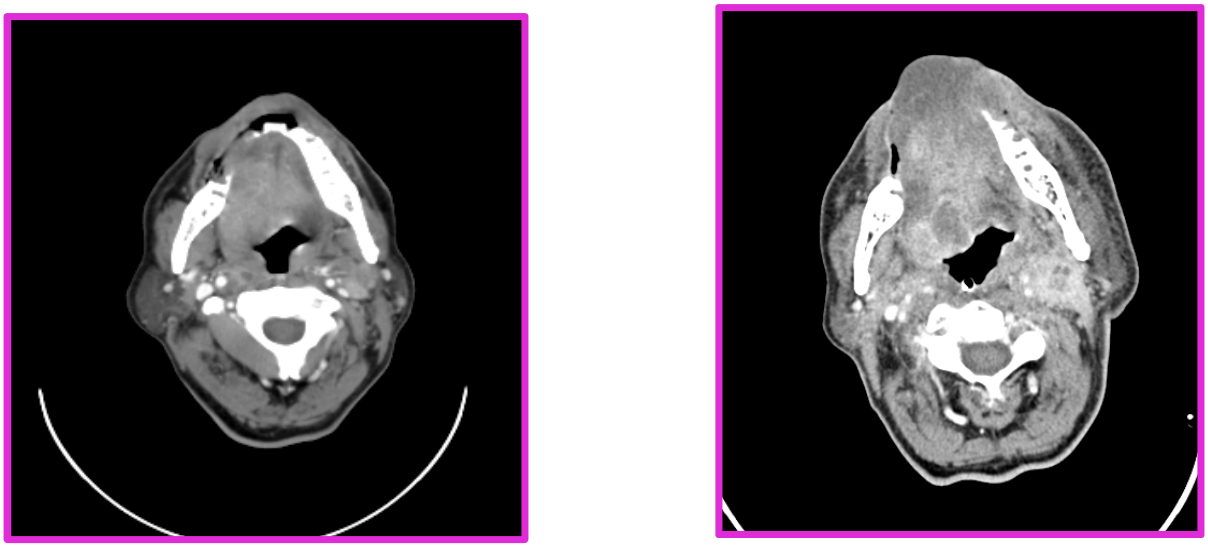


Fig 22: 73 year old gentleman diagnosed to have right sided carcinoma Tongue , the lesion measuring 5.3 x 5.2 cm ,post treatment there is increase in the bulk of the lesion measuring 9 x 5.5 cm and edema suggestive of disease progression.

4.61 SYMPTOM ASSESMENT:

On first follow up all the six patients complained of dryness of mouth, difficulty in swallowing with occasional choking sensation and tastelessness.

Pain control was adequate at the first follow up. Five patients had good pain control with STEP 2 analgesics and one patient with STEP 1 analgesics.

Out of five patients, four patients had severe pain at three months post treatment. They required initiation of Morphine, the doses ranging from 30 to 50 mg per day.

4.62 PERFORMANCE SCORE:

Post treatment the performance score worsened to ECOG 3 from ECOG 2 in three (50 %) patients. It remained the same in three patients (50 %) (ECOG 2 in two patients and ECOG 1 in one patient).

4.63 ASSESMENT OF QUALITY OF LIFE:

Quality of life was assessed in the patients with the help of EORTC questionnaires. The questionnaire had two parts, one to assess the functional, general symptomatology, global health and the second one was used to assess the site specific functions affected by radiotherapy in head and neck cancers.

Table 15: Comparative statistics of functional, symptom scale global health scale pre and post RT:

Scale	Pre RT Mean values	Post RT mean values
Functional scale	73.71	40.75
Symptom scale	32.70	51.93
Global health scale	36.10	30.55

The mean value of the functional scale, global health scale had decreased and means value of the symptom scale had increased post treatment. There was no statistically significant difference pre and post RT in the general health scale probably due to less sample size.

Table 16: Comparative statistics of symptom wise scales pre and post RT (six weeks):

Scores	Pre RT Mean values	Post RT mean values
Pain scores	40.2750	63.88
Swallowing	31.90	76.38
Senses	24.99	61.0
speech	33.2	57.3
social eating	29.1	69.4
Social contact	26.6	49.9
Sexuality	44.4	66.6
Teeth	11.1	33.3
Opening mouth	33.3	72.7
Dry mouth	38.8	72.2
Sticky saliva	44.4	77.7
Cough	44.4	72.2
Felt ill	55.5	66.6
Pain killers	83.3	83.3
Nutritional supplements	16.6	50.0
Feeding tube	0.00	66.6
Weight loss	100	83
Weight gain	0.00	16.6

The quality of life was assessed at six weeks by assessment of several functions and symptoms. Majority of the patients complained of sticky salivation, dry mouth, difficulty in opening the mouth and difficulty in eating. Many of them had to depend on ryles tube feeding or to take liquid diets orally.

The p values of mean scores of swallowing and social eating were significant. The rest of the p values were not significant.

4.64 SURVIVAL:

The median overall survival was 26 weeks (21.5 – 30.5 weeks). The median progression free survival was 5 months.

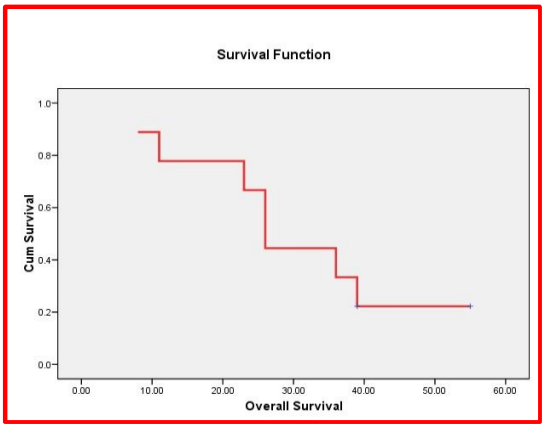


Figure 23 showing Kaplan meier survival analysis with median overall survival of 26 weeks

One patient who was diagnosed to have carcinoma hypopharynx stage T2N3M0 had partial regression of the disease at six weeks and complete response at three months and has a disease free survival of 25 weeks.

4.7 RETROSPECTIVE ANALYSIS OF PATIENTS WHO WERE TREATED WITH RADICAL CHEMO IRRADIATION:

The charts of ten patients diagnosed to have locally advanced head and neck cancers were retrospectively analyzed . The mean age of the patients was 46 years and range was 30 – 70 years All of them were diagnosed to have stage 4 cancers(70 % of stage 1V A cancers and 30 % of stage 1V B cancers respectively). The subsites were equally distributed among oropharynx, hypopharynx and tongue three in each and one patient was diagnosed to have carcinoma supraglottis. All of them received 66 Gy in 33 fractions with conventional fractionation along with concurrent weekly Cisplatin.

4.71 RADIOTHERAPY TREATMENT DETAILS:

All the patients except one completed the planned treatment. There was no break in therapy in 6 (60%) patients. The remaining 4 patients who had break in radiotherapy had only a single break and the major cause was mucositis (30% grade 3 and 10 % grade 4). Among the four patients two had break of 4 days, one of 9 days and one of 12 days and majority of the breaks were in the fourth and the sixth weeks. Two patients completed with 61/2 weeks, three patients within 7 weeks and three patients within 8 weeks. One patient completed treatment in 9 weeks. One patient discontinued treatment because of bilateral pneumonia, electrolyte imbalance and prolonged hospitalization.

Table 17: Duration of radiotherapy, treatment breaks, discontinuation and contributing reasons:

S.no	Duration of radiotherapy	Breaks in treatment	Duration of break	Week of break	Reasons	Discontinuation
Pt 1	6 weeks 3 days	Nil	-	-	-	-
Pt 2	7 weeks	yes	2 days	Week 4	LRTI*	
Pt 3	7 weeks	Nil	-	-	-	-
Pt 4	7 weeks	Nil	-	-	-	
Pt 5	9 weeks	yes	9 days	Week 6	Gr 4 mucositis	
Pt 6	8 weeks	yes	4 days	Week 6	Gr 3 mucositis	
Pt 7	5 weeks 4 days	-	-	-	-	Discontinued RT due to pneumonia
Pt 8	8 weeks	yes	4	Week 6	Gr 3mucositis	
Pt 9	6 weeks 4 days	nil	-	-	-	
Pt 10	8 weeks	yes	12	Week 4	Gr 3mucositis	

*lower respiratory tract infection

4.72 CHEMOTHERAPY DETAILS:

The majority of causes for discontinuation of chemotherapy were persistent higher grades of mucositis(40%), infection (20%), haematological toxicity (20%), worsening of renal function(10%),and allergic reaction to first chemotherapy(10%).

Table 18:Details of planned chemotherapy cycles and reasons for deviation from the planned treatment:

S.No	Chemotherapy cycles planned	Chemotherapy cycles received	reasons
Pt 1	6	3	LRTI*
Pt 2	6	2	pneumonia
Pt 3	6	1	Allergic reaction
Pt 4	6	4	URTI# and mucositis
Pt 5	6	4	Mucositis
Pt 6	6	4	mucositis
Pt 7	6	4	Low creat clearance
Pt 8	6	4	mucositis
Pt 9	6	2	Haematological toxicity
Pt 10	6	6	-

*Abbreviations:*lower respiratory tract infection, #upper respiratory tract infection*

4.73 RYLES TUBE FEEDING:

Six patients required ryles tube feeding due to odynophagia and poor oral intake.

4.74 HOSPITALISATION:

Two patients were hospitalized for duration of 8 and 12 days respectively in the fourth and fifth weeks for management of pneumonia. Among them one patient discontinued radiotherapy and the rest continued treatment.

4.75 HAEMATOLOGICAL TOXICITY:

Two patients had hematological toxicity because of which further chemotherapy was discontinued.

Table 19: Hematological toxicity in patients who received chemotherapy

Pt .No	Hematological toxicity	Week of treatment	No of cycles of chemotherapy
1	Low WBC count (grade 1)	Week 4	4 cycles
2	Low WBC count and Thrombocytopenia(grade 1)	Week 5	2 cycles

4.76 RESPONSE ASSESSMENT AT SIX WEEKS:

Response to treatment was assessed by clinical examination or by NPL scopy. At six weeks four patients had no disease clinically both at the primary and the nodal site. Four patients had no disease at the primary but had residual at the nodal site. One patient had no nodal disease and had disease at the primary site. The response of one patient could not be assessed as he could not complete the treatment due to poor general condition.

Table 20: Response details of patients at six weeks

Pt No	Primary site	Nodal disease
Pt 1	No disease	Residual present
Pt 2	No disease	No disease
Pt 3	No disease	Residual present
Pt 4	No disease	Residual present
Pt 5	Residual present	No disease
Pt 6	No disease	No disease
Pt 7	Not assessable	Not assessable
Pt 8	Residual present	No disease
Pt 9	No disease	No disease
Pt 10	No disease	No disease

4.77 RESPONSE ASSESSMENT AT THREE MONTHS:

Response evaluation to treatment after three months showed complete response in 4 patients, partial response in 3 patients and progressive disease in one patient. Among the remaining two one patient did not complete the treatment and the other did not come for follow up.

Table 21 : Response details of the patients at three months

Pt NO	Response of primary site at 3 months	Nodal Response at 3 months	Radiological response	Comments
Pt 1	No disease	Residual present	Partial response	PR[#]
Pt 2	No disease clinically	No disease	Complete response	CR[*]
Pt 3	Not available	Not available	-	-
Pt 4	No disease	Residual present	Partial response	PR[#]
Pt 5	Recurrence	No disease	Progressive disease	PD[$]
Pt 6	No disease	No disease	Complete response	CR[*]
Pt 7	Not assessable	Not assessable	-	
Pt 8	Residual present	No disease		PR[#]
Pt 9	No disease c	No disease	complete response	CR[*]
Pt 10	No disease c	No disease clinically		CR[*]

Abbreviations: CR[*]: complete response, PR[#]: partial response, PD[$]: progressive disease

4.78 SURVIVAL ANALYSIS:

The median overall survival was12.5 and the median Progression free survival was 11.5 months.

4.8 RETROSPECTIVE ANALYSIS OF PATIENTS WHO WERE TREATED WITH 6/7 FRACTIONATION:

We had retrospectively reviewed data of 10 patients treated with 6/7 fractionation. This data is taken from the study done in our institution. Ten patients with inoperable head and neck cancer unfit for concurrent chemo irradiation were included in this study. The mean age was 59.3 years. Primary site was Oropharynx (7), oral cavity (1), hypopharynx (1) and larynx. All patients had advanced inoperable lesions (80% IV A, 20 % III). All the patients completed treatment the planned treatment. The mean duration was 45.6 days (The mean duration was 45.6 days compared to planned duration of 37 days. Only one patient required hospitalization for supportive care. Grade III radiation mucositis was observed in 4 patients (36.36%). There was no incidence of significant hematological toxicity. Clinical assessment of primary lesion at the end-of-RT showed disease regression in all cases.

5. DISCUSSION

Locally advanced head and neck cancers constitute about 25 % of the cancer burden in our country (82). About 70 % of head and neck cancer patients present in locally advanced stage (83). The five year survival rates are 32 % for stage IVA, and 25% for stage IV B (84) with a median survival of about 12 months (85). Response of these patients to aggressive measures including chemo irradiation is poor with treatment related toxicities (86). In view of this, achieving good palliation of distressing symptoms with minimal toxicity and reasonably lesser duration regimens (87) is what is important and essential but poses a challenge. Therefore the primary aim in these patients should be to improve the quality of life.

Hyperthermia is a clinical treatment for malignant diseases in which tumour tissues are heated to a temperature of 40 – 42°C for 30 – 60 minutes. The biological rationale of addition of hyperthermia is that it acts as a potent radio sensitizer. This treatment is presumably beneficial for the hypoxic region of the tumor and to eliminate the radio resistant clone of cells. The aim in this study was to evaluate the feasibility of addition of hyperthermia to radiation therapy for locally advanced inoperable head and neck cancer.

Huilgol et al (88) had treated 28 patients with 70 Gy using conventional fractionation along with 5 to 7 sittings of hyperthermia once a week for 30 minutes prior to radiotherapy. We followed the above mentioned protocol except for the pre cooling measures and invasive thermometry as described in their study. We have compared the results of our patients with the data obtained by retrospective analysis from similar patients treated by other regimens such as 40 Gy in 10 fractions (2 fractions twice a week, hypofractionation), patients treated with six fractions a week

(6/7,two fractions on the fifth day) and patient treated with chemo irradiation (66 Gy in 33 fractions along with weekly Cisplatin).

In this present study 60 % of patients completed the planned treatment and 30 % had completed without a break in the treatment. Among the patients who had undergone chemo irradiation, 60 % completed without a break in treatment and 73 % of patients treated with hypofractionated radiotherapy completed the treatment without a break. The incidence of mucositis and dermatitis was slightly higher in our patients when compared to that in other treatment regimens. The incidence of grade 3 mucositis, grade 4 mucositis and grade 3 dermatitis was 42%, 14 % and 28 % respectively in the present study, whereas in the patients treated by chemo irradiation it was 30 %, 10 % and nil respectively. In the patients treated with 40 Gy in 10 fractions the incidence of grade 3 mucositis and grade 3 dermatitis was 18 % and 3 %respectively. The only treatment related toxicity in the patients treated with 6/7 fractionation was grade 3 mucositis in 36.36%.

The average duration of break in treatment was 10 days in our patients and 6 days in the patients treated with chemo irradiation. The average total duration required for treatment was similar in both the studies (52.8 days).

There were three deaths in the study, reasons being aspiration pneumonia in two patients and sudden death in one patient. Two patients were hospitalized during treatment for an average duration of 11.5 days for treatment of aspiration pneumonia. Out of them, one patient had progressive disease and was advised supportive care due to poor general condition who died later at home. The other patient could not recover from massive pneumonia and died of respiratory failure.

The incidence of aspiration pneumonia was more in our patients with an incidence of 20 %(2 out of 10 patients) , whereas the incidence in the literature is between 5 % to 7% (89)(90). The contributing factors could have been dysphagia, disturbances in swallowing function related to either the tumour, radiotherapy related edema or mucositis which have been described in literature. Our patients who had this complication had extensive local disease in the Tongue and hypopharynx. The incidence of pneumonia requiring hospitalization (average duration was 12.5 days) in the chemo irradiation study was 20 % (2 out of 10 patients). These patients also had primary disease in the Tongue and hypopharynx which is similar to our patients. One patient among them was discharged after recovery but the other one could not continue further treatment and went home on supportive care. There were no reported deaths in the patients treated with chemo irradiation. Among the patients treated with 40 Gy in 10 fractions and 6/7 regimen only one patient in each study required hospitalization.

During the first follow up at six weeks post treatment, 5 patients had adequate pain control with STEP 2 analgesics and 1 patient with STEP 1 analgesics. During second follow up at three months, 3 patients (50%) had worsening of pain requiring STEP 3 analgesics (Morphine), 2 patients continued to have pain control with STEP 2 analgesics and one patient had died.. Majority of the patients complained of difficulty in swallowing, dry mouth, difficulty in eating and restricted mouth opening. The requirement of ryles tube had increased post treatment and almost all the patients tolerated only liquid diet. Post treatment the performance score worsened to ECOG 3 from ECOG 2 in three of the patients. It remained the same in three patients (ECOG 2 in two patients and ECOG 1 in one patient).

In our study, at a follow up period of six weeks four patients had disease regression and two patients had disease progression. There was good response to therapy at the nodal site with 70%

mean reduction in the nodal size. Progression of disease in these 2 patients was noted in the form of increase in the disease at primary site and distant metastases in the lung.

At three months all patients had progressive disease except one patient who had complete response both clinically and radiologically. Progression was noted at the primary site in two patients. Metastatic disease was present in two patients, out of which one patient already had lung metastases who progressed to have liver lesions and the second patient had new onset lung metastases. CT scans done showed decrease in the mean nodal size of all patients which was statistically significant. The median overall survival was 26 weeks and the median progression free survival was 25 weeks. The patient who had complete response has a disease free survival of 25 weeks.

Huilgol etal had done a study randomizing patients between hyperthermia and radiation. The treatment compliance was 82 % in their study. There was no reported toxicity of higher grades of dermatitis and mucositis in their study and therapy was well tolerated. Response assesment was done after 10 days of completion of treatment. Complete response was observed in 22 of 28 (78.6%) patients in their study. Five deaths were reported in their study (18 %) which was unrelated to treatment. The median survival was 34.2 weeks.

In another randomized trial conducted by Datta etal , they had treated patients with 60 - 66 Gy using conventional fractionation with twice a week treatment with hyperthermia. Assesment was done at 8 weeks. Complete response was seen in 83% in the combined group and 60% in the patients who received only radiotherapy in stage 3 patients. In stage 4 patients complete response was seen in 63% of patients who received the combined treatment and 36 % in the patients who received only radiotherapy. At the end of 18 months 25 % of patients were disease

free when compared to 8 % in the control group. They did not report any higher grades of toxicity.

In another randomized control study performed by Valdagni etal which has a five year follow up period (conducted from 1985 – 86), the radiotherapy dose was 64 – 70 Gy in 2.0 – 2.5 Gy per fraction, five times a week and hyperthermia was delivered twice a week. In the combined arm, complete response was seen in 15/18 (83%), 2/18 (11 %) had progressive disease and 1/18 (6 %) had partial response at three months while in the radiotherapy only arm it was 9/22 (40%) , 4/22 (18 %) and 9/22 (40 %) respectively. The five year survival favored the combined arm over the radiotherapy only arm which was 53 .3% versus 0 % respectively. The incidence of distant metastases was 12.5 % in the combined arm and 24 % in the radiotherapy only arm. There were four deaths in the combined arm due to non - neoplastic causes. There were no significant acute toxicities and very minimal late toxicities (bone necrosis in two patients).

In a study conducted by Amichetti etal (73), 15 patients diagnosed to have unknown primary with neck nodes were treated with radiotherapy and local microwave hyperthermia. All the patients received Radiotherapy (57.50 – 74.40 Gy) with 6 MV linear accelerator or cobalt machine. Hyperthermia also was added to radiotherapy twice a week for a total of 2 – 7 sessions with a desired temperature of 42. 5 °C. Complete response was seen in nine (9/15) patients and 4 patients had partial response (4/15) with an overall response rate of 86.5 %. The reported acute and late toxicities were mild. Distant metastases developed in 5 patients who died because of the disease, nodal disease recurred in 2 patients and the remaining 2 patients died of other unrelated causes. This study showed benefit of hyperthermia when added to radiotherapy in patients who have unknown primary with large metastatic neck nodes.

In another study conducted by Arcangeli etal (91) complete response rates were 79% and 42% in the patients who received combined treatment and radiotherapy only respectively. They reported local control rates of 58 % and 14 % at the end of 28 months.

The total duration of treatment, average duration of hospitalization and the duration of the longest break in radiotherapy were almost similar in our patients and those treated with chemo irradiation. The published results of a study conducted in our institution of hypofractionated radiotherapy (40 Gy in 10 fractions treated twice a week) showed better results in terms of palliation of pain (30 % in our patients and 12 % of patients who received 40 Gy in 10 fractions required Morphine after completion of treatment), and other distressing symptoms(82). The performance status worsened in 50 % in the present versus 7 % of patients in the study treated with hypofractionated radiotherapy. In our study though the symptoms were palliated for a limited duration, there was no improvement in quality of life beyond a short period (2 months). There was not much of benefit in the physical, functional and social wellbeing of the patients post treatment. Though there was considerable nodal response, this did not translate into increased local control rates at the primary, prevention of metastases and improved progression free survival rates.

The reasons for these outcomes in this study might be a combinations of factors like improper and in homogenous thermal dose distribution, probable thermo tolerance, poor general condition of the patient, extensive local disease (N2, N3 disease) and the site of primary disease. The necessity of thermal dosimetry in hyperthermia study was emphasized by Manning et al (92), who concluded that only then, response to hyperthermia can be effectively evaluated and optimized. The main aim of palliation could not be achieved in our study and the procedure of delivering hyperthermia followed by radiotherapy prolongs the treatment time and is

cumbersome. Therefore when there are other palliative radiotherapy regimens (of shorter duration, less difficult to carry out, less toxicity) the utility of hyperthermia along with conventional fractionation (longer duration) would not be an ideal option in a busy oncology centre.

LIMITATIONS OF THE STUDY:

1. There were more number of patients with primaries from the hypopharynx, locally advanced disease and poor performance status. This selection bias could have probably contributed to more incidence of aspiration pneumonia, more toxicity and poor outcomes.

2. Lack of precooling measures might have added to more local reactions and acute toxicity. Lack of thermal dosimetry is a main disadvantage which might have helped to analyze the temperature distribution and would have avoided non homogeneity.

3. This treatment is technically difficult and time consuming as it requires 30 minutes for each sitting under technical supervision.

4. Cannot conclude on the benefits or inferiority of this treatment in view of less sample size.

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6.CONCLUSIONS

1. Hyperthermia treatment along with radiation resulted in more acute toxicity.

2. Moderate pain relief was achieved but this lasted only for a very short duration.

3. Hyperthermia studies might produce better results when conducted with more well planned adequate infrastructure, thermometric dosimetry and meticulous monitoring of temperature.

4. Response at the nodal site was good and so may be beneficial for patients with large fixed nodes. Therefore this could be considered for such patients, but should be carried out with the required facilities to have minimal and acceptable acute and late toxicity.

5. The sample size was not adequate to draw conclusions regarding response to therapy.

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8. Appendix 1

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

January 4, 2013

Dr. Jeba Karunya
PG Registrar
Department of Radiotherapy-Unit II
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms.
Dr. Jeba Karunya, PG Registrar, Radiotherapy-Unit 2, Dr. Subhashini John, Radiotherapy, Dr. Suparna Kanti Pal, Dr. Saikat Das, Dr. Rajesh Isaiah, Radiotherapy-Unit II

Ref: IRB Min. No. 8054 dated 06.11.2012

Dear Dr. Jeba Karunya,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms." on November 6, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Proforma
3. Information Sheet and Consent Form (English, Hindi, Bengali and
4. Tamil)
5. Cvs of Drs. Jeba Karunya, Subhashini John, Saikat Das, Rajesh
6. Isaiah, Suparna Kanti Pal.
7. A CD containing documents 1 – 4

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on November 6, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr. Srinivasa Babu	M.Sc, M.Phil, PhD	Sr. Scientist, Neurological Sciences, CMC	Internal, Clinician
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Internal, Clinician
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Vinitha Ravindran	M.Sc Nursing, PhD	Professor, Child Health Nursing, CMC.	Internal, Nurse
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing, CMC.	Internal, Nurse

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Internal, Social Scientist
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

A sum of Rs 40,000/- (Rupees Forty thousand only) will be granted for one year.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Subhashini John, Department of Radiotherapy-Unit II

Appendix 2

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No: ECR/32/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

Ref: IRB-A5-30-10-2013

November 05, 2013

Dr. Jeba Karunya
PG Registrar
Department of Radiotherapy
Christian Medical College
Vellore 632 004

Ref: IRB min no 8054 dated 06.11.2012

Dear Dr. Jeba Karunya,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following amendments for the study titled "A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms" on October 30th 2013.

1. To compare age and stage matched historical control of 40 patients treated with different palliative radiotherapy regimens on a retrospective basis with the 10 study patients treated with hyperthermia and radiotherapy.
2. We would wish to compare the toxicity profile, tolerability, response rates, local control, time to progression(local/systemic),of the patients treated with hyperthermia and radiotherapy and the other 40 patients treated with different regimens.

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on October 30th 2013 at 9.45 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. George Thomas, D Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB.	External, Clinician
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMCH.	Internal, Basic Medical Scientist
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMCH.	Internal, Clinician
Dr. Molly Jacob	MBBS, MD, PhD	Professor, Biochemistry, CMCH.	Internal, Clinician
Dr. B.S. Ramakrishna	MBBS, MD, DM, PhD, FAMS, FA Sc, AGAF, FNA	Retired Professor, Vellore	External, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor, Child Health, CMCH.	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMCH.	Internal, Clinician
Dr. Vinod Joseph Abraham	MBBS, MD, MPH	Professor, Community Medicine, CMCH.	Internal, Clinician
Dr. Sukriya Nayak	MBBS, MS	Professor, General Surgery, CMCH	Internal, Clinician
Dr. Deepak Abraham	MBBS, MS	Professor, Endocrine Surgery, CMCH.	Internal, Clinician
Rev. Dr. T. Arul Dhas	M.Sc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMCH.	Internal, Social Scientist

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMCH.	Internal, Basic Medical Scientist
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Clinical Pharmacology CMCH.	Internal, Pharmacologist
Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing	Internal, Nurse
Dr. B. Antonisamy	M.Sc, PhD, FSMS, FRSS	Professor, Biostatistics, CMCH, Member Secretary, Research Committee, IRB.	Internal, Statistician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Mrs. Selva Titus Chacko	M.Sc	Professor, Medical Surgical Nursing, CMCH.	Internal, Nurse
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Scientist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMCH.	Internal, Legal Expert
Dr. Jayaprakash Muliyil	B. Sc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist

Ethics Committee Silver, Office of Research, 1st Floor, Carmen Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin), FRCP (Glasg)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the above amendments as presented.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284491 E-mail : research@cmcvellore.ac.in

OFFICE OF THE VICE PRINCIPAL (RESEARCH)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002

Ref: FG/8054/11/2012

16th January, 2013

The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Denzil,

Sub: **FLUID Research grant project NEW PROPOSAL:**
A Pilot study to evaluate the feasibility, tolerance and efficacy of addition of hyperthermia to external beam radiotherapy (EBRT) on patients with locally advanced non metastatic inoperable head and neck cancer for palliation of symptoms. Dr. Jeba Karunya, PG Registrar, Radiotherapy-Unit 2, Dr. Subhashini John, Radiotherapy, Dr. Suparna Kanti Pal, Dr. Saikat Das, Dr. Rajesh Isaiah, Radiotherapy-Unit II

Ref: IRB Min. No. 8054 dated 06.11.2012

The Institutional Review Board at its meeting held on 6th November, 2012, vide IRB Min. No.***8054*** accepted the project for *1 Year* at a total sanction *Rs 40,000/- (Rupees Forty thousand only)*. Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Drs. Jeba Karunya & Subhashini John

Thank you.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Appendix 3

Department Of Radiation Oncology, Unit II

Christian Medical College & Hospital, Vellore

Information sheet for participants

Study Title : A pilot study to evaluate the feasibility, tolerability and efficacy of addition of hyperthermia with external beam radiotherapy [EBRT] on patients of locally advanced non-metastatic inoperable head and neck cancer for palliation of symptoms.

Study No : **Subject's Name :**

Subject's Initial : **Date of Birth /Age :**

You are being requested to participate in this study to see if you will tolerate the addition of hyperthermia to radiation therapy and to check to what extent this can cause reduction in size of the cancer.

1. **What is this study about?**

This study aims to test how well the addition of hyperthermia or heating to radiation therapy in patients diagnosed to have carcinoma of the head and neck is tolerated. The study will also look at how your disease is controlled after completion of treatment.

2. **How does Hyperthermia work?**

Hyperthermia is mild heating of the tumor area once weekly before the radiation therapy. It is known to increase blood circulation to the tumor. Radiation therapy needs good blood circulation to tumor to act properly. Therefore the tumor is expected to respond better to the radiation therapy when hyperthermia is added. Moreover, there are

evidence that there are some damage to the proteins and DNA during the process which help in selectively killing the tumor tissue.

3. What is done in the study?

After the diagnosis is confirmed and you are planned for radiation, you will be along with radiation therapy additional treatment with hyperthermia. Hyperthermia will involve mild heating of the tumor once every week before the radiation therapy to up to 40 degree Celsius. This would just provide warmth in the tumor area. Hyperthermia is expected to cause minimal side effects. It may be added that water boils at 100 degree Celsius. Radiation therapy is usually given five days in a week (Monday to Friday) for about seven weeks. Hyperthermia is delivered once a week for thirty minutes half an hour before radiotherapy with the help of a hyperthermia machine. Care is taken care the temperature is not exceeded very high with the help of a thermometer. You will undergo check up once a week to assess whether you are tolerating the treatment well and check for any side effects. You will also be asked to answer a set of questions at the beginning and completion of the treatment regarding your symptoms.

4. What are the side effects of the treatment?

Radiation therapy has side effects. Although hyperthermia is not known to increase these side effects, it can potentiate them. The side effects of hyperthermia are feeling of warmth at the local area while on treatment darkening of the skin color. There may be some increase in the radiation dermatitis and radiation mucositis.

5. Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. In addition, if you experience any serious side effects or your condition worsens, the study will be stopped and you may be given additional treatment.

6. What will happen if you develop any study related injury?

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you**.** The expenses incurred due to any sickness, hospitalization will be covered by the internal collaborative insurance provided by the institution.

7. Will you have to pay for the study treatment?

The study treatment or hyperthermia will be provided free of cost. You are required to pay only for radiation, and investigations as required for radiotherapy.

8. What happens after the study is over?

Once the study is over, you will be kept on follow up. You will continue to receive the necessary follow up advise and treatment which is the standard of care like any other patient. After six weeks of the treatment a scopy will be done and after three months a CT scan will be done for assessment of the disease status.

9. Will your personal details be kept confidential?

The results of this study might be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Informed consent form

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth____/____/_____(DD/MM/YYYY) / Age: _____yrs

Study Title : A pilot study to evaluate the feasibility, tolerability and efficacy of addition of hyperthermia with external beam radiotherapy [EBRT] on patients of locally advanced non- metastatic inoperable head and neck cancer for palliation of symptoms.

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

Appendix 4

CLINICAL RESEARCH FORM (CRF)

HYPERTHERMIA AND RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCERS

Study number:
Serial number of the patient:
Hospital number: RT number:
Name of the patient:
Age:
Gender:
Local address: Permanent address:

Occupation:
Marital status:
Education:
Phone Number:
Socioeconomic status:

Diagnosis:

Patient details:
Chief complaints:

History and presenting illness:

Past history:

Family history:

Personal history:

Treatment history:
Outside Investigations/Diagnosis:

Surgery – (At CMCH/Outside)
Chemotherapy – (At CMCH/ Outside)
Radiotherapy - (At CMCH/ Outside)

Clinical examination:
Vital signs:

Pulse:	Blood pressure:	Respiration:	Temperature:
Ht:	Wt:	BSA:	Creatinine clearance

General examination:

Ryles tube:
Tracheostomy tube:
IDL FINDINGS:

LOCAL EXAMINATION:

NPL SCOPY FINDINGS:

NECK EXAMINATION:

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

SYSTEMIC EXAMINATION:

INVESTIGATIONS :

Biopsy No:

Haemoglobin: Total blood counts: Differential count:

Platelet count: Creatinine:

Liver function tests:

Blood borne Virus screen:

Blood sugars:

Chest xray:

CT scan of head and neck:

FINAL DIAGNOSIS AND STAGING:

Date of starting radiotherapy:

Dates of delivering Hyperthermia:

1.		4.	
2.		5.	
3.		6.	

EORTC QOL H & N QUESTIONNAIRE:(PRE RT)

WEEKLY ASSESMENT CHART:

	WEEK 1	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		

Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 1	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Lymphocyte count		
Platelet count		

NECK EXAMINATION: (WEEK 2)

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 2	COMMENTS
DAY/ DOSE		

HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 2	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Lymphocyte count		
Platelet count		

NECK EXAMINATION: (WEEK 3)

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		

SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 3	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 3	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Platelet count		

NECK EXAMINATION: (WEEK 4)

	RIGHT NECK	LEFT NECK

LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 4	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 4	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		

Lymphocyte count		
Platelet count		

NECK EXAMINATION: (WEEK 5)

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 5	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 5	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Lymphocyte count		
Platelet count		

NECK EXAMINATION: (WEEK 6)

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 6	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		
Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		

Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 6	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Lymphocyte count		
Platelet count		

NECK EXAMINATION: (WEEK 7)

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

WEEKLY ASSESMENT CHART:

	WEEK 7	COMMENTS
DAY/ DOSE		
HYPERTHERMIA SITTING		
Pain[1]		
Dryness of mouth[2]		
Nausea[2]		
Vomiting[2]		
Taste alteration[2]		
Difficulty in swallowing[2]		
Throat pain[1]		
Hoarseness of voice[2]		
Cough[2]		
Dyspnoea[2]		
Ear pain or Discharge[2]		
Nasal bleeding[3]		
Asthenia[2]		
Anorexia[2]		
Trismus[2]		
Loss f weight[2]		
Others		
EXAMINATION[2]		
Nasal cavity		
Lips		
Tongue		
Buccal Mucosa		

Alveolus		
Floor of mouth		
Hard palate		
Soft palate		
Tonsil		
Base of tongue		
PPW		
Candidiasis		
Skin reactions		
Others		
Weight		
Neck Separation		

HAEMATOLOGICAL PROFILE:

	WEEK 7	COMMENTS
Haemoglobin		
Total WBC		
Neutrophil count		
Lymphocyte count		
Platelet count		

NOTE:
1. Pain will be graded according to Numerical rating scale (scale from 1 to 10)
2. Toxicity(Dermatitis, Mucositis, Haematological) will be graded according to CTCAE criteria(1 to 4)
3. Quality of life will be assessed by EORTC QOL H& N questionnaire

END OF HTRT ASSESMENT:

Clinical examination:
Vital signs:

Pulse: Blood pressure: Respiration: Temperature:

Ht: Wt: BSA: Creatinine clearance

General examination:

Ryles tube:
Tracheostomy tube:
IDL FINDINGS:
LOCAL EXAMINATION:

NPL SCOPY FINDINGS:
NECK EXAMINATION:

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

SYSTEMIC EXAMINATION:

INVESTIGATIONS :

Haemoglobin: Total blood counts: Differential count:

Platelet count: Creatinine:

EORTC QOL H& N QUESTIONNAIRE (AFTER RT)

AFTER SIX WEEKS ASSESMENT:
Clinical examination:
Vital signs:
Pulse: Blood pressure: Respiration: Temperature:

Ht: Wt: BSA: Creatinine clearance

General examination:

Ryles tube:
Tracheostomy tube:
IDL FINDINGS:
LOCAL EXAMINATION:

NPL SCOPY FINDINGS:

NECK EXAMINATION:

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

SYSTEMIC EXAMINATION:

INVESTIGATIONS :

Haemoglobin: Total blood counts: Differential count:

Platelet count: Creatinine:

EORTC QOL H& N QUESTIONNAIRE (SIX WEEKS AFTER RT)

AFTER THREE MONTHS:
Clinical examination:
Vital signs:

Pulse: Blood pressure: Respiration: Temperature:

Ht: Wt: BSA: Creatinine clearance

General examination:

Ryles tube:
Tracheostomy tube:
IDL FINDINGS:

LOCAL EXAMINATION:

NPL SCOPY FINDINGS:

NECK EXAMINATION:

	RIGHT NECK	LEFT NECK
LEVEL AND SIZE		
NUMBER		
TENDER /NON TENDER		
CONSISTENCY (HARD/FIRM/SOFT)		
MOBILITY (MOBILE/ FIXED)		
SKIN OVER THE NODES		

SYSTEMIC EXAMINATION:

INVESTIGATIONS :

Haemoglobin: Total blood counts: Differential count:

Platelet count: Creatinine:

CT scan :

EORTC QOL H& N QUESTIONNAIRE (THREE MONTHS AFTER RT)

Appendix 5

Name	
Hosp. No	
RT No	
Diagnosis	
Protocol - HTRT	

Hyperthermia to be given 30 minutes before radiotherapy on the following days

Date	Day	HT Time	sign	RT Time	sign	comments

TEMPERATURE RECORDINGS

	TEMP 1		TEMP 2		TEMP 3	
	10 MIN		20 MIN		30 MIN	
DAY 1						
DAY 2						
DAY 3						
DAY 4						
DAY 5						
DAY 6						
DAY 7						

Appendix 6

RTOG CRITERIA FOR TOXICITY GRADING:

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamatiom other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis

Appendix 7 : CTCAE version 4

	1	2	3	4	5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated		
Hoarseness of voice	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech		
D**ysphagia**	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences urgent intervention indicated	
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL		
Throat pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	death
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest;	Fatigue not relieved by rest,		

		limiting instrumental ADL	limiting self care ADL		

(CTCAE) Version 4.0

Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count	<LLN - 75,000/mm3	<75,000 - 50,000/mm3;	<50,000 - 25,000/mm3;	<25,000/mm3;	Death
Anaemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL;	Hgb <10.0 - 8.0 g/dL	Hgb <8.0 g/dL	Life threatening consequences	Death
Neutrophil count decreased	<LLN - 1500/mm3	<1500 - 1000/mm3	<1000 - 500/mm3	<500/mm3	Death

Appendix 8

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some

centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

The 95% confidence intervals should be provided.

Appendix 9

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

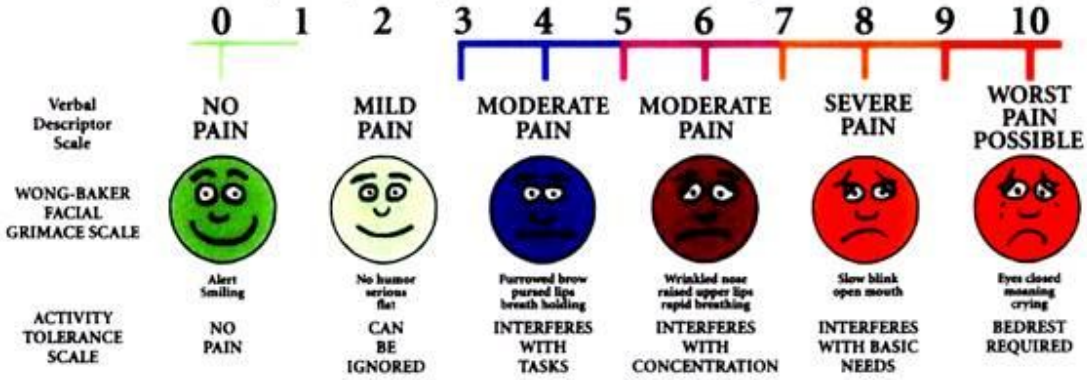
During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.



STATISTICAL ANALYSIS:

Analysis of quality of life scales:

Scales	Mean	N	Std. Deviation	Std. Error Mean
Functional Pre RT	73.7183	6	12.78805	5.22070
Functional Post RT	40.7567	6	38.23184	15.60809
Symptom Pre RT	32.7033	6	15.63838	6.38434
Symptom Post RT	51.9383	6	29.48609	12.03765
Global PreRT	36.1033	6	25.64769	10.47062
Global Post RT	30.5533	6	31.47403	12.84922

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	funcprert & funcpostrt	5	.042	.947
Pair 2	symptomprert & symptompostt	5	-.645	.240
Pair 3	globalprert & globalpostt	5	.152	.807

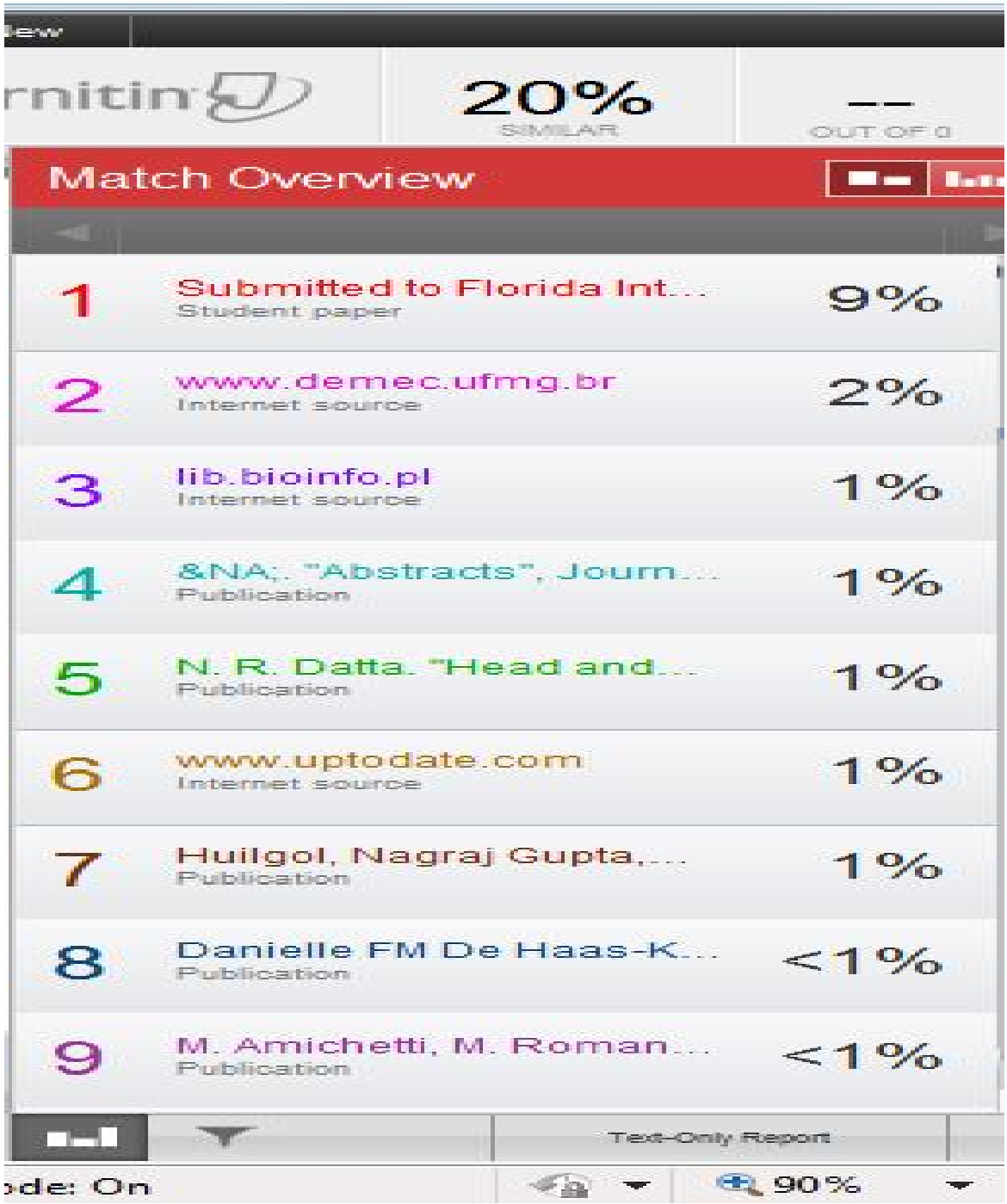
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		Mean	Std. Deviation	Std. Error Mean
					Lower	Upper			
Pair 1	HNPA Pre RT - HNPA Post RT	-23.60667	59.72459	24.38246	-86.28377	39.07044	-.968	5	.377
Pair 2	HNSW Pre RT - HNSW Post RT	-44.48167	36.00084	14.69728	-82.26223	-6.70110	-3.027	5	.029
Pair 3	HNSE Pre RT - HNSE Post RT	-36.10667	48.76673	19.90893	-87.28421	15.07088	-1.814	5	.129
Pair 4	HNSP Pre RT - HNSP Post RT	-24.06000	64.15814	26.19245	-91.38984	43.26984	-.919	5	.400
Pair 5	HNSO Pre RT - HNSO Post RT	-40.29000	30.00284	12.24861	-71.77605	-8.80395	-3.289	5	.022
Pair 6	HNSC Pre RT - HNSC Post RT	-23.32833	58.25391	23.78206	-84.46206	37.80539	-.981	5	.372
Pair 7	HNSX Pre RT - HNSX post Rt	-22.22833	58.37935	23.83327	-83.49370	39.03704	-.933	5	.394

Pair 8	HNTE Pre Rt - HNTE post RT	-22.22333	65.54433	26.75836	-91.00789	46.56122	-.831	5	.444
Pair 9	HNON preRt - HNOM post Rt	-38.87667	61.17601	24.97500	-103.07695	25.32362	-1.557	5	.180
Pair 10	HNDR pre Rt - HNDR post RT	-33.33333	76.01199	31.03176	-113.10302	46.43636	-1.074	5	.332
Pair 11	HNSSpre Rt - HNSS post rt	-33.34000	69.92409	28.54639	-106.72083	40.04083	-1.168	5	.295
Pair 12	HNCOpre rt - HNCOpost rt	-27.77333	71.23274	29.08065	-102.52751	46.98085	-.955	5	.383
Pair 13	HNFI prert - HNFIpost rt	-11.10833	58.37212	23.83032	-72.36611	50.14945	-.466	5	.661

Statistical analyses between pre and post CT values

	CT PRE RT – POST T P	CT PRE RT –POST T N
Z	.000(a)	-2.023(b)
Asymp. Sig. (2-tailed)	1.000	.043

a The sum of negative ranks equals the sum of positive ranks.
b Based on positive ranks.
c Wilcoxon Signed Ranks Test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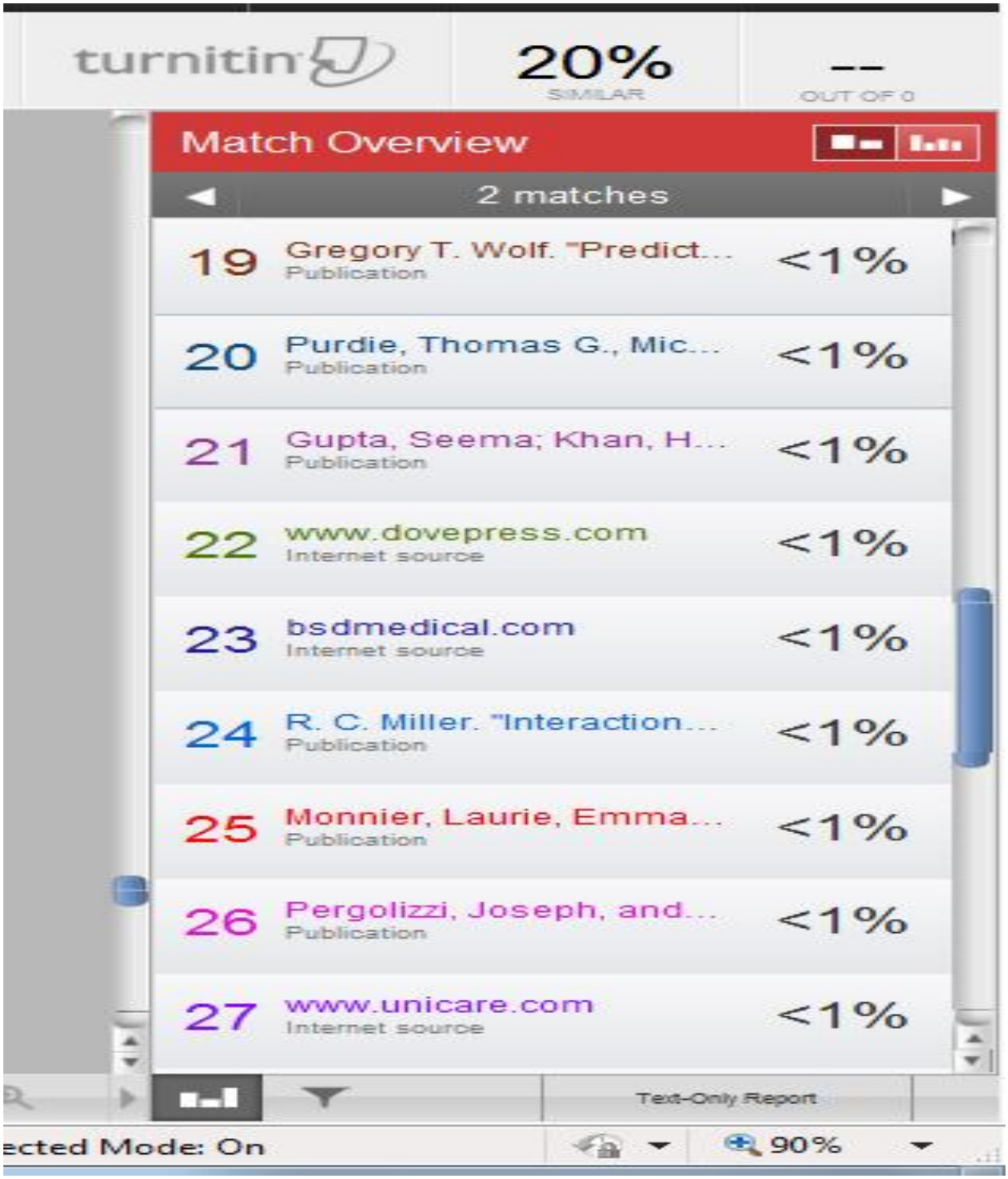
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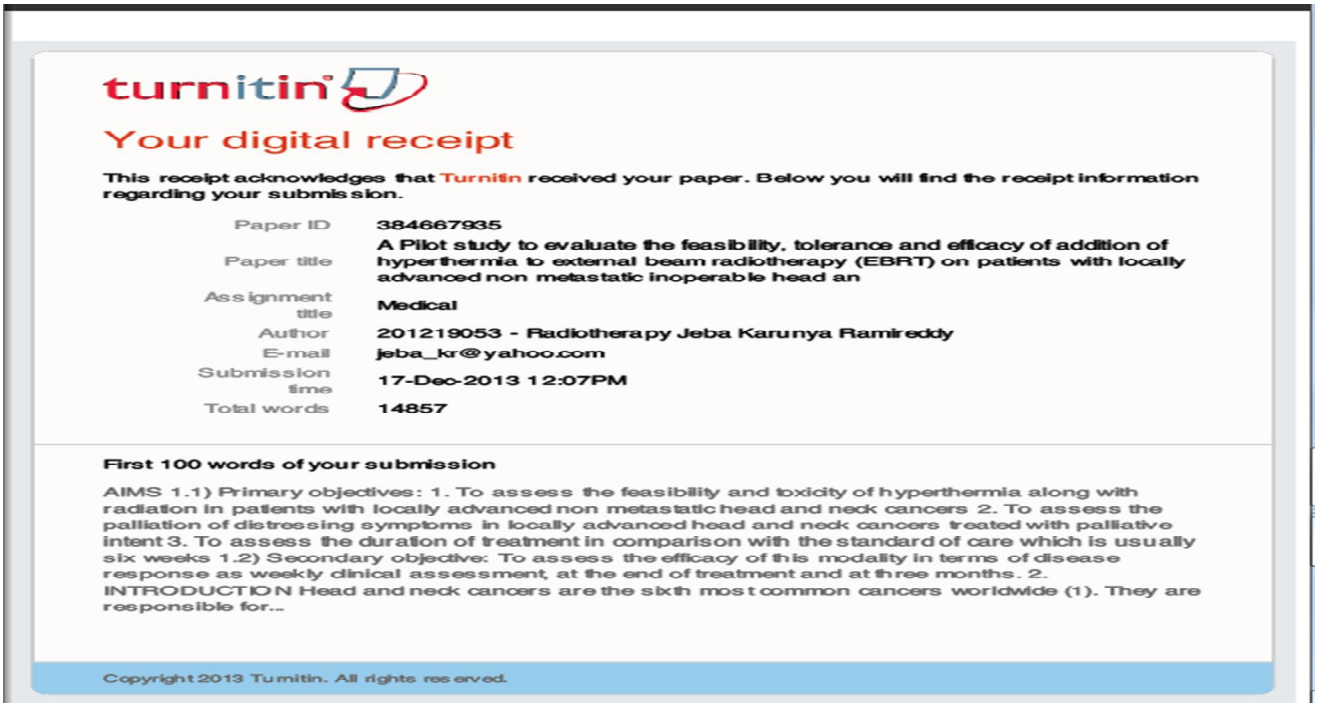

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E-mail	jeba_kr@yahoo.com
Submission time	17-Dec-2013 12:07PM
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First 100 words of your submission

AIMS 1.1) Primary objectives: 1. To assess the feasibility and toxicity of hyperthermia along with radiation in patients with locally advanced non metastatic head and neck cancers 2. To assess the palliation of distressing symptoms in locally advanced head and neck cancers treated with palliative intent 3. To assess the duration of treatment in comparison with the standard of care which is usually six weeks 1.2) Secondary objective: To assess the efficacy of this modality in terms of disease response as weekly clinical assessment, at the end of treatment and at three months. 2. INTRODUCTION Head and neck cancers are the sixth most common cancers worldwide (1). They are responsible for...