FOCUS - HEAD & NECK CANCER

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Editorial Office
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RCC Bulletin
Regional Cancer Centre
JIPMER
Puducherry– 605006
rccjipmer@gmail.com

This publication aims at the disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product / process / producer / or technology by RCC, JIPMER.
Greetings to you all…

I am pleased to inform that we have successfully organized three Continuing Medical Education (CME) programs on different themes viz., Colorectal cancers (13th September, 2009), Gynecological cancers (4th April, 2010), and Current Management of Early and Locally Advanced Breast Cancer (8th August, 2010). We got overwhelming response to all our CME programs and received a lot of feedback with appreciations from the participants, which led to us choosing “Head and Neck Cancers” for this 4th CME.

The consistent evolution of our understanding of biology, pathophysiology and the response of cancer cells to multimodality treatment besides the rapid developments in the technology of radiation therapy have equipped us better in dealing with the disease. However, it is an irrefutable fact that the definitive cure for cancer still eludes us all. Cancer is a very challenging disease to treat and it is a field showing one of the most rapid advances both at the basic science level and at the clinics.

The recent increase in the incidence of head and neck cancer is alarming. The worldwide incidence exceeds half a million cases annually. Over one third of all cancers in India occur in the head and neck. The primary reason for this unusually high incidence is the indiscriminate use of tobacco in its various forms. This CME is designed to foster discussions on the management principles, screening methodology, the challenges and the latest developments in the field of head and neck cancer, so as to provide the delegates a comprehensive review of the subject. The junior faculties are encouraged to present the latest research and developments that are taking place in head and neck cancer and the senior faculty from JIPMER, other medical colleges & hospitals in Puducherry will be sharing with us their wisdom and their sound personal clinical experience. I believe the interactions will help hone the skills of the young physicians as well as students and equip them to face the future clinical challenges. This way the CME will be useful in connecting the dots of the past to the matrix of the future.

This bulletin includes the articles presented during the CME and covers recent development like “role of PET-CT, sentinel lymph node biopsy, newer molecular targeted therapies, and newer equipments in the field of radiation oncology”. This issue will also serve as a record of some of the latest developments in the head and neck cancer at this point of time. I congratulate the authors and the entire editorial team who sifted through all the articles, making it as a quality reference material.

My best wishes to the young team of CME programme for taking their time off from their busy schedule and making all the efforts for another successful CME.

Dr.K.S Reddy
Director of RCC
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**Abstract**


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- Paradigm Shift in the Treatment of Head and Neck Cancer: The Role of Neoadjuvant Chemotherapy
- Improved Results with Accelerated Hyperfractionated Radiotherapy of Advanced Head and Neck Cancers
- The role of Human Papillomavirus Infection in Head and Neck Cancers
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- Radical Radiotherapy with Concurrent weekly Cisplatin in Loco-regionally Advanced Squamous Cell Carcinoma of the Head and Neck: a single-institution experience
Epidemiology of Head and Neck cancers

(Prof. K.S. Reddy, Director, RCC, JIPMER)

Head and neck cancers” is a collective term defined on anatomical-topographical basis to describe malignant tumors of the upper aerodigestive track. This anatomical region includes the oral cavity, pharynx and larynx. There are similarities in their natural history, epidemiology and control. A major subgroup of the head and neck carcinomas are the ones referred to as “oral cancers” arising in the mucous membranes of the mouth, i.e., lip, the base of tongue, gum, floor of mouth and palate, and pharynx (comprising the oropharynx, hypopharynx, and nasopharynx). Other tumors that occur in this area (such as those of the brain, thyroid, and melanoma) are conventionally not included in term “head and neck cancers”.

Non-communicable diseases including cancer are already emerging as major public health problems in India. These diseases are lifestyle related, have a long latent period and need specialized infrastructure and human resource for treatment. The risk factors of the major non-communicable diseases (diabetes mellitus, cardiovascular diseases and many types of cancer) are tobacco, dietary habits, inadequate physical activity and alcohol consumption. With the control of infectious diseases and increased longevity of the growing population in a country like India, the spectrum of disease changes and the burden of cancer are on the increase.

Head and neck cancers have been the subject of intensive laboratory research and clinical investigations. The last decade has witnessed many exciting accomplishments in head and neck cancer research. Advancements in molecular biology and the methodology and emergence of new data have improved our understanding of the carcinogenesis and behavior of a number of head and neck cancers. Because of the ease of clinical assessment and a relatively low incidence of systemic spread, head and neck cancers are good models for testing the efficacy of new therapy concepts that are aimed primarily at improving local-regional disease control. These serve as the basis for the development of novel multidisciplinary therapy strategies. Many new therapy approaches are undergoing preclinical and a few have moved on to phase I-II clinical trials.

Globally the burden of new cancer cases in 2000 was estimated to be around 10 million with more than half of these cases originating from the developing world population. Although estimates vary it is estimated that by the year 2020 there will be almost 20 million new cases. Worryingly, it is not only in the number of new cases that will increase, the proportion of new cases from the developing world will also rise to around 70%. The estimated age standardised rates per 100,000 were 96.4 for males and 88.2 for females.

In India, head and neck cancers account for 30 – 40% of cancers at all sites. Head and neck squamous cell cancer (HNSCC) is a major concern in India. In the USA, head and neck cancer accounts for 3 – 5% of all cancers. Worldwide, 15% of male cancers, 600,000 cases annually, are HNSCCs. Head and neck cancers affect both sexes and all races, but preponderance continues to be seen in males, African Americans, and Asians. The incidence of head and neck cancers increases with age and normally beyond 40 years of age.
The regional cancer center (RCC) in JIPMER gets substantial number of Head and Neck cancers for the treatment, where the head and neck cancers form around 32 – 35% of all cases (Table 1, Figs. 1, 2 & 3). A network of Hospital-based cancer registry is being established in RCC. In a year's time, this will enable telemedicine facility rendering consultancy services to all other cancer centers in and around this region, and also enabling networking with all other Regional Cancer Centers in India.

Table 1: Sitewise distribution of Head and Neck cancer patients treated in RT dept., JIPMER
Diagnostic Aids in the Screening of Oral Cancer

(Dr. Aravind Kumar, Junior Resident, Dept. of Radiation Oncology, Regional Cancer Centre, JIPMER)

Introduction
Cancer of the head and neck (H&N cancer), including all oral, laryngeal and pharyngeal sites, is the sixth most common cancer. It is well established that virtually all oral squamous cell carcinomas (OSCCs) are preceded by visible changes in the oral mucosa, like leukoplakia and erythroplakia. It is believed that identification and monitoring of these potentially malignant lesions and conditions allows clinicians to detect and treat early intraepithelial stages of oral carcinogenesis, all of which generally precede the development of invasive OSCC. The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have recently stressed that we can reduce a third of predicted 15 million cancer cases in the future and more effectively manage another third by planning effective cancer control and screening strategies.

Screening Methods

Oral Examination
A conventional oral examination (COE), using normal (incandescent) light, has long been the standard method for oral cancer screening. In 2005 Sankaranarayanan and co-workers reported the first solid evidence that periodic examination of the oral cavity can reduce mortality from oral cancer in high-risk individuals. Their 9-year screening study reported a significant 32% reduction in mortality in high-risk individuals in the intervention group, suggesting that oral visual screening in high-risk patients could prevent about 40,000 deaths from oral cancer worldwide.

Although COE may be effective as a screening test, there are still many problems with this approach. First, approximately 5–15% of the general population has oral mucosal abnormalities, the vast majority of which are clinically/biologically benign. Second, only a small percentage of leukoplakias are progressive or become malignant and a COE cannot discriminate between these lesions and their non-progressive counterparts. Furthermore, recent data suggests that some precancerous lesions may be lurking within mucosa that appears clinically normal by COE alone. Therefore, while COE may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant lesions, nor does it accurately detect the small proportion of biologically relevant lesions that are likely to progress to cancer.

Brush Biopsy
The oral brush biopsy consists of a method of collecting a trans-epithelial sample of cells from a mucosal lesion. A specially designed brush is used for epithelial cell collection and samples are eventually fixed onto a glass slide, stained with a modified Papanicolaou test and analyzed microscopically via a computer-based imaging system. The test is considered an intermediate diagnostic step as scalpel biopsy must follow when an abnormal result is reported.

Several studies have been performed in an attempt to test the sensitivity and specificity of brush biopsy in detecting dysplasia or OSCC. In the majority of studies, scalpel biopsy was performed after brush biopsy of lesions with high-risk clinical features, but not after brush biopsy of innocuously-looking lesions. This is believed to alter results regarding sensitivity and specificity of the test in the clinical context where accuracy is much needed and supports the criticism an intermediate non-diagnostic test would be superfluous when clinical features are highly suspicious for dysplasia/OSCC and a biopsy has to be performed anyway.

Toluidine Blue Staining
Toluidine blue (TB), is a vital dye that is believed to stain nucleic acids. Hence, it has been used for many years as an aid to the identification of clinically occult mucosal abnormalities and as a useful way of demarcating the extent of a potentially malignant lesion prior to excision. Analysis of current evidence suggests that TB is good at detecting carcinomas, but its sensitivity in detecting dysplasias is significantly lower. Furthermore, controversy exists regarding the subjective interpretation of mucosal staining and criteria for positive results.

Chemiluminescence
Clinical inspection of oral mucosa with the aid of chemiluminescent blue/white light was recently suggested to improve the identification of mucosal abnormalities with respect to the use of normal incandescent light. The technology involves the use of an oral rinse with a 1% acetic acid solution for 1 minute.
followed by the examination of the oral mucosa under diffuse chemiluminescent blue/white light. The theory behind this technique is that the acetic acid removes the glycoprotein barrier and slightly desiccates the oral mucosa, the abnormal cells of the mucosa then absorbing and reflecting the blue/white light in a different way with respect to normal cells. Hence normal mucosa appears blue, whereas abnormal mucosal areas reflect the light (due to higher nuclear/cytoplasmic ratio of epithelial cells) and appear more aceto-white with brighter, sharper and more distinct margins.

Some studies report that this technique can improve the detection of intra-oral abnormalities and identifying occult lesions that cannot be seen with incandescent light; others report that the overall detection rate was not significantly improved and the chemiluminescent light produced reflections that made visualization even more difficult than with incandescent light.

Tissue Fluorescence Imaging

The concept behind tissue autoflorescence is that changes in the structure and metabolism of the epithelium, and the sub-epithelial stroma can alter the distribution of tissue fluorophores and as a consequence the way they emit fluorescence after stimulation with intense blue excitation light, a process defined autoflorescence. The autoflorescence signal is finally visualized directly by a human observer. With regards to the oral cavity, normal oral mucosa emits a pale green autofluorescence when viewed through the instrument handpiece whilst abnormal tissue exhibits decreased autofluorescence and appears darker with respect to the surrounding healthy tissue. Autofluorescence imaging of the oral mucosa has been reported to possibly improve lesions’ contrast and therefore increase the ability to distinguish between mucosal lesions and healthy mucosa .Overall the technique seems to show high sensitivity, but low specificity. However, it should be highlighted that these results are from case series and case reports rather than clinical trials and that no published studies have assessed the system as a diagnostic adjunct in screening lower-risk populations.

Tissue Fluorescence Spectroscopy

The autofluorescence spectroscopy system consists of a small optical fiber that produces various excitation wavelengths and a spectrograph that receives and records on a computer and analyzes, via dedicated software, the spectra of reflected fluorescence from the tissue. This technique has the clear advantage of eliminating the subjective interpretation of tissue fluorescence changes. However, the downside is that more variables have to be tested and considered and this has led to controversial and often unclear results .Overall, autofluorescence spectroscopy seems to be very accurate for distinguishing lesions from healthy oral mucosa, with high sensitivity and specificity. However, the ability of the technique to distinguish and classify different types of lesion has been reported to be low. Further research is needed to support its clinical application.

Conclusion

WHO has clearly identified prevention and early detection as the major targets in the battle to control the oral cancer burden worldwide. Prevention and early detection of OSCC and its pre-invasive intra-epithelial stages is still largely based on visual examination of the mouth. Simple visual examination, however, is well known to be limited by subjective interpretation and by the potential, albeit rare, occurrence of dysplasia and early OSCC within areas of normal-looking oral mucosa. As a consequence, adjunctive techniques like Chemiluminescence, autofluorescence ,Toluidine Blue and brush biopsy have been suggested to increase our ability to differentiate between benign abnormalities and dysplastic/malignant changes as well as identify areas of dysplasia/early OSCC that are not visible to naked eye. At present, the utilization of these techniques in clinical practice is largely anecdotal. Further research with clear objectives, well-defined population cohorts and sound methodology is required before supporting the extensive use of oral cancer diagnostic aids in both primary and specialty settings.

References

Role of PET-CT in Head and Neck Cancers:

(Dr. Dhanpathi Halanaik, Assistant Professor, Dept. of Nuclear Medicine, JIPMER)

Introduction

Positron emission computed tomography (PET) is a functional diagnostic imaging technique, which has ability to study various biological processes like glucose, amino acid, phospholipids, receptors etc. Positron emission tomography (PET) with 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) has been used to diagnose, stage, and restage head and neck cancer. FDG PET is more sensitive and specific than computed tomography (CT) or magnetic resonance imaging in the detection of recurrent neoplasm. However, if PET alone is performed, limited spatial resolution and lack of anatomic landmarks hinder accurate tumor localization, particularly in the dense and complex anatomic structures of the head and neck. Addition of CT to PET has shown better specificity and sensitivity than either PET or CT alone as it has the ability to demonstrate functional and structural details in the same setting. This technique of fusion imaging offers the potential for improved detection and localization of head-and-neck cancer with one imaging tool. PET-CT has become an accepted and widely used imaging modality for the staging and follow-up/surveillance of head-and-neck cancer.

Evaluation of Primary Tumor

The PET portion of the PET-CT scan is performed approximately 1 hour after intravenous injection of 6 to 15 mCi of FDG. Helical CT data is immediately acquired preceding acquisition of 3-dimensional emission data (5 to 10 min per bed position, 2 to 5 bed positions per patient). Patient preparation typically includes fasting, control of the blood-sugar level, etc. Necessary measures are taken to reduce FDG uptake in brown fat. When PET-CT images are used for radiation therapy planning, patients are imaged with the same immobilization devices that would be used during their radiation therapy. The PET scans are corrected for attenuation with coefficients obtained by scaling the CT numbers to the PET energy level (511 kV). The helical CT scans are reconstructed into 512 pixel × 512 pixel images with a section thickness that matches the PET scans (2.4 mm to 3.4 mm).

PET-CT has role in evaluation of primary tumor, nodal metastatic disease, unknown primary presenting with cervical nodal metastases, treatment response assessment and surveillance and radiotherapy planning.

Evaluation of Nodal Metastatic Disease

For evaluating metastatic disease in cervical lymph nodes, FDG PET-CT has been previously shown to be comparable to, or superior than, conventional imaging in detecting regional lymph nodal metastases during initial staging. An average sensitivity of 87% to 90% and a specificity of 80% to 93% were reported for FDG PET-CT; compared with a sensitivity of 61% to 97% and a specificity of 21% to 100% for MRI or CT (Figure 1 & 2).

Fig. 1: (A) Pre-op. PET-CT Fused image showing primary tumor in right tonsil. (B) Post op. CT obtained after 4 months reveals no evidence of recurrence. (C) Follow up PET-CT Fused image shows small foci of increased FDG uptake at the posterior flap margin. Subsequent surgery confirms the recurrence at the superficial posterior aspect of the muscle flap.

Evaluation of Primary Tumor

The conventional work-up often provides sufficient information to determine the extent of primary disease. PET has been shown to be highly sensitive and specific in detecting clinically evident primary disease in >90% of patients. But it has a limited role in providing additional information with regard to the extent of primary disease following conventional work up. However, PET provides valuable additional information in relation to nodal and distant disease staging.
FDG PET-CT plays an important role in identifying disease in lymph nodes in unexpected locations and detecting unsuspected distant metastatic disease. PET-CT has an advantage over conventional imaging, in this setting, because of its whole-body coverage and its sensitivity to lesions that may be missed by conventional imaging such as subtle bone metastases that may not be detectable on a routine chest or abdominal CT scan. PET can detect occult distant metastatic disease in as many as 10% of patients with advanced local-regional disease. PET-CT also has another advantage in detecting a synchronous malignancy specifically involving the upper aero-digestive tract, as the risk factors for these malignancies is the same and include tobacco chewing, smoking and alcohol ingestion.

**Evaluation of Unknown Primary Tumor**

Ten percent of head-and-neck malignant lesions present with lymph nodal metastases without clear evidence of a primary tumor site. The prognosis of patients with unknown primary is generally unfavorable with average survival of only a few months. However, patients with cervical lymph node metastases are an exception to this rule since they can be treated by surgical resection and local radiotherapy. Furthermore, at least in patients with an upper- or mid-jugular lymph node metastasis, the corresponding primary tumor is likely (85%) to be head and neck carcinoma and thus is potentially curable.

(FDG-PET) has been shown to be the most efficient method capable of localizing unknown primary tumors and it provides additional staging information. Detection rates ranging from 24 to 90% have been described in the literature. A large review by Schoder and Yeung of 11 studies, which included more than 300 patients, has shown a sensitivity ranging from 10% to 60% for PET evaluation for unknown primary tumor site. Another meta analysis involving patients who had an initial negative physical examination and MRI results, showed that FDG PET and PET-CT were able to detect the primary tumor in 27% of patients (40 of 150 patients).

**Role of PET-CT in Radiotherapy Planning**

Integrated FDG PET-CT scanning provides a bridge between anatomic imaging and functional imaging for optimal radiotherapy planning. Use of PET-CT has shown modification of target volumes in ≥20% of cases in many publications compared with CT alone. Accordingly, PET-CT can be used as an adjunct imaging study for radiation treatment planning after definition of the target by CT or MRI, which have higher spatial resolution and are better at depicting marrow space infiltration and perineural spread of tumor (both are better shown by MRI). PET-CT is used to identify the normal size and normal-appearing lymph nodes with high metabolic activity as part of high-dose target volume for radiation. PET-CT also has a role in defining or contouring the primary tumors whose borders are difficult to distinguish by anatomic imaging alone. However, the abnormal appearing nodes or tumors on CT and MRI with equivocal metabolic activity on PET are also included in the treatment volume.

**Treatment Response Assessment and Surveillance**

Assessment of treatment response and surveillance for recurrence in head-and-neck cancers poses diagnostic challenges. Most head-and-neck cancers are treated with different approaches including surgery, chemotherapy and radiotherapy in different combinations. Neck dissection and surgical flap reconstructions distort the normal neck anatomy and make detection of recurrent neoplasm challenging on the basis of structural changes alone. Radiation therapy can further complicate imaging by making tissue planes indistinct and by causing edema that may produce an increase in tissue volume. These changes can obscure persistent or residual disease as well as recurrent disease and limit evaluation by physical examination and anatomic imaging modalities like CT and MRI. FDG PET/CT provides high diagnostic accuracy of 100% compared to 28% alone for CT for residual disease, when performed eight weeks after the conclusion of radiation therapy. A positive scan obtained at least six weeks after the end of therapy suggests residual disease, unless there are clinical signs of inflammation/infection.
to explain the abnormalities on PET. FDG-PET/ PET-CT are also more sensitive and specific in detecting residual and recurrent lymph node metastasis. PET/CT can be used in prognostic stratification and has significant clinical impact on management. In a study by Connell et al, on 76 patients, the complete metabolic response was predictive of overall survival; it changed radiotherapy planning technique in 29% and altered TNM staging in 34% of the patients.

**Evaluation of Thyroid Carcinoma**

FDG-PET/CT may not be a substitute for I-123 or I-131 whole-body scintigraphy in the evaluation of metastatic or recurrent thyroid cancer. However, in patients with increased thyroglobulin levels and negative I-123 or I-131 scan, especially under TSH stimulation, the utility of FDG-PET/CT scan has been confirmed in several studies, and the sensitivity of FDG-PET in detecting metastases in these cases ranges from 71% to 94%. In patients with medullary thyroid cancer somatostatin receptor scintigraphy may be more sensitive than FDG-PET. However, when fluorine-18 dihydroxyphenylalanine or 8F-DOPA is used, the results are very impressive. In one study, it was shown that for lymph node staging the sensitivity was 63% for fluorine-18 dihydroxyphenylalanine PET, 44% for FDG-PET, and 52% for somatostatin receptor scintigraphy.

**Limitations of PET-CT**

**False Positive:**
2. Variable FDG uptake in normal structures such as nasal turbinates, pterygoid muscles, salivary glands, extraocular muscles, and lymphoid tissues of the adenoids and Waldeyer ring.
3. PET-CT performed immediately after surgery or chemoradiation.

**False Negative:**
1. Smaller lesions with less FDG uptake.
2. Low-grade tumors

**Future Perspectives**

A number of other radiopharmaceuticals are being investigated and appear very promising for answering specific questions about tumor biology and in selecting and directing appropriate therapy. These include cell proliferation tracers [C-11]-thymidine and [18F]-fluorothymidine; amino acids, such as [C-11]-methionine; membrane synthesis tracers [C-11]-acetate; and hypoxia tracers, such as [18F]-fluoro-misonidazole (FMISO). However, all these tracers are still in the research stage and are not yet approved for clinical use. They hold the promise for successful applications in specific clinical situations. Use of multiple tracers and diagnostic modalities will help personalize cancer therapy for the individual patient, with PET-CT playing a major role in this regard.

**Conclusion**

FDG-PET has become a standard clinical imaging modality in patients with head and neck cancer. It contributes valuable information in localizing a primary tumor in patients with neck nodal metastases from an unknown primary, in the staging of primary head and neck cancer, and in the detection of recurrent disease. Combined PET-CT imaging optimizes the interpretation of FDG PET findings in head-and-neck cancer. Superior localization of radiotracer uptake with this technique can improve diagnostic accuracy and help avoid interpretative pitfalls.

**References:**

Surgical Treatment of Laryngeal Cancer

(Dr. Arun Alexander, Assistant Professor, Dept. of ENT, JIPMER
Dr. S. Gopalakrishnan, Prof & Head, Dept. of ENT, JIPMER, Puducherry)

Abstract
Laryngeal cancer is on of the commonest cancers in the head and neck. Surgical treatment of cancer of the larynx was historically the first method used in treatment. However with the advent of radiotherapy and chemotherapy more and more patients are undergoing these modalities of treatment as it has been found to provide comparable survival rates with the added benefit of voice preservation. Surgical methods include total or partial laryngectomy depending on the extent of primary lesion. Partial laryngectomies have the added benefit of voice preservation. However all is not lost even with a total laryngectomy and reasonable voice can be assured with tracheoesophageal puncture prosthesis or electro-larynx.

Introduction
Laryngeal cancer is on of the commonest cancers in the head and neck. Cancer of the larynx is particularly distressing for the patient because of the loss of voice and in many patients because of the associated swallowing problems. The voice is after all considered by many as the window into our soul. Treatment of laryngeal cancer initially consisted of surgical ablation of the larynx which invariably left the patient without the ability to speak. However with time, the innovations in surgery and improved understanding of cancer biology have led to the concept of organ preservation. These meant patients could be treated without surgery and preserving their voice yet giving them cure rates comparable to surgery.

History
The first recorded laryngectomy was performed by H. Albers on a dog in 1829. The dog lived 9 days. In 1866, Patrick Watson of Edinburgh performed the first laryngectomy on a 36 year old man with tertiary syphilis of the larynx. He died several weeks later from pneumonia. In 1873, Billroth, of Vienna, performed what is considered to be the first successful. The patient survived for a year and then died of local recurrence. From the first 103 total laryngectomies performed, 39% died from the immediate effects of the operation and over half of these died from pneumonia. Another 20% had a recurrence which resulted in death after an average of about 6 months. Only 9 of the first 103 survived for more than 1 year, and the longest survivor lasted 5 years. In order to be considered successful, a laryngectomy had to insure a survival of more than 1 year because it was believed that this length of survival could be achieved by tracheostomy alone. Standard treatment options for laryngeal cancer today can be summarized for each stage as given below

Stage I Laryngeal Cancer
Supraglottis
Standard treatment options:
1. External-beam radiation therapy alone. (Preferred due to good results and voice preservation)
2. Supraglottic laryngectomy.
3. Total laryngectomy reserved for patients unable to tolerate potential respiratory complications of surgery.

Glottis
Standard treatment options:
1. Radiation therapy
2. Cordectomy for very carefully selected patients with limited and superficial T1 lesions.¹ ²
3. Partial or hemilaryngectomy, depending on anatomic considerations.
4. Laser excision.³

Subglottis
Standard treatment options:
1. Radiation therapy alone

Stage II Laryngeal Cancer
Supraglottis
Standard treatment options:
1. External-beam radiation therapy alone. (Preferred)
2. Supraglottic laryngectomy or total laryngectomy, depending on location of the lesion, clinical status of the patient, and expertise of the treatment team.
3. Postoperative radiation therapy is indicated for positive or close surgical margins.

Glottis
Standard treatment options:
1. Radiation therapy.³ ⁴
2. Partial or hemilaryngectomy or total laryngectomy, depending on anatomic considerations.
3. Laser microsurgery may be appropriate

Subglottis
Standard treatment options:
- Lesions can be treated successfully by radiation therapy alone with preservation of normal voice.⁵ ⁶

Stage III Laryngeal Cancer
Supraglottis / Glottis
Standard treatment options:
1. Surgery with or without postoperative radiation therapy.⁵
2. Definitive radiation therapy with surgery for salvage of radiation failures.⁶
3. Concurrent chemotherapy and radiation for patients who would require total laryngectomy for control of disease. Laryngectomy would be reserved for patients
with less than a 50% response to chemotherapy or who have persistent disease following radiation.

Subglottis

Standard treatment options:
1. Laryngectomy plus isolated thyroidectomy and tracheoesophageal node dissection followed by postoperative radiation therapy.
2. Radiation therapy alone is indicated for patients who are not candidates for surgery. Patients should be closely followed, and surgical salvage should be planned if needed.

Stage IV Laryngeal Cancer

Supraglottis / Glottis

Standard treatment options:
1. Total laryngectomy with postoperative radiation therapy,
2. Definitive radiation therapy with surgery for salvage of radiation failures
3. Concurrent chemotheraphy and radiation for patients who would require total laryngectomy for control of disease. Laryngectomy would be reserved for patients with less than a 50% response to chemotherapy or who have persistent disease following radiation.

Supraglottis

Standard treatment options:
1. Laryngectomy plus total thyroidectomy and bilateral tracheoesophageal node dissection usually followed by postoperative radiation therapy.
2. Treatment by radiation therapy alone is indicated for patients who are not candidates for surgery.

Recurrent Laryngeal Cancer

Treatment of recurrent supraglottic, glottic, and subglottic cancer includes further surgery or clinical trials.

Standard treatment options:
- Salvage is possible for failures of surgery alone or of radiation therapy alone and further surgery and/or radiation therapy should be attempted, as indicated.
- Selected patients may be candidates for partial laryngectomy after high-dose radiation therapy has failed.
- Re-irradiation for laryngeal salvage following radiation therapy failure has resulted in long-term survival in a small number of patients; it may be considered for small recurrences after radiation therapy, especially in patients who refuse or are not candidates for laryngectomy.
- Salvage after previous combined total laryngectomy and radiation therapy is poor.

Surgical Procedures for Laryngeal Cancer

Surgical procedures can be classified as
1. Partial laryngectomy
2. Near total laryngectomy
3. Total laryngectomy

Partial laryngectomy is a surgical procedure to preserve portion of the larynx during resection of the tumor so as to preserve some amount of voice. Partial laryngectomy however does not compromise tumor margins and is indicated is smaller tumors.

The various procedures for different situations are classified below
1. Trans oral endoscopic resection with CO2 laser
2. Open partial laryngectomy

Glottic cancer

1. Laryngofissure & Cordectomy
2. Vertical partial laryngectomy (hemi, frontal, bi-frontal, sub-total)
3. Extended vertical partial laryngectomy with arytenoidecetomy
4. Supra-cricoid laryngectomy with crico-hyoido-epiglottopexy

Supraglottic cancer

1. Supraglottic laryngectomy
2. Extended supraglottic laryngectomy with excision of base tongue
3. Extended supraglottic laryngectomy with excision of pyriform fossa
4. Extended supraglottic laryngectomy with arytenoidecetomy

Transglottic cancer

1. Three quarter laryngectomy
2. Supra-cricoid laryngectomy with crico-hyoidopexy

Principles of Partial Laryngectomy

Partial laryngectomy is feasible because of the embryological compartmentalization of the larynx which allows oncologically safe resection of tumors confined to these compartments and still allows the larynx to function after resection. The cricoid cartilage is the base on which the larynx is built. For a successful partial laryngectomy the laryngeal remnant must have an intact cricoid cartilage and at least one mobile arytenoid cartilage. Laryngeal innervation by the superior laryngeal nerve above the glottis and the recurrent laryngeal nerve below must be preserved for proper functioning of the laryngeal sphincter. Preoperative imaging is mandatory in assessing tumor stage. Every patient for partial laryngectomy must be counselled on the need for total laryngectomy as tumor extent may require change of plans on table.

Rehabilitation of Voice after Laryngectomy

The loss of voice is very traumatic to most patient following laryngectomy. Every effort must be made to restore some amount of voice in these patients. The options available include the following:
1. Esophageal voice
2. Artificial larynx
   a. Pneumatic
   b. Electro-larynx
3. Tracheo-esophageal puncture prosthesis
   a. Indwelling
   b. Removable
Conclusion
In conclusion treatment of cancer of the larynx requires a multidisciplinary approach. However due to the need for organ preservation more and more cases are treated with radiation and chemotherapy with surgery being used for salvage or for advanced tumors. Partial laryngectomies when used in carefully chosen patients can preserve voice. Finally with the advances in prosthetic devices speech can be restored even in patients with total laryngectomy.

References:

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Neck Dissection in Head and Neck Cancer
(Dr. Pradipta Kumar Parida, Assistant Professor, Dept. of ENT Dr.S. Gopalakrishnan, Prof & Head, Dept. of ENT, JIPMER).

History
Cervical nodal metastases are the worst prognostic indicator and decreases survival by 50% in head and neck malignancies. The operation of neck dissection dates back to 1906 when George W. Crile first described the classical radical neck dissection (RND). Martin’s refinement of Crile’s operation became the template for the modern RND. Bocca and Pignataro later described the functional neck dissection (FND). In the last thirty years, the trend towards more conservative surgical therapy has been accompanied by improved efficacy of radiation therapy. Anatomy (six groups by the Sloan-Kettering Memorial Group)

Level I - Submental (Level Ia) and submandibular nodes (Level Ib).
Level II - Upper jugular nodes, Boundaries: Superior – skull base, Inferior – level of the hyoid bone (clinical landmark) or carotid bifurcation (surgical landmark).
Level IIa & IIb - anterior and posterior to XI nerve respectively. Level III - Middle jugular nodes, Boundaries: Superior – hyoid bone (clinical landmark) or carotid bifurcation (surgical landmark). Inferior – cricothyroid notch (clinical landmark) or omohyoid muscle (surgical landmark).
Level IV - Lower jugular nodes, Boundaries: Superior – cricothyroid notch (clinical landmark) or omohyoid muscle (surgical landmark), Inferior - clavicle.
Level V - Posterior triangle
Level Va - Lymphatic structures that follow the spinal accessory nerve.
Level Vb - Lymphatic structures that lie along the transverse cervical artery.
Level VI - Anterior/central compartment (Prelaryngeal, pretracheal, paratracheal, and precricoid (Delphian) nodes).

Assessment of Cervical Metastases
Clinical palpation: Sensitivity and specificity of palpation ranges from 60-70%. A short obese neck, previous radiation or surgery makes the physical examination more difficult. Imaging: CT reveals metastatic adenopathy by central necrosis and extracapsular spread by enhancement of the nodal capsule. MRI is less precise than CT scan in identifying tumor necrosis and extracapsular spread. Ultrasound-guided aspiration cytology has a higher specificity than CT and MRI in analyzing lymph nodes of less than 10 mm. However, the yield of this technique is directly related to the experience of the ultrasonographer and the pathologist.

Positron Emission Tomography (PET): Tissues with squamous cell carcinoma cells capture \[^{18}F\] fluoro-2-deoxy-D-glucose (FDG) at increased rates compared with normal tissues. PET has a positive role in the identification of occult metastases and early diagnosis of recurrent cancer.
**Staging System** (by AJC/UICC)
Thyroid and nasopharyngeal carcinomas have unique nodal classifications that are based upon tumor behavior and prognosis.

**TNM Classification of Regional Nodes (N)**
Lip, oral cavity, oropharynx, hypopharynx, larynx, trachea, paranasal sinuses, major salivary glands, nasopharynx, and thyroid nodal classifications are unique and based upon tumor behavior and prognosis.

- **Nx** - Regional lymph nodes cannot be assessed
- **N0** - No regional lymph node metastasis
- **N1** - Single ipsilateral lymph node <3 cm
  - **N1a** - Single ipsilateral lymph node >3 but <6 cm
  - **N1b** - Multiple ipsilateral nodes ≤6 cm
- **N2** - Bilateral/contralateral lymph nodes ≤6 cm
  - **N2a** - Multiple ipsilateral nodes >3 but <6 cm
  - **N2c** - Bilateral/contralateral lymph nodes >6 cm
- **N3** - Any node >6 cm
  - **N3a** - Bilateral metastasis in lymph node(s) >6 cm above the supraclavicular fossa
  - **N3b** - Bilateral metastasis in lymph node(s) >6 cm below the supraclavicular fossa

**Classification of Neck Dissection** (by the American Society for Head and Neck Surgery)
The following neck dissection can be performed:
1. Classic radical neck dissection (RND)
2. Modified radical neck dissection (MRND, type 1-3)
3. Selective neck dissection
4. Extended radical neck dissection.

- **Preoperative preparation** - It may be advisable to perform an elective tracheostomy for a patient who is undergoing bilateral or a second neck dissection or neck dissection following previous radiotherapy.

**Position** - Supine position, head extended on a head ring, a sand bag is placed under the shoulder and head turned to the opposite side.

**Incision** - Neck dissection can be performed through a number of incisions (Crile, Schobinger, Horizontal -T, McFee, Lateral Utility, Utility, H- Incision and Visor flap) and design of incision is based on blood supply. The decision to use a certain incision based on personal preference, previous radiotherapy, the number of levels required for access purpose and site of the primary tumor if that is being resected as well. **Incision design**: Try not to use trifurcation, if possible. If trifurcation is used, it should not lie over the carotid artery.

**Radical Neck Dissection**
It involves removal of all lymphatics from levels I-V and all three non-lymphatic structures namely the XI nerve, the sternocleidomastoid muscle and IJV.

- **Indications** -
  1. Significant operable neck disease (N2a, N2b, and N3) present in an untreated patient or in a patient treated with surgery, irradiation, chemotherapy, or a combination thereof
  2. Access prior to pedicled flap reconstruction.

- **Contraindications** -
  1. Untreatable primary tumor
  2. Distant metastases
  3. Inoperable neck disease (involvement of deep cervical fascia and muscle, brachial plexus, extension onto and into the skull base and circumferential or near circumferential involvement and invasion of the carotid vessels if the patient cannot tolerate a balloon occlusion test and
  4. Patient unfit for major surgery.

**Corners of consternation in RND**
- **Lower End of IJV**
- **Junction of lateral border of clavicle with the lower edge of trapezius (supraclavicular fossa)**
- **Upper end of IJV**
- **Submandibular triangle**

**Critical steps in RND**
Lower neck:
- Divide the lower end of sternocleidomastoid in corner, isolate and ligate IJV, look for and avoid the thoracic duct and/or branches of the jugular lymph duct in Chaissaicanac's triangle, remove any scalene nodes, divide and retract the omohyoid muscle upwards, mobilize the fat pad overlying the prevertebral fascia, identify and preserve the brachial plexus and phrenic nerve.

Upper neck:
- Divide the upper end of sternocleidomastoid, retract the posterior belly of digastric upwards, identify and ligate IJV, identify and preserve the hypoglossal nerve.

**Modified Radical Neck Dissection**
Modified radical neck dissection involves excision of the same lymph node bearing tissues from one side of the neck as is performed in a RND with the preservation of one or more non-lymphatic structures. Type-1 MRND preserves XI nerve, type-2 MRND preserves both XI nerve and IJV and type-3 (functional neck dissection) is when all three are preserved.

- **Indications (usually an intraoperative assessment)**
  1. MRND type 1 - Metastasis (N1, N2a, and N2b) not involving XI nerve.
  2. MRND type 2 - Metastases involving the sternocleidomastoid but not IJV or XI nerve, second side operation, when there is need for microvascular anastomosis, and differentiated thyroid cancer.
  3. MRND type 3 - Metastasis not infiltrating the non lymphatic structures, N0 neck and differentiated thyroid cancer.
Selective Neck Dissection
Preservation of lymphatic groups normally removed in a RND is a selective neck dissection. There are several types of selective neck dissection. They focus on removing the highest risk nodal groups depending on the site of the primary tumor. The Supraomohyoid neck dissection (SOHND) removes levels I-III and is performed in patients with oral cavity primaries, Merkel cell carcinoma, and some melanoma of the face and SCCA of the parotid. Bilateral SOHND are considered with anterior oral cavity and cutaneous lesions along with lateral lesions that approach or cross the midline. The lateral neck dissection removes levels II-IV. It is performed for patients with oropharyngeal, hypopharyngeal or laryngeal primaries. The posterolateral neck dissection removes levels II-IV, suboccipital and postauricular nodes. It is performed primarily for patients with cutaneous lesions on the posterior scalp or neck. Then anterior or central neck dissection removes the anterior compartment (level VI) and is indicated in some types of differentiated thyroid carcinoma, parathyroid carcinoma, subglottic carcinoma, and lesions of the cervical esophagus.

Extended Radical Neck Dissection
This operation consists of removal of the structures resected in a RND, along with one or more additional lymph node groups (retropharyngeal lymph nodes, parotid nodes or level VI and VII lymph nodes) or non-lymphatic structures (part of mandible, parotid gland, mastoid tip, prevertebral fascia and muscles, diacastric muscle, hypoglossal nerve, ECA and skin) or both.

Complications

Intra-operative complications
1. Hemorrhage
2. Carotid sinus reflex
3. Pneumothorax
4. Embolism
5. Air embolus: This may occur following injury to the IJV. Large emboli can produce sudden falls in end-tidal carbon dioxide and arterial blood pressure. A pre-cordial Doppler probe may detect the characteristic murmur of venous embolus. Local pressure should be applied and the anaesthetist informed so the patient can be placed in the Trendelenburg position and rotated to the left. In severe cases attempts can be made to pass a catheter and aspirate air from the right side of the heart. Hyperbaric oxygen therapy, if available, is the ultimate and effective treatment
6. Nerve damage: damage to marginal mandibular nerve, hypoglossal nerve, lingual nerve, vagus, phrenic nerve, brachial plexus and sympathetic chain may occur.
7. Chylous fistula: Most chylous fistulas occur on the left side. If it occurs, ligate the thoracic duct. Ask the anesthesiologist to apply positive pressure to reevaluate if further leaking occurs. A suture ligation with a figure 8 using 4-0 silk is usually satisfactory.
8. Electrolyte disturbances
9. Shoulder syndrome: This is the most crippling long term complication of RND characterized by long standing pain in the shoulder and the inability to perform abduction beyond 75 degree and flexon beyond 45 degree from the trunk. The best way to prevent this syndrome is to preserve both the spinal accessory nerve and branches from the cervical plexus (C3 & C4) to the trapezius muscle. If both nerves are divided, it is then important to refer the patient post operatively to a physiotherapist.

Postoperative complications
1. Hematoma
2. Wound infection
3. Skin flap loss
4. Salivary fistula
5. Chylous fistula: Chylous fistula occurs in approximately 1-2% of patients and identified by the appearance of a milky clouded fluid in drains. Chyle accumulation can cause redness and swelling of the flap with induration of the surrounding tissues. The leak, if minimal, is usually controlled by aspiration, pressure dressings, and a low-fat diet. Ligation of the offending thoracic duct is required when the leak is more than 500 mL and when conservative management fails.
6. Facial edema
7. Electrolyte disturbances
8. Carotid artery rupture: Prevention- preservation of the adventitia, avoid suction catheters adjacent to the carotid artery, divert the fistula away from the carotid, use adequate moist dressings, cover the carotid artery with a dermal graft using the levator scapulae or posterior scalene muscle and treat infection aggressively.

Outcome and Prognosis
Outcome: RND results include the following:
1. The recurrence rate is 3-7% and 20-70% in a neck with negative and positive histologic findings respectively.
2. Extracapsular spread commonly is found in small nodes (25%) and large nodes (75%).
3. Macroscopic extracapsular and microscopic extracapsular spreads are associated with a recurrence rate of 45% and 25% respectively.
4. Multiple levels of involvement are associated with a recurrence rate of 70%; only one level of involvement is associated with a recurrence rate of 35%.

Prognosis: In general, the following characteristics of nodal metastasis carry poor prognosis in neck dissection: Extracapsular spread, perivascular and perineural invasion, multiple sites and multiple involved nodes (>4), node fixation, involvement of surgical margin, recurrent disease and less degree of differentiation

Future and Controversies
Controversies: In general, the management is not standardized and varies between institutions, geographical areas, and surgeons. The selection of a modified radical neck dissection is controversial because the decision to preserve nonlymphatic structures remains an intraoperative decision. The N0 neck is a controversial subject. Many treatment choices exist including...
whether to treat electively with surgery or radiation or to wait and observe.

Future: Future considerations in the management of neck metastasis include the following: Develop better techniques for evaluation of neck metastasis, define and standardize the clinical criteria worldwide for a particular neck dissection, define and standardize indications for an N0 neck and for an N+ neck, define and standardize the role of PET/CT in assessment and identification of neck metastasis and investigate and analyze the prognostic factors.

References:

Chemoradiation in Head and Neck Cancer - Current Perspectives

(Dr. Gunaseelan.K, Assistant Professor, Dept. of Radiation Oncology, Regional Cancer Centre, JIPMER)

Abstract

The advent of concurrent chemoradiation has significantly contributed to the curability of head and neck cancer, including locoregionally advanced disease. Preserving organ function and reducing toxic effects are increasingly the focus of clinical trials. Throughout the last 2 decades, great strides have been made in managing patients with locally advanced head and neck squamous cell carcinoma. In many clinical settings, they translated to significant advances in treatment efficacy and improvements in disease prognosis. To achieve this, most strategies, ranging from induction to postoperative treatments, are essentially based on multidisciplinary approaches. Nowadays, the indication and sequencing of surgery, radiotherapy, and systemic treatments are carefully weighted in the function of risk levels, efficacy results, and quality of life. Along this track, the coadministration of chemotherapy and radiotherapy was shown, as definitive or adjuvant treatment, to improve the results of conventional radiotherapy alone. However, recent prospective trials showed that the compliance of patients to aggressive approaches is more of a concern for poor tolerability and reduced compliance inevitably impact on treatment dose intensity, leading to the delivery of suboptimal regimens. Therefore, further efforts to tailor novel, multidisciplinary approaches based on drug-radiation interactions have been put forth to optimize treatment outcomes in terms of both disease control and quality of life. Because therapy is becoming more intense, a careful recording and reporting of treatment-related morbidity is also a crucial element in estimating the therapeutic gain from competing strategies.

Introduction

To be successful, the management of locally advanced squamous cell carcinomas of the head and neck (SCCHN) requires a high degree of medical expertise, a careful assessment of the risk levels, and an appropriate selection of patients entering a given treatment protocol. In this perspective, the therapeutic approach of SCCHN is nowadays driven by the clinical and histopathologic features of the disease, host-related factors including comorbidities, and the expected treatment impact on patients' quality of life. Treatment for locoregionally advanced disease remains challenging, and an aggressive treatment approach is necessary to achieve a cure. Concurrent chemoradiotherapy is aimed at improving the outcome for this group of patients. The objective of this article was to review the current state of the-art for chemoradiation and propose a critical appraisal of the concepts that might shape the future implementation of drug-radiation interactions in various clinical settings.

Multimodality Approach

Radiotherapy alone is not sufficient to successfully treat most HNC cancers at intermediate or advanced stages. Currently, three multimodality treatment approaches are used.

1. Surgery followed by adjuvant concurrent chemoradiotherapy, which enables precise pathologic staging and identification of high-risk features that influence the choice of adjuvant
treatment. This approach can have limitations, such as poor organ preservation, depending on the anatomic location (e.g. larynx), and the majority of locoregionally advanced tumors are unresectable, especially if organ preservation is the goal.

2. **Definitive concurrent chemoradiotherapy with surgery as an optional salvage or completion treatment.** Although no pathologic information is obtained with this approach, it has the advantage of improved organ preservation. This benefit is most clearly established for laryngeal cancer but is increasingly recognized for other anatomic locations.

3. **Induction chemotherapy followed by definitive local therapy.** Advantages include the potential to decrease the risk of distant failure and a rapid reduction in tumor bulk in responders. A response to induction appears to predict responsiveness to chemoradiotherapy. Nonetheless, this can result in prolonged treatment and additional chemotherapy-related toxic effects from systemic doses. This approach remains controversial, but data from recent clinical trials seem to support its use. Induction chemotherapy lies beyond the scope of this article and is discussed elsewhere.

**Rationale for Chemoradiation**

In the past, survival at 5 years for loco regionally advanced disease was reported to be only 40% (10–30% for patients with stage IVa and IVb tumors) and locoregional failure was the predominant cause of recurrence. More than 50% of patients who die from head and neck cancers (HNC) have locoregional disease as the only site of failure, and almost 90% of patients with distant failure also have persistent locoregional disease. Therefore, the efficacy of any curative approach is measured by its ability to achieve locoregional control.

The biologic rationale for this type of combination of radiation with chemotherapy is found in a number of drug-radiation interactions at the cellular level,

- **a)** Shift of cell-survival curves toward higher cell-killing levels and lower cell-surviving fractions for a given dose of irradiation,
- **b)** Cooperation to prevent the emergence of resistant clones, a decrease in tumor mass and subsequent reoxygenation,
- **c)** Specific toxicity for hypoxic cells, selective toxicity depending on the cell-cycle phase, cytokinetic cooperation, action on DNA repair, and increased apoptosis.

**Mechanisms of Chemoradiation**

There are 3 basic mechanisms by which the combination of chemotherapy and radiotherapy may result in a therapeutic gain.

1. **Temporal modulation:** this type of modulation enhances tumor response to fractionated radiotherapy through the “4 R’s” of radiotherapy, namely, repair, repopulation, reoxygenation, and redistribution. Among the various chemoradiation regimens, an example of temporal modulation is the repair inhibition achieved (eg. Cisplatin)

2. **Biological cooperation:** this type of cooperation refers to strategies targeting distinct cell populations or using different mechanisms of cell killing or inducing tumor regrowth delays. The 2 modalities may be given concurrently by combining radiation with bioreductive drugs such as mitomycin C to target specifically hypoxic tumor cells.

3. **Cytotoxic enhancement:** this mechanism enhances cell killing by modulating the induction or processing of intracellular damage. An example of cytotoxic enhancement is the incorporation of halogenated pyrimidines such as 5-FU into DNA enhancing the initial induction of DNA damage by radiation.

**Single agent-based chemoradiotherapy**

**Cisplatin**

Cisplatin is a potent radiosensitizer and most commonly used for chemoradiotherapy in HNC. A meta-analysis examining various chemoradiotherapy regimens indicated that platinum containing regimens might provide a survival advantage compared with noncisplatin-containing regimens. Currently, the most widely used standard regimen is 100 mg/m² cisplatin every 3 weeks, combined with ~70 Gy radiation delivered in 1.8–2.0 Gy daily fractions. This regimen causes severe toxic effects, such as nephro-, oto- and neurotoxic effects, nausea and vomiting, as well as severe mucositis, which make the treatment suitable only for patients with normal creatinine clearance and a good performance status. This cisplatin regimen has been extensively studied and is the only evidence-based cisplatin regimen available. To limit toxic effects, alternative administration schedules are used, but equivalent efficacy has not been established. For the 30 mg/m² cisplatin weekly regimen, no nephrotoxic effects were reported, but mucositis and neutropenia were prominent. Owing to the lack of comparative (level I) evidence, the use of once-weekly cisplatin should be limited to clinical trials and to patients who are unable to tolerate the usual dose. Theoretically, once-weekly administration of cisplatin has the potential to optimize its radiosensitizing properties, but empirical data are needed to support this hypothesis.

Platinum-based (single-agent) chemoradiotherapy versus radiotherapy for head and neck squamous cell carcinoma were shown in the table1.
(Table 1) Platinum-based (single-agent) chemoradiotherapy versus radiotherapy for head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Primary treatment</th>
<th>Adjuvant therapy</th>
<th>Grade 3 and 4 toxic effects</th>
<th>Increased local control rate</th>
<th>Difference in overall survival in favor of chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22931 (2004)¹</td>
<td>167 with high-risk features on pathology</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 41%; RT 21%</td>
<td>Chronic: difference NS</td>
<td>Yes: CRT 82%; RT 69% (at 5 years)</td>
</tr>
<tr>
<td>RTOG 9501 (2004)²</td>
<td>459 with high-risk features on pathology</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 77%; RT 34%</td>
<td>Chronic: difference NS</td>
<td>Yes: CRT 82%; RT 72% (at 2 years)</td>
</tr>
<tr>
<td>Bachaud et al. (1996)³</td>
<td>83 with high-risk features on pathology</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 41%; RT 18%</td>
<td>Chronic: difference NS</td>
<td>Yes: CRT 77%; RT 59% (at 4 years)</td>
</tr>
<tr>
<td>Intergroup 91-11 Larynx (2003)³</td>
<td>510 with laryngeal cancer</td>
<td>CRT (P); RT plus induction chemotherapy; RT alone</td>
<td>NA</td>
<td>Acute: CRT 77%; RT +I 51%; RT 47%</td>
<td>Chronic: CRT 30%; RT +I 24%; RT 36% (difference NS)</td>
<td>Yes: CRT 80%; RT + I 64%; RT 58% (at 2 years)</td>
</tr>
<tr>
<td>Al - Sarrafe et al. (1198)⁵</td>
<td>193 with NPC</td>
<td>CRT (P) plus consolidation with PF; RT alone</td>
<td>NA</td>
<td>Acute: CRT 75.6%; RT 50%</td>
<td>Chronic: not reported</td>
<td>Yes: CRT 89.2%; RT 74.0%</td>
</tr>
<tr>
<td>Adelstein et al. (2003)⁶</td>
<td>295 with unresectable tumors</td>
<td>RT alone; CRT (P); CRT (PF) split course</td>
<td>NA</td>
<td>Acute: RT 52%; CRT 85%; CRT 72%</td>
<td>Chronic: not reported</td>
<td>Not reported but raised CR rate after therapy: RT 27%; CRT 41%; CRT 37%(S)</td>
</tr>
<tr>
<td>Jeremic et al. (2003)⁷</td>
<td>130 with stage III or IV disease</td>
<td>HFX (RT); HFX (CRT and daily P)</td>
<td>NA</td>
<td>Acute: difference NS</td>
<td>Chronic: difference NS</td>
<td>Yes: RT 27%; CRT 53%</td>
</tr>
</tbody>
</table>

**Abbreviations:**

CRT, concurrent chemoradiotherapy; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; FHX, 5-fluorouracil, hydroxyurea and concomitant radiotherapy; HNSCC, head and neck squamous cell carcinoma; I, induction chemotherapy; NA, not applicable; NPC, nasopharyngeal carcinoma; NS, not significant; OS, overall survival; P, cisplatin; PF, cisplatin and 5-fluorouracil; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.
Other single agents based chemoradiotherapy platforms for head and neck cancer (Table 2)

<table>
<thead>
<tr>
<th>Agent and Studies</th>
<th>Doses</th>
<th>RT regimen</th>
<th>Survival data (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Jeremic et al. (1997)</td>
<td>25mg/m² daily as CRT</td>
<td>70 Gy (once-daily fractionation)</td>
<td>55% 2-year OS (53)</td>
<td>Limited data as a single agent. Carboplatin is less-well established as a radiosensitizer. Comparative data show no survival difference when compared with cisplatin but superior to RT alone</td>
</tr>
<tr>
<td>5-FU</td>
<td></td>
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</tr>
<tr>
<td>Browman et al. (1994)</td>
<td>1200mg/m²/day, 72h infusion during weeks 1 and 3 of RT</td>
<td>66 Gy (Once-daily fractionation)</td>
<td>63% 2-year OS (88)</td>
<td>Commonly used in combined regimens (e.g. FHX or cisplatin/5-FU). Superior to radiation alone</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovey et al. (2003)</td>
<td>2mg/m² three times weekly as CRT</td>
<td>66-70 Gy (Once-daily fractionation)</td>
<td>46% 2-year OS (26)</td>
<td>Commonly used in combination (e.g. Cisplatin/paclitaxel or TFHX)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Calais et al. (2004)</td>
<td>20mg/m² weekly as CRT</td>
<td>70 Gy (Once-daily fractionation)</td>
<td>47% 3-year OS (63)</td>
<td>Commonly used in combined regimens (e.g. Cisplatin/docetaxel or DFHX)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bonner et al. (2006)</td>
<td>400mg/m² loading, then 250mg weekly</td>
<td>70 Gy (variable RT, including once-daily, hyper-fractionation and concurrent boost)</td>
<td>62% 2-year OS and 55% 3-year OS (211)</td>
<td>Possible treatment standard, especially in the elderly and patients with poor performance status. Superior to radiation alone. Role compared with cytotoxic CRT remains unclear owing to control arm (RT only)</td>
</tr>
</tbody>
</table>

Abbreviations:
CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; DFHX, docetaxel, 5-fluorouracil, hydroxyurea, and concurrent radiotherapy; FHX, 5-fluorouracil, hydroxyurea, and concurrent radiotherapy; HNC, head and neck cancer; NPC, nasopharyngeal carcinoma; OS, overall survival; RT, radiotherapy; TFHX, paclitaxel, 5-fluorouracil, hydroxyurea, and concurrent radiotherapy.

Multiagent-based Chemoradiotherapy

- The combination of cisplatin and 5-FU with radiation therapy is highly efficacious. No randomized trial has adequately compared cisplatin with cisplatin and 5-FU chemoradiotherapy; however, on the basis of the data from Adelstein et al., the cisplatin and 5-FU combination therapy might offer improved survival.
- The combination of cisplatin and paclitaxel can be considered a safe and efficacious alternative to cisplatin-based chemoradiotherapy and should be considered for poor-risk patients and those who can tolerate a more intense treatment approach.
- The combination of cetuximab with cisplatin based chemoradiotherapy is currently being investigated in two randomized, multiinstitutional trials established by the RTOG and the University of Chicago.
- The combination of carboplatin and paclitaxel with radiation is one of the more widely used chemotherapeutic approaches for HNSCC. The improved tolerability offered by this regimen, compared with that for cisplatin therapy, is a major advantage. Although definitive phase III evidence comparing this combination with cisplatin therapy is lacking, phase II trials indicate excellent activity and good tolerability. On the basis of the excellent efficacy, this regimen is an acceptable treatment standard and an alternative to cisplatin-based regimens.
- 5-Fluorouracil, hydroxyurea and radiotherapy-based regimens (FHX) was as efficacious as cisplatin and paclitaxel combination therapy and superior to combined cisplatin and 5-FU therapy. To further improve locoregional control for patients with locally advanced squamous cancers paclitaxel was added and twice-daily radiation was administered (TFHX). This regimen provided a 3-year overall survival of 60%. A
combination regimen of docetaxel and FHX is currently being examined in a large multicenter, phase III trial examining the role of induction chemotherapy.

- A phase II study investigated the use of gefitinib (Anti-EGFR therapy) in combination with the FHX platform. Preliminary results demonstrate one of the highest efficacies reported so far in loco regionally advanced HNC, with a 2-year overall survival of 89%.
- The VEGF-targeted antibody bevacizumab was studied in patients with HNSCC and given concurrently with FHX in a phase I trial of patient’s with recurrent disease. The feasibility and signs of activity were demonstrated preliminarily.

Organ Preservation

Up-front concurrent chemoradiotherapy is an attractive organ-sparing approach because it achieves locoregional control without surgical resection of important anatomical structures. The large Intergroup trial 91-11 assessed larynx preservation in patients with resectable stage III and IV (but excluding T4) laryngeal cancer. Three treatment arms were used comparing radiotherapy alone, sequential chemotherapy and radiation, and concurrent cisplatin-based chemoradiotherapy. Laryngectomy (a surrogate for treatment failure) was used as a salvage treatment. Larynx preservation at 2 years was significantly improved with concurrent chemoradiotherapy (88%) compared with sequential chemoradiotherapy (75%) and radiotherapy alone (70%). Although acute toxic effects were increased with chemotherapy use (both sequential and concurrent), late adverse effects and swallowing function at 2 years were equivalent. As a secondary outcome, the chemoradiotherapy regimen showed the highest locoregional control rate. Concurrent chemoradiotherapy is, therefore, the standard of care for locally advanced laryngeal cancers. In other HNC anatomical locations, no phase III, randomized evidence is available, but data from multiple phase II trials also show high rates of organ preservation. In summary, concurrent chemoradiotherapy is highly effective and safe as a primary treatment modality and allows for improved organ preservation compared with surgical approaches although a case-by-case decision is necessary.

The meta-analysis of chemotherapy on head and neck cancer (MACH-NC) by Pignon et al. and a preliminarily report update at ASCO 2004, both suggested a possible survival benefit for this approach in comparison to radiation alone is now widely accepted. Overwhelmingly, trial results indicate that the concurrent addition of chemotherapy sensitizes tumors to radiation and increases locoregional control and thereby survival. Nevertheless, there is an ongoing debate of whether single-agent cisplatin-based chemoradiotherapy or multiagent chemoradiotherapy platforms are preferred. On the basis of the available data discussed herein, multiagent chemoradiotherapy may offer improved survival and should be considered for patients with a good performance status.

Conclusions

Concurrent chemoradiotherapy has a central role in the management of locoregionally advanced HNC and a survival benefit for this approach in comparison to radiation alone is now widely accepted. Overwhelmingly, trial results indicate that the concurrent addition of chemotherapy sensitizes tumors to radiation and increases locoregional control and thereby survival. Nevertheless, there is an ongoing debate of whether single-agent cisplatin-based chemoradiotherapy or multiagent chemoradiotherapy platforms are preferred. On the basis of the available data discussed herein, multiagent chemoradiotherapy may offer improved survival and should be considered for patients with a good performance status.

References:


Altered fractionation in Head and Neck Radiotherapy

(Dee M Joseph, Senior Resident, Dept. of Radiation Oncology, Regional Cancer Centre, JIPMER)

Introduction
The treatment of head and neck carcinoma (HNC) is generally based on surgery and radiation therapy, which allows for locoregional control rates of 70% to 80% in early-stages, but is markedly inferior in the locally advanced stages. Because radiation therapy plays a key role in the management of these cancers, several approaches have been developed to improve its efficacy, while maintaining acceptable toxicities. Among them, the addition of concomitant chemotherapy has been shown to improve survival, compared with radiotherapy alone. Conventional radiation therapy for definitive treatment of HNC delivers 1.8 to 2.0 Gy/fraction, five fractions/week, to a total dose of 66 to 70 Gy over six and half to seven weeks.

An alternative to chemoradiation has been to use altered fractionated RT. Altered fractionation schedules include

- Hypo fractionation
- Hyper fractionation (HFRT)
- Accelerated fractionation (AFRT)

Hyperfractionation and accelerated fractionation are used in radical radiation of HNC. Hypo fractionation is used mainly in palliative setting in HNC.

Basic Facts of Altered Fractionation

<table>
<thead>
<tr>
<th>Hyper fractionation</th>
<th>Accelerated fractionation</th>
<th>Hypo fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Of fractions/day</td>
<td>↑</td>
<td>Unchanged or ↑</td>
</tr>
<tr>
<td>Dose per fraction</td>
<td>↓</td>
<td>Remain same or ↓</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>May remain the same</td>
<td>↓</td>
</tr>
<tr>
<td>Total Dose</td>
<td>↑</td>
<td>Remain same or ↑</td>
</tr>
</tbody>
</table>

In hyper fractionation, more than one fraction is delivered per day with an inter fraction interval of minimum six hours to allow for recovery of normal tissue, the dose per fraction is reduced and the total dose delivered is increased (Eg: 81.6 Gy given in 1.2 Gy per fraction, twice a day with 6-hour intervals, over 7 weeks). Total treatment duration may essentially remain unchanged. Decreasing the dose per fraction (< 1.2 Gy) can protect late-responding normal tissues more than tumor cells, leading to a differential effect that allows the delivery of a total dose that is higher than the conventional dose in the same overall time and constitutes the basis of HFRT.

In accelerated fractionation, overall treatment time is significantly reduced. The number of fractions, total dose and size of dose per fraction are unchanged or somewhat reduced depending on the overall time reduction. Rationale for AFRT is a reduction of overall treatment time, thereby decreasing the opportunity for tumor cells to regenerate during treatment and therefore increasing the probability of tumor control for a given total dose. Another argument to evaluate AFRT in HNSCC is related to the rapid tumor cell kinetics of these cancers, with a potential doubling time of less than 3 days in the majority of cases.
Types of Accelerated Fractionation:

- Pure acceleration
- Hybrid acceleration:
  - Type A: Continuous Hyperfractionated Accelerated Radiotherapy (CHART) Eg: 54 Gy in 12 days, 3 fractions per day, 1.5 Gy per fraction, 36 fractions as in RTOG trial.
  - Type B: Split course Eg: 67.2 Gy, 2 fractions per day, 1.6 Gy per fraction, 42 fractions over 6 weeks with a gap of 2 weeks in between.
  - Type C: Accelerated Concomitant Boost (ACB) Eg: 54 Gy given in 30 fraction over 6 weeks plus 18 Gy boost dose given in 1.5 Gy fraction, as second daily fraction during the last 2.5 weeks.
  - Type D: Escalating Dose

In pure accelerated fractionations, the overall treatment time is reduced without concurrent changes in the fraction size or total dose which can be achieved if weekly number of fractions be increased without increasing the dose per fraction (6 fractions per week instead of the 5 fractions in conventional radiation). A therapeutic gain should be realized, provided the size of dose per fraction is not increased and the interval between dose fraction is sufficient for complete repair to take place.

In Type A accelerated fractionation is an intensive short course of treatment; overall duration of treatment is markedly reduced, and total dose is substantially decreased.

In Types B and C duration of treatment is more modestly reduced, and total dose is kept in the range as conventional treatment by using split-course or concomitant-boost technique.

In type D accelerated fractionation, the total dose delivered per week progressively increases during treatment; less-intensive therapy at the outset of treatment stimulates a regenerative response in normal mucosa so that it can better tolerate more intensive treatment as course progresses. There is a slightly greater reduction in overall time without decreasing total dose than with Types B or C.

Biological Basis of Fractionation

From various experiments it was evident that the benefits of fractionation were due to four factors, which are now popularly known as the ‘4 Rs’ of Radiobiology.

1. Repair
2. Reassortment
3. Repopulation
4. Reoxygenation

1. Repair
This refers to the process by which the function of DNA is restored. Evidence for this came from studies of strand breaks in DNA, which disappear during the few hours after irradiation. This is the potential mechanism by which the normal tissue damage that is caused by irradiation is repaired during the course of radiotherapy.

2. Reassortment
The radio sensitivity of cells varies considerably as they pass through the cell cycle. ‘S’ phase is the most resistant phase of cell cycle whereas cells which are in ‘G-2’ phase during irradiation are more radiosensitive.

Cells that survive a first dose of radiation will tend to be in a resistant phase of cell cycle and within few hours they may progress into a more sensitive phase. This is the factor which increases the radio sensitivity by more cells kill in a fractionated radiotherapy.

3. Repopulation
During an extended course of radiotherapy cells that survive irradiation may proliferate faster and thus increase the number of cells that must be killed.

4. Reoxygenation
In a tumour, cells that survive a first dose of radiation will tend to be hypoxic but thereafter their oxygen supply may improve leading to an increase in radiosensitivity.

Clinical Outcomes of Altered Fractionation:

- HFRT is better than standard fractionation in locoregional control of intermediate to locally advanced head and neck carcinoma. This was also associated with an improvement in survival in three trials.  
- Significant increase in acute mucosal toxicity in HFRT, but does not seem to induce significantly more severe late effects compared with conventional fractionation.
- ACB and pure acceleration without dose reduction yields superior loco-regional control of head and neck carcinomas without increase in late toxicity but without clear impact on survival. RTOG trial using ACB showed a nonsignificant increase in overall survival.
- Acceleration by more than 3 weeks with a 10% total dose reduction (<6 to 7 Gy) also improves the locoregional control without demonstrable increase in late complications. However, a further 5% to 8% total dose reduction abrogates the gain in tumor control but appears to reduce the severity of some late normal tissue complications, such as fibrosis and edema. (British MRC CHART and RTOG trials).
- Split course: A significant improvement of loco-regional tumour control was observed with high late toxicity in EORTC trial.
References:
5. Ahamad A, Altered Fractionation Schedules: Perez and Brady's Principles and Practice of Radiation Oncology, Lippincott Williams & Wilkins; 2008

Understanding Intensity Modulated Radiotherapy (IMRT)
Part I: Multileaf Collimators (MLCs)

(N.Vijayaprabhu, Lecturer in Radiology (Medical Physics), Dept of Radiotherapy, RCC, JIPMER)

Introduction
Radiotherapy is a century-old science and has evolved over times. With the advent of new artificially radioactive sources with their availability at lower costs, the developments in computing technology, better understanding of tumor biology, radiotherapy treatments have undergone paradigm shifts. Radiotherapy started with rough application of radium source over tumor (skin lesions) is now reached a stage that treatments are delivered precisely to the tumor, wherever located, but at the same time, sparing as much normal tissues as one would like to spare. The stages of developments in Radiotherapy are: Brachytherapy (or Curietherapy), Teletherapy using uniform intensity beams, 3D Conformal Therapy (3D-CRT), Intensity Modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGRT), Adaptive Radiotherapy (ART), Gated Radiotherapy.

The conventional external beam radiotherapy is delivered using well collimated uniform intensity beams that treat both tumor and also, inevitably, a sizeable volume of normal tissue that lie close to the tumor. Sometimes, the treated volume includes whole or part of the organs that could be more radiosensitive than tumor itself, and worse, with less tolerance to radiation, are also included. Usually, such situations are avoided by careful planning using CT-based 3-D treatment planning. However, when the tumor volume is concave and enveloping a radiosensitive organ, inclusion of these organs in the treatment field becomes unavoidable. Consequently, in conventional radiotherapy planning, the radiation dose has to be restricted to the tolerance level of the enclosed radiosensitive organs.

In such situations IMRT gives the best solution. In IMRT, the beam is delivered with modulated intensity so that the resultant treated volume tightly encloses the tumor volume so that one can effectively deliver tumoricidal dose to it and at the same time spare the normal radiosensitive organs at risk.

IMRT can be delivered either by using Multileaf collimators (MLCs) or by non-MLC based methods. Of the two, MLC-based IMRT is widely practiced. MLCs are motor-driven which are in turn controlled by computers. IMRT treatments can be classified as:

1. The segmented MLC (SMLC) mode, often referred to as the Step-and-shoot method or Static IMRT
2. The dynamic MLC (DMLC) mode, sometimes referred to as the sliding window mode, and
3. Intensity modulated therapy (IMAT).

The Multileaf collimators (MLCs)

Modern Medical Linear Accelerators (Linacs) can be equipped with MLCs that contain from 20 to 60 pairs (40 to 120 leaves) of narrow, closely abutting tungsten leaves, with each leaf projecting a typical width of 1 cm (10 mm) or less at the Linac Isocenter.

Depending on the leaf widths, MLCs are classified as:
1. MLCs – when the leaf width at Isocenter is 10 mm (1 cm)
2. Mini-MLCs – when the leaf width at Isocenter is between 5 and 10 mm (0.5 to 1 cm)
3. Micro-MLCs – when the leaf width at Isocenter is between 1.5 and less than 5 mm

Micro-MLCs are required for Stereotactic Radio Surgery (SRS) and for Stereotactic Radiotherapy (SRT) treatments. Sometimes, combination of two different widths of MLCs are available, with central 20 cm x 20 cm field containing 5 mm width leaves and the rest outer 20 cm of field containing leaves having 10 mm widths. Depending on the position of MLCs with respect to Linacs head, MLCs are classified as:
1. **Integrated MLCs**: when MLCs form Integral part of Linac head replacing upper or lower secondary collimator jaws, or

2. **Accessory-type MLCs**: when MLCs can be attached to the Linac head as an external, add-on MLC so it can be used in conjunction with both the upper and lower collimator jaws.

The following technical parameters are often used while using MLCs:

To describe Geometrical and Mechanical Properties
- Configuration of the MLC with respect to collimator jaws
- The maximum field size
- The leaf width
- Maximum overtravel
- Interdigitation

To describe Physical Properties
- Focusing properties and penumbra
- Interleaf leakage
- Leaf transmission (or intra-leaf transmission)

A brief note on each of the above parameters is as follows:

### a. Configuration of the MLC with respect to collimator jaws

In integrated MLCs, the MLC configurations with respect to rectangular collimator jaws are:

- Total replacement of the upper jaws
- Total replacement of the lower jaws
- Tertiary collimator configuration

The three main vendors of integrated MLCs have chosen different configurations leading to different performances. The above configurations are shown in the figure - 1

### b. The maximum field size

The maximum field size that is available in Linacs without MLCs is 35 cm x 35 cm (without clipping) and 40 cm x 40 cm (with clipping at the corners). With MLCs, this maximum field size is either retained or reduced (due to maximum leaf over travels). The table showing the availability of maximum field sizes in various Linacs supplied by different vendors is shown in table-1 and 2.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product name</th>
<th>Leaf width at isocenter (mm)</th>
<th>Midline over-travel (cm)</th>
<th>No. of leaves</th>
<th>Maximum field size (cm²)</th>
<th>Focusing properties</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elekta-1</td>
<td>Integrated MLC</td>
<td>10</td>
<td>12.5</td>
<td>40×2</td>
<td>40×40</td>
<td>Single focusing</td>
<td></td>
</tr>
<tr>
<td>Elekta-2</td>
<td>Beam modulator</td>
<td>4</td>
<td>11</td>
<td>40×2</td>
<td>16×22</td>
<td>Single focusing</td>
<td></td>
</tr>
<tr>
<td>Siemens-1</td>
<td>3D MLC</td>
<td>10</td>
<td>10</td>
<td>29×2</td>
<td>40×40</td>
<td>Double focusing</td>
<td></td>
</tr>
<tr>
<td>Siemens-2</td>
<td>Optifocus</td>
<td>10</td>
<td>10</td>
<td>41×2</td>
<td>40×40</td>
<td>Double focusing</td>
<td></td>
</tr>
<tr>
<td>Siemens-3</td>
<td>160 MLC</td>
<td>5</td>
<td>20</td>
<td>80×2</td>
<td>40×40</td>
<td>Single focusing</td>
<td>Announced for 2006</td>
</tr>
<tr>
<td>Varian-1</td>
<td>Millennium MLC-52</td>
<td>10</td>
<td>20</td>
<td>26×2</td>
<td>26×40</td>
<td>Single focusing</td>
<td></td>
</tr>
<tr>
<td>Varian-2</td>
<td>Millennium MLC-80</td>
<td>10</td>
<td>20</td>
<td>40×2</td>
<td>40×40</td>
<td>Single focusing</td>
<td></td>
</tr>
<tr>
<td>Varian-3</td>
<td>Millennium MLC-120</td>
<td>Central 20 cm of field: 5 mm; outer 20 cm of field: 10 mm</td>
<td>20</td>
<td>60×2</td>
<td>40×40</td>
<td>Single focusing</td>
<td></td>
</tr>
</tbody>
</table>

*aRequires movement of the complete leaf bank and leads to reduced maximum field sizes

The Siemens 3D MLC consists of 2×27 inner leaves with 1-cm leaf width and two outer leaves with 6.5-cm leaf width

Table -1 Maximum field sizes in integrated MLCs
c. Leaf width

MLCs integrated into the Linac head: Computer-controlled MLCs integrated into the head of the accelerator usually have a spatial resolution of 0.5 – 1 cm in the isocenter plane, perpendicular to the leaf motion direction, and a positional accuracy of 1 mm in the direction of the motion. The leaf width (measured in the isocenter plane) should be adapted to the size and complexity of the target volumes. For this an effective leaf width of 10 mm (1 cm) may be adequate for large volume tumors. But for small target volume located around the spinal cord, 10 mm is too large and hence a leaf width of 5 mm is considered to be a good compromise. Leaf width is illustrated in the Fig.2.

Accessory-type MLCs: The leaf resolution ranging from 10 mm to 1.5 mm depending on the supplier are available. For SRS/SRT treatments, the leaf width required is between 1.5 mm to 5 mm, but 3 mm is widely used.

Optimum leaf width: The higher the spatial resolution of the MLC, the better the quality of the resulting dose distributions formed with such a MLC. However, there is a limiting physical constraint in principle: form a MLC with the penumbra p (= distance between the 20 and 80% isodose produced by the leaf edge) a leaf width finer than p/2 does not lead to further improvement in the dose distribution. For a 6-MV photon beam, for instance, the optimum leaf width of a stereotactic add-on MLC with a penumbra of approximately 3 mm therefore is in the range of 1.5 – 2 mm. An integrated MLC is much closer positioned to the target and has a penumbra of 8 – 10 mm. The optimum leaf width is thus in the range of about 5 mm.

d. Maximum Overtravel

The overtravel characterizes how far a leaf can be moved over the midline of the MLC. A large overtravel is important for very complexly shaped target volumes, but more for the IMRT treatments. The complete overtravel is possible, but for this the whole leaf bank will be moved, hence the maximum field size is reduced. The fig.2 shows the concept of maximum overtravel.

e. Interdigitation

In some cases, one leaf cannot pass an adjacent opposing leaf without collision, thus fields designed without considering such constraints cannot be delivered with such an MLC. Not a problem in conventional RT treatments, but assumes great importance in IMRT treatments, where many small and often complexly shaped segments have to be delivered, and such leaf “Interdigitation” is often required. (Figure - 3)
f. **Focusing properties and penumbra**

The penumbra is an important design feature of a beam defining device. Most often penumbra is a constraint to better MLC designing. Penumbra effect can be minimized by using focus-type MLC movements or by designing the MLC leaf edges to be rounded or by using rotating leaf edges.

g. **Interleaf leakage**

In order to avoid friction, adjacent leaves will have a small gap of about 0.1 mm. This gap causes leakage radiation, which has to be minimized below a level of about 4%. To minimize this interleaf leakage, the leaves are manufactured using a tongue-and-groove design. Recently, the entire leaf bank is given a slant with respect to the direction of the divergent rays.

h. **Leaf transmission**

When high energy x-rays have to be collimated, there is always a small fraction of x-rays which will penetrate through the jaws or leaves. To minimize this intra-leaf transmission, MLCs are usually made of high atomic number elements like tungsten. For tungsten, the thickness of the material has to be in the range of 8 – 10 cm in order to reduce the transmission below 1%. Restrictions for leakage radiation of MLCs are as follows: For add-on MLCs, leakage radiation must be less than 5% of an open 10 cm x 10 cm field; otherwise, maximum leakage should be less than 2% and average leakage less than 0.5% (Fig. 4)

References:
Complications of Radiotherapy in Head and Neck Cancer and their Management

(Dr. Muzamil Asif, Junior Resident, Dept. of Radiation Oncology, Regional Cancer Centre, JIPMER)

Radiation for Head and Neck Cancer treatment is associated with adverse effects which can be classified as acute and chronic reactions. The type and severity of the adverse effects depend on various factors such as Site of Malignancy, Type of Malignancy, Radiation Technique, Dose of Radiation, Type of Radiation Fractionation used, General Condition of the patient, to name a few.

Examples of Acute Reactions include mucositis (ulcer), sore throat, loss of taste, and xerostomia (if any of the major salivary glands are in the treatment portal). The skin experiences erythema, peeling, epilation and pigmentation.

The late effects after definitive RT can include xerostomia, dental caries, altered sense of taste, swallowing problems, dysphagia, altered quality of voice, lymphedema, hypothyroidism, trismus, cervical fibrosis, atrophy of the mucosa and skin, as well as soft tissue and bone necrosis.

Supportive care and prompt and adequate management of reactions will help avoid any delays in treatment and ensure patient compliance. A brief outline of management of radiation reactions is presented below.

Dental Care

Evaluation, treatment, and prevention of any pre-existing oral or dental pathology are an integral part of management of patients with head and neck cancer. Underlying pre-existing silent pathology can become prominent in a patient receiving radiation, and particularly so in combined therapy. Oral complications can be minimized, and in some cases eliminated, if identified and addressed early by a dental team. It is, therefore, important to assess the patients' access to dental care and their commitment to daily oral hygiene procedures.

Oral treatment plans should be designed to correct restoration overhangs, rough or sharp edges in teeth, and any other defects likely to cause soft tissue irritation. Patients should be instructed to avoid abrasive food that could traumatize soft tissues. Ill-fitting intraoral prostheses should not be worn during radiation therapy. Any potential source of oral infection should be identified and eliminated.

In general, patients are instructed to maintain oral hygiene and undergo brush training. They also receive custom-made carriers for fluoride prophylaxis, to prevent caries and hypersensitivity of teeth; and mouth guards, made of flexible plastic material, to prevent biting irradiated tissues that may become edematous.

To ensure bone coverage and adequate wound healing, extractions should be performed 2 to 3 weeks before initiation of therapy.

Good oral hygiene during and after therapy is essential for improving oral comfort and for reducing the risk of oral pathology. Oral rinsing with a solution of sodium bicarbonate dissolved in water many times each day reduces oral microorganisms and aids in maintaining mucosal hydration. This measure, along with the elimination of secondary sources of irritation, such as alcohol, smoking, coarse or hot foods, alcohol-or phenol-containing mouth rinses, and sodium products, can help in minimizing mucositis. The daily use of a fluoride gel can help minimize dental decay.

Conventional oral physiotherapy is recommended during and after radiation, especially if the pterygoid muscles are within the radiation portals. Fibrosis of this musculature leads to trismus, which may be irreversible. Therefore, patients should be encouraged to perform mouth-stretching exercises before, during, and after radiation therapy. When needed, sophisticated means of oral opening exercises with opening devices may be recommended.

Radiation diminishes cellular elements of bone, thereby reducing its ability to heal after infection, trauma, or surgical procedure (e.g., dental extraction, alveoloplasty), which may result in osteoradionecrosis (ORN). Therefore, periodontal surgical intervention should be planned carefully and the use of parenteral antibiotics and hyperbaric oxygen should be considered.

Nutritional Support

Assessment and Guidance

Nutritional care is crucial in the radiation treatment of most patients with head and neck cancer. Patients receive dietary advice to help maintain their weight and nitrogen balance during the course of radiotherapy and the ensuing recovery period. The attending physician and nutritionist should review the chart and recommend dietary adjustments when necessary.

Patients receiving radiation treatment of cancers of the oral cavity, oropharynx, nasopharynx, and hypopharynx are particularly prone to develop difficulties with food intake because of irradiation of a large area of mucous membranes and salivary glands. Therefore, they are encouraged to take supplemental calories at the beginning of treatment before the onset of reactions.

Taste distortion (metallic flavor), loss of appetite, and burning sensation in the throat when swallowing citrus juices and acidic or spicy food become prominent during the second and third weeks. Helpful measures include the use of bland fruit nectars or fruit-flavored drinks fortified with vitamin C, elimination of highly seasoned foods, addition of food aroma, and serving meals at room temperature.

Mucosal edema and denudation, resulting in dysphagia and pain, dominate the latter part of the treatment. At this time, the patient and family need constant support from the medical team. During this period, the diet should contain sufficient calories and supplementary protein to promote normal tissue regeneration. It is important to adjust the diet individually in terms of texture, consistency, and portion size. In general, soft diet (blended meat and vegetable) and frequent intake of small meals are recommended. Analgesics taken before meals can ease the pain.

Tube Feeding

If weight reduction exceeds 5%, feeding through a gastrostomy tube, inserted by percutaneous fluoroscopic or...
endoscopic procedure, is usually recommended. Occasionally, a nasogastric feeding tube is used.

Diet after Completion of Radiotherapy

Instructions for future meal plans are provided at discharge. Generally, nutritional problems continue for 2 to 3 weeks after completion of radiotherapy. The recovery period can be longer after altered fractionation or combination of radiation and chemotherapy. Subsequently, the patient can progress gradually to a normal diet except for the adaptation required to circumvent dryness of the mouth.

Swallowing Assessment and Rehabilitation

Both acute and late effects of radiation can disrupt a patient’s ability to swallow. Early assessment by speech pathologists with expertise in swallowing rehabilitation is desirable, preferably before initiation of radiation, for planning strategies for the prevention of chronic dependence on feeding tubes or swallowing dysfunction that can lead to aspiration. Specific swallowing exercises designed to potentially prevent the debilitating effects of post-radiation fibrosis, when recommended, need to be implemented as early as possible. Patients with postirradiation swallowing difficulties are also referred to speech pathologists for rehabilitative purposes. A modified barium swallow, a study designed to examine the oropharyngeal movement while swallowing various food consistencies, provides information on bolus movement patterns, motility problems, and the cause of aspiration. A specific rehabilitation program can be implemented based on the findings.

Symptomatic Management of Reactions

Careful management of acute reactions manifesting during treatment is important for decreasing discomfort and for avoiding interruption of radiotherapy, which is shown to compromise local-regional control of head and neck carcinoma.

Acute Mucositis

Treatment of acute mucositis is mainly symptomatic. In addition to pain management, patients receive instruction and encouragement to maintain good oral hygiene. The role of amifostine, a radioprotector, in reducing the incidence of mucositis is not yet clearly defined. The role of systemic or topical administration of growth factors or prostaglandins for the prevention of mucositis remains investigational. Antiulcer medications such as sucralfate (Carafate) rinse have been used, but numerous randomized trials have not shown its benefit in reducing the incidence of mucositis or in diminishing the duration of mucositis.

Analgesics

Almost all patients receiving head and neck radiotherapy need pain management to get through a period of acute radiation reactions. Various combinations of paracetamol with hydrocodone, codeine, or oxycodone can be used. Severe and refractory pain, which can occur during the second half of the radiotherapy regimen, may necessitate therapy with stronger opioids. Examples include morphine sulphate (10 or 20 mg per 5 mL elixir, 10 to 30 mg orally every 4 to 6 hours); hydromorphone tablets (2 to 4 mg every 4 to 6 hours) or oral liquid (5 mg per 5 mL every 4 to 6 hours); or suppositories (3 mg every 4 to 6 hours). Sustained-release opioids may help in maintenance therapy for severe pain. Examples include morphine sulfate tablets (30 mg, 60 mg, or higher dose, every 12 hours) and fentanyl transdermal patch (25, 50, 75, 100 µg per hour, every 3 days). Also, lidocaine gel 2% can be prescribed for topical application or swish-and-swallow/spit, up to four times a day. Frequently, minor oral or pharyngeal pain can be ameliorated with a solution of viscous lidocaine, diphenhydramine hydrochloride, and aluminum hydroxide/magnesium hydroxide.

Antiemetics

Depending on the site and size of radiation portals, a variable proportion of patients experience nausea and occasional vomiting. Useful medications include prochlorperazine maleate and metoclopramide hydrochloride. Serotonin 5-HT3 receptor antagonists such as ondansetron hydrochloride are also effective, especially for patients receiving concurrent chemotherapy. However, nausea and vomiting are often secondary to poor oral fluid intake, resulting in dehydration and, therefore, intravenous fluids rather than antiemetics are required to correct the problem.

Skin Reactions

With megavoltage radiotherapy, skin care generally consists of prevention of local irritation by encouraging the use of soft clothing and avoiding sunlight exposure. Small areas of moist skin desquamation that occur occasionally require cleaning with a diluted 1% hydrogen peroxide solution to prevent secondary infection. Larger areas of moist skin desquamation can be managed with hydrogel sheet wound dressing. Aquaphor ointment is routinely prescribed for topical application after completion of radiotherapy. Patients are also instructed to use sunblock over the irradiated skin surface.

Prevention and Management of Xerostomia

Efforts to alleviate this problem involve both prevention and symptom management. Prevention of xerostomia: Reducing radiation dose to the salivary glands and using chemical protectors. Advances in intensity-modulated radiation therapy technology enable sparing of the salivary gland even in patients not suitable for receiving unilateral irradiation. Amifostine has been studied extensively for prevention of various radiation side effects, particularly xerostomia. A randomized trial comparing intravenous amifostine, 200 mg per m² daily before each radiation fraction, to no treatment demonstrated a reduction of the incidence of grade 2 xerostomia from approximately 50% to 30%. The study demonstrated no obvious “tumor protection” because the disease-free and overall survival rates were no different between the two treatment arms. There was a significant increase in the incidence of nausea in patients receiving the drug along with a low incidence of amifostine-induced hypotension. Based on the results of this trial, the US Food and Drug Administration approved the use of amifostine for prevention of xerostomia in patients receiving postoperative radiotherapy. The role of pilocarpine, a cholinergic agonist, in the treatment of xerostomia has been studied extensively. A recently completed randomized trial of the Radiation Therapy Oncology Group
revealed that pilocarpine administered during the course of radiotherapy increased the salivary flow at 3 months after treatment, but without detectable improvement in quality of life endpoints. Sialogogues and saliva substitutes are available and may benefit some patients.

Other Supportive Care
Moisturizing nasal spray is recommended during the period of confluent mucositis occurring in the nasal cavity to prevent crusting and bleeding. Topical antibiotic (Neosporin ointment) is prescribed when infection develops. Antitussive expectorant without suppressant or with suppressant can relieve symptoms of cough in a number of patients.

References:

Role of Neoadjuvant Chemotherapy in Head and Neck Cancer: "Standard of Care or Still Evolving"

(Dr. Ankit Jain, Assistant Professor, Dept. of Medical Oncology, Regional cancer center, JIPMER)

Abstract:
Induction therapy followed by definitive chemoradiotherapy (CRT) has emerged as an option for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck. In this setting, the most studied induction regimen is docetaxel, cisplatin, and 5-fluorouracil (TPF). However, the role of induction therapy remains to be fully validated by studies comparing TPF followed by CRT versus CRT alone. Novel combination regimens that incorporate molecularly targeted agents are increasingly being evaluated in the induction therapy setting. Promising results were shown in phase II trials in which the anti-epidermal growth factor receptor monoclonal antibody cetuximab was added to induction therapy with TPF, docetaxel/cisplatin, or paclitaxel/carboplatin, and in some of these studies, to subsequent CRT. Several issues remain to be addressed, including identifying which patients are most likely to benefit from induction therapy, determining how to optimally incorporate targeted agents into induction therapy and subsequent CRT, and evaluating biomarkers that could be used to select patients for induction therapy containing molecularly targeted agents.

Introduction
Worldwide, >500,000 individuals are affected annually by head and neck cancer, including malignancies of the oral cavity, pharynx, and larynx, of which the vast majority are squamous cell carcinomas. For the approximately two-thirds of patients who present with locally advanced squamous cell carcinoma of the head and neck (SCCHN), with either significant local extension of primary tumor or regional lymph node involvement, multimodal treatment often involving concurrent chemoradiotherapy (CRT) is required. CRT has been shown to significantly improve overall survival (OS), progression-free survival (PFS), and/or local disease control compared with radiotherapy (RT) alone.

Induction Chemotherapy:
Induction chemotherapy or primary Neoadjuvant chemotherapy is defined as chemotherapy treatment offered prior to any locoregional treatment like surgery or radiation treatment. This method has established role in breast cancer and bone tumors like osteosarcoma.

The main advantages of Induction therapy are:
1) Invivo assessment of response of tumors to chemotherapeutic agents.
2) Organ preservation
3) Acts as a biomarker for future locoregional treatment (especially in head and neck cancers)

In head and neck cancers most important drugs used in induction regimens are 5-fluorouracil, cisplatin/carboplatin, taxanes like paclitaxel or docetaxel and targeted therapies like cetuximab. Induction (or neoadjuvant) chemotherapy for locally advanced SCCHN has shown high overall responses rates (RRs), including complete responses (CRs). Most studies comparing induction chemotherapy followed by surgery or RT with definitive local treatment alone did not detect a survival benefit, with the notable exception of two phase III trials that utilized cisplatin plus 5-fluorouracil (5-FU) (PF) 14. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study showed that adding induction chemotherapy to locoregional treatment did not produce a significant benefit in OS; the hazard ratio (HR) was 0.96 [95% confidence interval (CI) 0.90–1.02, P = 0.18], with an absolute improvement of 2.4% at 5 years 15. In the MACH-NC metaanalysis, concomitant CRT improved both locoregional and distant control, whereas induction chemotherapy improved only distant control, but the effect on distant control was more pronounced than that of concomitant CRT.
Induction regimens incorporating new chemotherapy and targeted drugs have been evaluated in an effort to further improve patient outcome. In addition, insights gained on the role of human papillomavirus (HPV) in etiology and prognosis may contribute to refining the management of this disease.

**Patient Selection for Induction therapy in Head and Neck Cancers:**

It is also undetermined which patients may be better candidates for induction. In general, patients who are not likely to tolerate chemotherapy, such as those with PS 2, are not good candidates for induction therapy. The choice to use induction could be made based on extent of anatomical involvement. In an analysis of phase II clinical trials with or without induction preceding CRT, the use of induction appeared to have reduced the risk for distant failure compared with CRT alone. For patients receiving CRT alone, advanced nodal stage (N2c–N3) predicted risk for distant failure and was associated with worse OS, without increasing risk for locoregional failure. These observations would suggest that the effect of induction on distant control may be particularly beneficial for patients with advanced nodal stage disease.

The most common sites where induction chemotherapy can show benefits is larynx and hypopharynx.

**Taxane-containing induction therapy**

Two pivotal phase III studies evaluated the addition of docetaxel to induction PF (TPF) before definitive RT or CRT (Table 1): (i) the EORTC 24971/TAX323 study, in which induction TPF was administered for four cycles followed by RT alone in patients with unresectable SCCHN, with PFS as primary end point and (ii) the TAX324 trial that evaluated induction TPF for three cycles followed by CRT with weekly carboplatin in patients with either resectable and unresectable SCCHN, with OS as primary end point. Across all these studies, severe toxic effects have been generally comparable with or without the taxane, although TPF seems to produce higher rates of grade 3/4 neutropenia and febrile neutropenia than PF.

**Newer induction therapy regimens**

There are multiple new chemotherapy regimens which are under investigation for head and neck cancers which are incorporating monoclonal antibodies like cetuximab. Taxanes and platinum regimens without 5-flurouracil is an interesting regimen with less toxicities.

**Biomarkers for Induction therapy**

The most important prognostic marker for head and neck cancer especially oropharynx is association with human papilloma virus (HPV). These patients have better prognosis than

non HPV associated H&N cancers. Infutur induction chemotherapy will be more useful in non HPV associated H&N cancers.

The other prognostic markers are beta tubulin II for taxase based regimens, hypoxia related cytokines like vascular endothelial growth factor receptor (VEGF) and platelet derived growth factor receptor (PDGF). Increased levels of these markers is associated with poor prognosis.

**Conclusions and future directions**

At present induction chemotherapy is not the standard of care for locally advanced SCCHN. The picture will become more clear once the results of randomized trial directly comparing concurrent chemoradiotherapy with Induction chemotherapy followed by concurrent chemoradiotherapy will be out. At present it can be used as biomarker for patients selection for type of locoregional treatment like radiotherapy or surgery especially in tumors of base of tongue, hypopharynx and larynx. If patients are responding to one or two cycles of chemotherapy they can be taken for CCRT and if not for surgery.

The results of doublets like docetaxel and cisplatin are awaited because TPF regimen is very toxic and requires a lot of supportive care. Therefore this approach is still evolving and the best modality of treatment for locally advanced SCCHN remains as concurrent chemoradiotherapy.

**References:**

Molecular Targeted Therapies in Head and Neck Cancer.

(Targeted therapies have made their way into clinical practice during the past decade. They have caused a major impact on the survival of cancer patients in many areas of clinical oncology and hematology. Recent data have now shown that molecular targeted therapy might display efficacy in patients with head and neck squamous cell carcinoma (HNSCC) as well. The evaluated biologicals are generally well tolerated from HNSCC patients, who usually have the burden of multiple co-morbidities that interfere with conventional systemic treatment options. Therefore, molecular targeted therapies offer new treatment options even for heavily pretreated and seriously ill patients usually unable to tolerate chemotherapy or radiation therapy. The two most promising and advanced strategies are the blockage of growth-factor based cellular signalling and interference with angiogenesis-related pathways.

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents the eighth leading cause of cancer worldwide. Despite recent advances in surgery and radiotherapy, overall cure is achieved in less than 50% of patients. In contrast to many other cancers, distant metastases are rarely present at diagnosis, but due to better local control, the incidence of systemic spread is rapidly increasing. Those with recurrent or metastatic disease have a poor prognosis, with median survival rates of 6-10 months. Systemic chemotherapy remains the only effective treatment option, but it is associated with significant toxicity rates in HNSCC patients, who usually have a high prevalence of co-morbidities and problematic lifestyle habits. Therefore, additional treatment options that have the potential to improve outcome and that show a toxicity profile different from cytotoxic agents are desperately needed to complement presently available treatment tools. New agents that specifically target cellular pathways associated with carcinogenesis are promising candidates, because they are already successfully used in other hematological malignancies as well as in solid tumours, such as colorectal or lung cancer. Two primary strategies that might have the potential to change clinical routine within the near future will be discussed in this review: first, blocking epidermal growth factor-based cellular signalling (EGFR-associated) and second, blocking angiogenesis related cellular signalling (VEGFR-associated).

The role of EGF-R signalling in HNSCC

The EGF-R is a member of the human epidermal receptor (HER)/Erb-B family, a group of tyrosine kinases that transduce extracellular signals to intracellular responses influencing cell proliferation, apoptosis, angiogenesis, and the capacity of tumour cells to metastasize. Among EGF-R-targeting therapies, there are two large categories of molecules: monoclonal antibodies, which recognize the ligand-binding domain and interfere with receptor activation, and tyrosine kinase inhibitors which bind to the cytoplasmatic region and influence with downstream signalling events.

Anti-EGF-R antibodies

Cetuximab is a chimeric human/murine monoclonal antibody of the IgG1 isotype that binds to the EGF-R with a higher affinity than its endogenous ligands, preventing dimerization, internalisation and autophosphorylation.

Preclinical studies show at least three different mechanisms by which cetuximab affects tumour cells. First, it enhances tumour-cell apoptosis and inhibits proliferation as well as invasiveness by blocking the tyrosine-kinase-mediated pathways. Second, antibody-dependent cell-mediated toxicity, which is associated specifically with the IgG1 isotype, contributes to the anticancer activity. Finally, cetuximab may block the nuclear import of EGF-R, preventing activation of the DNA repair mechanism that protects cells from radiation- or chemotherapy-induced DNA damage. Two other anti-EGF-R MoAbs are currently tested in large clinical trials. Panitumumab is a fully human, IgG2 EGF-R-targeting antibody that is already approved for metastatic colon cancer and is tested in locally advanced disease in combination with radiotherapy. Zalutumumab, also a fully human antibody of the IgG1 type, is currently being evaluated in a randomized phase III trial concerning best supportive care for advanced platinum refractory patients.

Cetuximab in locally advanced HNSCC

Cetuximab is approved in combination with irradiation in locally advanced disease based on a multinational, randomized phase III trial comparing radiotherapy plus cetuximab with radiotherapy alone. Results published by Bonner in 2006 demonstrated significantly prolonged locoregional control and overall survival without adversely affecting quality of life. Risk of locoregional failure was significantly reduced, resulting in a 9-month increase in median locoregional control. Median overall survival could be prolonged to a median of 49 months (vs. 29 months). In addition, preservation of larynx function, which is a major determinant of life quality, seemed to be better in the cetuximab arm. As expected from the experiences in other malignancies, acneiforme rash and infusion-related reactions were the only reported toxicities. Although no data are available from studies comparing cetuximab plus radiotherapy to the standard treatment of platin-based radio-chemotherapy, this regimen has to be considered an important alternative, particularly for patients in poor medical condition.

Cetuximab in metastatic HNSCC

In previously untreated patients with metastatic HNSCC, cisplatin-based chemotherapy is considered standard. This approach is now challenged by the recently published results of the EXTREME study (Erbitux in First-line Treatment of...
Recurrent or Metastatic Head and Neck Cancer). In this controlled randomized phase III trial, 442 patients who were not amenable to local therapy and had not received any systemic treatment received either cisplatin or carboplatin, together with 5-fluorouracil or a combination of this chemotherapy with cetuximab. Preliminary data demonstrated median survival times that differed significantly between the two study arms. The addition of cetuximab prolonged OS from 7.4 months to 10.1 months and disease-free survival from 3.3 to 5.6 months. Although these data support the use of cetuximab in first-line combinations, still many patients receive platin-containing chemotherapy combinations without cetuximab up front. In case of recurrence, cetuximab monotherapy might then offer a second-line option with significant antitumour activity to these platin-resistant patients.

**EGF-R-targeted tyrosine-kinase inhibitors**

TKIs bind intracellularly to EGF-R tyrosine-kinase and block downstream signalling pathways. Gefitinib and erlotinib, both administered orally once a day, are the two most advanced TKIs and are both approved for certain indications in non-small cell lung cancer. They have been evaluated in phase I/II trials as monotherapies in recurrent or metastatic HNSCC with response rates of 4-10%. Unfortunately, the only available phase III study involving 486 patients with recurrent HNSCC reported no improvement in response rates and overall length of survival with the addition of gefitinib at different dosing schedules to methotrexate when compared to methotrexate treatment alone. The use of gefitinib and erlotinib remains experimental, and important questions have to be answered before clinical use can be recommended.

**EGF-R and HER-2 combined targeted tyrosine-kinase inhibitors**

HER-2 has also been found to be expressed in a significant proportion of EGF-R-positive HNSCCs. In one of these studies lapatinib, which is already approved for breast cancer treatment, showed disease stabilization rates of about 20% in patients pretreated with anti-EGFR compounds, and therefore its efficacy in the adjuvant setting is currently being explored in ongoing phase III studies.

**The role of angiogenesis in HNSCC**

Similar to other solid tumours, angiogenesis plays an important role in the pathogenesis of HNSCC.

**VEGF ligand targeted therapy**

Bevacizumab is a fully humanized monoclonal antibody binding VEGF with proven activity in colorectal, breast, and non-small cell lung cancer. In HNSCC, bevacizumab shows little single agent activity, but a small phase I/II study in combination with erlotinib in metastatic or incurable recurrent disease showed an overall response rate of about 15% and a median survival of 7.1 months.

**Small molecules targeting VEGF-receptor**

Sorafenib and sunitinib are multikinase inhibitors that are already approved for several other cancer types and have shown their ability to inhibit the intracellular activity of VEGF-R and to block downstream signalling. Promising early clinical results were obtained in a small trial in refractory or metastasizing HNSCC patients, with single agent sorafenib achieving stable disease in 10/26 patients and a median overall survival of 8 months.

**Other potential targets**

Src kinases are involved in the regulation of a variety of normal cellular signal transduction pathways, and they influence cell proliferation, survival, angiogenesis, migration, and adhesion. Dual targeted treatment approaches directed at both EGF-R and Src might, therefore, be a feasible strategy for overcoming or preventing acquired resistance to cetuximab. Dasatinib is a potent inhibitor of multiple oncogenic kinases including Src, cKIT, BCR-ABL, PDGFR, and ephrin A. Because of its ability to inhibit BCR-ABL, it was approved for treatment of chronic myeloid leukemia in 2006. Currently dasatinib is being evaluated in phase I clinical trials for solid tumours either alone or in combination with cetuximab.

**Conclusion**

Molecular targeted therapies are promising novel treatment options for patients with HNSCC. While EGF-R-targeting approaches have shown significant but limited efficacy and are already approved for treatment in advanced HNSCC, other options, such as inhibitors of antiangiogenesis, proteasomes, or multifunctional tyrosine kinases are currently evaluated in phase I or II studies, either as single agent treatment or in combination with conventional cytotoxic drugs. Though multiple questions regarding dosing, combination and patient selection need to be answered, molecular targeted treatment will complement conventional chemo- and radiation therapy in patients with HNSCC in the near future. Especially the low toxicity profiles of these new agents are very promising. So far however, all molecular targeted therapies with the exception of cetuximab should be used in the context of clinical trials only.

**References:**


Overview on Oral Cancer

(Dr. R. Aravind, Assistant Professor, Dept. of Surgical Oncology, JIPMER)

Oral cancer counts for approximately half of all tumors that occur in the head and neck. It is the sixth most common cancer. More than 600,000 new cases of oral cavity tumors are reported worldwide and the incidence is increasing. Oral cancer is the most common form of cancer and cancer-related death in men in India. According to data from the Bombay Cancer Registry, the 5-years relative overall survival for patients with oral cancer is about 40%. Although Tobacco and excessive alcohol use are the most common causes, the incidence in human papilloma virus-induced tumors of the oral cavity is rising and it accounts for an estimated 5-10%. The incidence in females is also rising. The incidences in South-East Asia, parts of South America, Eastern Europe is remarkably higher than in the western world. Tobacco smoking or chewing, alcohol and betel quid are held responsible.

Due to increased knowledge of the carcinogenic process leading to squamous cell carcinoma of the oral cavity, the future may hold promise in terms of more tailored approaches.

That having been said it is still remarkable that still two thirds of the patients present with advanced staged disease and sometimes enormous tumors. It is therefore clear that the key to improved survival currently still lies in early detection.

The last decade has also witnessed increasing emphasis on quality of life after treatment for cancer and consequently surgeons have found procedures that preserve to the best of their ability function and form. Patients however, still prioritize cure of cancer understandably as main goal, with preservation of function and form and maintaining or improvement of quality of life after that. Another aim is prevention or early detection of second primary cancers. Attempts to influence the incidences of second primary cancers have thus far failed. Several treatments for oral cancer exist. Many patients are treated by surgery and/or radiotherapy or surgery followed by (chemo)radiotherapy or radiation therapy alone. Recently biological therapies such as anti-EGFR antibodies in combination with radiation therapy have entered the arena. Also of note is photodynamic therapy which is currently used by some for not too deeply infiltrating tumors.

In stages I and II single modality treatment is preferable, consisting of either surgery or radiation therapy. For stages III and IV multimodal therapy is warranted consisting mainly of surgery and radiation therapy or for inoperable or unresectable tumors chemoradiation therapy. Treatment is dictated by tumor factors that can be determined by imaging, examination and histology; patient factors consisting of age, comorbidity and patients wishes and expectations as well as physician, institutional, and provider factors.

Tumor factors: The size of the lesion has a determinant impact on treatment decision. Small and not too deeply infiltrating tumors of the oral cavity can be easily resected transorally, whereas more posterior located lesions or those that infiltrate deeply into the tongue or floor of mouth need wider exposure. The status of the neck nodes is also important and when neck stage is high, distant metastasis should be ruled out. Other factors that determine treatment are the proximity to mandibular or maxillary bone, multiplicity and previous treatment as well as pathological characteristics of the tumor. The depth of invasion in tongue cancers determines the incidence of occult nodal metastasis in clinically negative neck. Tumors that are thicker than 4 mm have a distinctly higher metastatic rate. Treatment of the neck is vital, since it determines to a large extend the survival of the patient. For the thicker T1-lesions and T2-lesions and above an elective neck dissection is often indicated. In lesions that can be resected transorally, the sentinel node procedure when negative may justify a policy of observation towards the neck. Unresectable tumors or those when resected would inflict great morbidity to the patient, may be treated with chemoradiation schedules. The morbidity of these protocols is often significant. Salvage surgery after failure after these protocols is often very disappointing. As said, most tumors of the oral cavity are treated surgically, even when large. Functional outcome is often acceptable. Tumors that have been non-radically excised or those that exhibit extranodal spread, need postoperative chemoradiation therapy in patients that can tolerate this treatment.

Patient factors: Co-morbid conditions rather than chronological age are important considerations, in managing patients with advanced oral cancer. A lengthy operation, even with modern day anaesthesiology, may be too much for patients with severe comorbidity, especially when microvascular reconstruction is necessary. Previous treatments in the same area may also contraindicate the ideal treatment and modifications have to be made.

Other factors: The experience of the multidisciplinary team that has taken care of the patient with oral cancer and its experience and local setting, may be a determining factor in the management of patients. It should be emphasized that patients with head and neck cancer need discussion within a multidisciplinary team in order to get the best available treatment proposal.

Surgical access to oral cancer: Several approaches may be employed, depending on the factors described above. They include a peroral approach, a pull through approach, a lower cheek flap or upper cheek flap approach or a mandibulotomy approach. The choice depends on tumor size and site and location, as well as proximity to bone and the need for neck dissection and reconstructive surgery. Small superficial lesions may be resected per orally, with or without a marginal mandibular resection or an infrastructure maxillectomy. For larger lesions when connection with the neck after dissection results, a flap reconstruction is necessary. Currently many institutions favor microvascular reconstruction by a fasciocutaneous flap for optimal...
postoperative outcome. Larger posteriorly located lesions may require a mandibulotomy approach for adequate exposure. Management of the mandible is an important consideration in the surgical treatment of oral cancer. If possible a marginal mandibulectomy when the tumor is close to the bone is favored. This is feasible if the tumor is superiorly to the mylohyoid muscle and only needed for adequate margins. Minimal erosion of the cortex or the alveolar process does not contraindicate marginal resection. In the dentate patient that has a relatively high mandible, it is also feasible to get away with marginal resection when there is limited invasion of the alveolar process. In other cases, for instance if there is clear invasion of the cortex, a segmental resection is indicated. Marginal resections should be preferably boat-shaped in order to avoid points of increased tension and risk of fracture of the marginal segment. For tumors located posteriorly, for instance retromolar trigone lesions a marginal resection including the coronoid process can be undertaken. The need for reconstruction and type of reconstruction obviously depends on the nature of the defect. For small superficial lesions primary closure or secondary intention healing is appropriate and can be used. For larger lesions a local flap, regional flap, or free flap is indicated. Free flaps can be fasciocutaneous, osteocutaneous or osteomucocutaneous, depending on the need for specific reconstructive tissue. The ultimate reconstruction for an oral cancer patient after surgery is placement of osseointegrated implants and teeth. Using modern day osteocutaneous free flaps, this is a very achievable goal, but often takes many months or even a year before the final result is obtained.

Photodynamic therapy When surgery and radiation therapy are contraindicated, in selected cases photodynamic therapy (PDT) is possible. It offers potential for improved function and cosmetic outcome while is claimed that it achieves comparable tumor control. It can only be used in fairly superficial lesions and it may take many weeks or months before healing has taken place. In the meantime many patients will require strong analgesics.

Outcome Failure after treatment for oral cancer is mainly local and/or regional, while some patients experience distant metastasis. Disease specific survival for T1/T2 lesions is 94 respectively 76 %, while for the more advanced lesions this drops to 60 %. Patients who have N1 necks have a disease specific survival of approximately 60 %, while dose having N0 fare much better with 84 %. Advanced neck nodal disease results in a disappointing 46 % survival. Positive margins holds distinctly worse results than when adequate margins can be achieved, while the same holds through for extranodal spread in the neck. This is the reason that attempts have been made to improve results in those patients by adding chemotherapy to postoperative radiation therapy. Two large randomized trials, (EORTC 22931 and RTOG 9501) have been conducted and they have shown improved loco-regional control. Studies that report on quality of life after treatment for oral cancer are emerging and may be helpful in future when determining between two treatment alternatives. Early detection of oral cancer remains very important. Adequate surgical removal using modern techniques, appropriate neck management and contemporary use of tissue and bone reconstruction yield the best results. Adjuvant (chemo)radiotherapy is indicated in high risk patients. Osseointegrated implants constitute the ultimate reconstruction in patients treated for oral cancer.

References:
Role of Sentinel lymph node biopsy in Head and Neck Cancer

(Dr. Sivakumar M, Dr. Neville JF, Senior Resident, Dept. of Surgical Oncology, JIPMER)

Introduction

The cervical lymph node metastasis predicts the cancer related outcomes most accurately in HNSCC. Its impact on disease related survival is much significant. Management of clinically N0 neck(cN0) is still a controversial topic. So accurate evaluation of cN0 neck for occult metastasis is necessary for guiding further treatment. Currently available diagnostic techniques have significant false positive and false negative rate. So the need for better diagnostic technique for evaluating the occult metastasis in cN0 neck has lead to the development of Sentinel lymph node biopsy(SLNB). SLNB is one of the evolving and promising tool for accurate evaluation of cN0 neck before any treatment is initiated for cN0 neck.

Evolution and concept of SLNB

The SLN is the first echelon node which most likely harbors cancer from the primary tumor if metastasis have occurred. It was first introduced by Catalona in 1970 for carcinoma penis. Later Morton et al in 1992 developed the technique of SLNB in patients with cutaneous melanoma. It was Alex and Krag who introduced the radiotracer injection technique in SLNB. The SLNB is based on the fact that metastasis travel sequentially from the primary tumor to the SLN and then to the other regional lymph nodes. Therefore the SLN histopathology reflects the pathological status of the regional lymph nodes accurately. So patients with negative SLN pathologically can be spared of the morbid regional lymphadenectomy. SLNB technique have gone through various refinement since its introduction.

SLNB technique

The SLNB technique utilizes both the radiotracer sulphur colloid and blue dye for its accuracy. The radiotracer is injected around the tumor and the gamma camera is used to locate the SLN which directs the surgeon to the lymphatic zone at risk. In the operating room the surgeon uses the gamma probe transducer and confirms the SLN location, then the blue dye is injected intradermally near the tumor. The SLN is exposed through a small incision and identified by the presence of blue staining and radiotracer uptake detected by the gamma probe. The SLN removed are sent to the pathologist for histological and IHC analysis. Therapeutic lymph node dissection is performed if the SLN is positive.

SLNB in HNSCC

In HNSCC the regional lymph node spread is in a stepwise fashion, so application of SLNB is feasible technique in evaluation of the occult metastasis. Many investigators and large multi-institutional trails has established that SLNB concept applies to HNSCC. More than 60 single institution trials, two international conference consensus documents, a meta-analysis, and recent joint practice guidelines have since been published concerning this topic. The preliminary experience of SLNB in HNSCC was summarized by Ross in 2002 which shows that SLN was identified in 95% with overall accuracy of 90% and sensitivity of SLNB was 94% relative to elective node dissection. Several large prospective clinical observational trials on SLNB, with selective neck dissection reserved only for proven positive lymphatic metastases, have been conducted to date. Three prospective studies of SLNB as primary neck management for stage I and II oral cavity cancer [Sentinel Node European Trial (SENT), the Danish National Group Trial (DAHANCA 22), and the Brazilian Head and Neck Group] are in progress.

The consensus in the literature regarding this topic is that: (1) the predictive value of a negative sentinel lymph node varies between 90 and 100%; (2) step-serial sectioning and immunohistochemistry is essential in proper evaluation of the sentinel lymph node; (3) this use of step-serial sectioning and immunohistochemistry can significantly improve the negative predictive value of this technique; (4) significant upstaging of the lymphatic basins occurs with this technique relative to standard formal lymphadenectomy; (5) unexpected patterns of lymphatic drainage can indeed occur, including unanticipated contralateral drainage to nodes that might be missed with standard lymphadenectomies, and (6) if immediate assessment of lymph nodes using frozen section, imprint cytology or molecular biological techniques reliably show a sentinel lymph node metastasis, a neck dissection can be performed at the same sitting.

The merits of SLNB is the accuracy and less morbidity in the evaluation of occult metastasis. There are several pitfalls in SLNB i.e false negativity in case of skip metastasis, pathological evaluation of SLN need to validated, cannot identify soft tissue tumor deposits and finally the learning curve.

Conclusion

Management of cN0 neck in HNSCC is controversial. SLNB is a feasible technique with excellent safety profile, oncological efficacy and good sensitivity in identifying the occult neck metastasis in HNSCC. At present SLNB can be offered to patients in good conscience and in the trail settings. SLNB needs reproducible level 1 evidence, defined learning curve and refinement to be incorporated in to a clinically useful staging system for cN0 neck in HNSCC.

References:


A Prospective non randomized three arm study of concurrent chemoradiotherapy in head and neck cancers comparing the acute toxicities of three weekly chemotherapy(CT) with Percutaneous endoscopic gastrostomy (PEG) feeding vs. three weekly CT without PEG feeding vs. weekly sensitizer CT without PEG feeding

Dr. CINIRAJ.R, Senior Resident, Dept. of Radiation Oncology, JIPMER
DR.VADHIRAJA.B.M, Associate Professor, Dept. of Radiotherapy & Oncology, Kasturba Medical College, Manipal

Introduction
Concurrent chemoradiotherapy is the mainstay of treatment for head and neck cancer. Although various meta-analyses have clearly shown that delivering chemotherapy and radiotherapy concomitantly (chemoradiation) significantly boosts the effects of radiation,1,2,3,4 this approach raises a number of practical challenges, most of them resulting from poor treatment tolerance and reduced compliance to the prescribed dose intensities of chemotherapy and radiotherapy.5 Cisplatin is among the most common agents used in combination with radiotherapy as well as one of the most studied. It has radiosensitizing properties and its toxicity does not overlap with that of radiotherapy. However, toxicity remains a major problem with concurrent cisplatin administration. In the 1980's and early 1990's most of the schedules used high dose cisplatin administration.6,7,8,9 By the mid to late 1990's daily low dose infusions were introduced with an idea of reducing the toxicity.10,11,12,13 Though the outcomes with these altered schedules were comparable, the toxicity profile was found to be different. At present there is no optimal schedule for treating head and neck cancers and the most efficient and least toxic cisplatin dose has still not been established. Also, malnourishment is very common in the head and neck cancer patient. Weight loss is associated with greater morbidity and poor tolerance to treatment. Previously, nasogastric tube feeding was used for enteral nutritional support in patients on treatment. Of late, however, there has been an increasing usage of Percutaneous endoscopic gastrostomy (PEG). The use of PEG can minimize weight loss and cause fewer treatment interruptions and hospitalization for patients.14,15

Aims and Objectives
1. To assess the acute toxicities of concurrent chemoradiotherapy with cisplatin in three groups of patients i.e; patients on three weekly chemotherapy with PEG feeding and patients on three weekly chemoradiotherapy without PEG feeding and patients on weekly chemotherapy without PEG feeding to help define an optimal CRT schedule with tolerable acute toxicity.

2. Secondary aim is to assess the compliance to treatment in the three groups in terms of delay in completion of radiotherapy and delay in chemotherapy administration and completion of chemotherapy, all of which are known to affect the outcome (local control, loco-regional control, and disease free survival).

Materials and Methods
This study was conducted at Shirdi Sai Baba Cancer Hospital and Research Centre, Manipal, between October 2007 and October 2009 (2 years)
A total of 80 patients with head and neck cancer were included in the study.
Patients were grouped as follows.
ARM - A Consisting of 29 patients on concurrent chemoradiotherapy with three weekly cisplatin and PEG feeding.
ARM - B Consisting of 27 patients on concurrent chemoradiotherapy with three weekly cisplatin without PEG feeding.
ARM - C  Consisting of 24 patients on concurrent chemoradiotherapy with weekly cisplatin without PEG feeding.

Patient selection criteria
Eligibility criteria
1. Patients with histological proof of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
2. Non metastatic disease.
3. Patients should be of Stage II, III or IV disease.
4. Patients must have Karnofsky Performance Status of ≥60.
5. Patients must be ≥20 years of age.
6. Creatinine clearance (CC) > 50 ml/min is determined by Modified Cockroft Gault formula.

Observation and Results
Following table shows the number of patients in each arm. The numbers are comparable in each arm. (Table-1) (Figure - 1)

<table>
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<td>24</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

Table - 1

Figure - 1

Age wise distribution of patients
All patients were above the age of 20 yrs and below 70 years. Majority of patients were in the 41-50 yr age group. Mean age of the patients was 50.8 years.

Sex wise distribution of patients
Majority of patients were males in all the three arms. Males constitute 79.31%, 85.19%, 66.67% in Arm A, Arm B, Arm C respectively.

Topographic distribution of patients
ICD-O coding was used to categorize the patients on topographic wise. In our study Ca tongue constitute the commonest cancer.

Distribution of patients morphology wise
ICD-O coding was use to classify patients morphology wise. Majority of cancers were squamous cell NOS variety, which constitute 86.21%, 92.59%, 87.5% in Arm A, Arm B, Arm C respectively.

Histologic grade wise distribution of patients
Majority of the patients in all arms were of grade I and grade II.

Major site wise distribution of patients
Majority of patients in all arms was constituted by oral cavity tumors. Ca Oropharynx ranked second.

Stage wise- distribution of patients
T3 and T4 patients constituted vast majority in all three arms.

Weight loss
A significant proportion of patients in each arm had grade I and grade II weight loss. The percentage of patients with grade I and grade II weight loss was more in the weekly chemotherapy arm. Only four patients had weight gain at the end of treatment. (Figure - 2)
Radiotherapy delays in various arms
Prolongation of Radiotherapy from the expected date of completion was calculated for all the three arms. The delay in radiotherapy completion was broadly divided into $\leq 7$ days and $> 7$ days. It was observed that the delay is more in the weekly chemotherapy arm. Only one patient in arm A had a delay of $< 7$ days. (Figure - 3)

Delays in administering chemotherapy
86.2% of the patients in arm A received the concurrent chemotherapy as per schedule, against only 22.22% of patients in arm B and 8.33% of patients in arm C. Similarly, while 3.5% of patients in arm A failed to complete the prescribed treatment, nearly 45% of patients in arm B and 88% of patients in arm C failed to complete the prescribed chemotherapy. Both of these findings were found to be statistically significant.

D 22 Chemotherapy
All patients received the Day 22 Chemotherapy. In the PEG arm (Arm A) 86.20% of patients were able to complete the Day 22 chemotherapy on time as compared to 44.44% in non-PEG arm. D 22 Chemotherapy delay by 1 week was 25.93% in Arm B as compared to 13.79% in Arm A. There was no delay $> 1$ wk in Arm A as compared to 26.93% in Arm B. All patients in Arm A and Arm B received D22 chemotherapy. (Figure - 4)

D 43 chemotherapy
86.21% of patients in arm A were able to complete the chemotherapy on time as compared to arm B. Chemotherapy delay $> 1$ week was only 6.9% in arm A as compared to 29.63% in arm B. About 44.44% did not receive D 43 in arm B as compared to 3.45% in arm A.
Chemotherapy details in weekly sensitizer arm

In the weekly chemotherapy arm, it was noticed that after the 3rd week there was a progressive increase in the percentage of patients who could not receive their scheduled chemotherapy. Delays were more after 3 week. There is a progressive decrease in the percentage of patients who could complete their chemotherapy on time as week progressed. (Figure - 5)

Clinical toxicities

1. Skin toxicities
Grade 2 skin reactions was only 20 % as compared to 59.26 % and 51.72 % in arm B and arm A respectively. Most of the toxicities of arm C was of grade I (70.83%).

2. Mucous membrane toxicities
Grade 2 and grade 3 toxicities predominate in all arms during RT. Arm B had more grade 2 and 3 compared to arm A and C. Grade 4 toxicities are predominantly seen in arm C.

3. Pharyngeal toxicities
Grade 2 and grade 3 toxicity predominate during treatment in all the three arms. A higher percentage (51%) of arm A had grade 2 toxicity compared to 37% in arm B and 33% in arm C a higher percentage (59.26%) of arm B had grade 3 toxicity compared to 37.93% in arm A and 45.83% in arm C. Grade 4 toxicities were predominantly seen in Arm C (8%).
Laryngeal toxicity
Grade 2 and grade 3 toxicities predominate during treatment in all the three arms. A higher percentage of patients in arm B had grade 2 toxicities (44.4%) compared to 31% in arm A and 33.3% in arm C. Grade 3 toxicities was 48.28% in arm A, 51.8% in arm B and 50% in arm C. Only one patient had grade 4 laryngeal toxicity, which was in arm C.

Hematological toxicities

1. WBC Toxicity
From week 4 onwards the percentage of patients having grade 1 and grade 2 toxicities in the weekly arm starts increasing. At week 5 the grade 2 toxicities are predominated by the weekly arm, 37.5% as against 3.4% and 7.4% in the arm A and arm B respectively. At week 6 the percentage of grade 2 toxicity in the weekly arm was 33% as against 13.7% and 3.7 % in arm A and arm B respectively.

2. Hemoglobin toxicity
Percentage of patients with Grade 1 Hb toxicity gradually increased for all the three arms as the treatment progressed. Grade 2 toxicity was noticed predominantly in the weekly arm in all weeks. At week 6 a higher percentage of patients on the weekly arm had grade 1 Hb toxicity (54%) as against 41.3% and 44.4% in arm A and arm B respectively.

Discussion
In our study, the three arms were reasonably well matched with respect to age, sex and sitewise distribution. However, while most patients receiving 3 weekly chemotherapy had stage IV disease, most of the group treated with weekly chemotherapy had stage III. Except for 2 patients receiving weekly chemotherapy, rest of the patients completed the prescribed radiotherapy. However, the toxicities observed to treatment were different among the three arms.

Weight loss: In our study grade 1 and grade 2 weight loss predominate in all the three arms. Grade 2 and grade 3 weight losses were more in Arm C (45.83% and 33.33%). The difference in weight loss in the three arms was statistically insignificant, which may probably due to less number of patients in the study. Nonetheless, the lesser degree of weight loss in Arm A suggests the benefit of PEG feeding in patients on concurrent chemoradiotherapy. Interestingly, patients with PEG feeding also continued to lose weight during treatment. In view of lack of other plausible reasons, this may have been due to the inadequate nutritional intake through PEG tube.

Radiotherapy delays: Patients in Arm A hardly had any delay in completion of treatment, with 97% of the patients completing treatment on time. In contrast, only 81% and 37% of patients in arm B and arm C completed the treatment on time. Two patients in the Arm C were not able to complete the prescribed dose as RT was stopped in short of two fractions due to poor patient tolerance. In a study by Ho et al., weekly and three weekly regimens had similar rates of treatment interruptions, with nearly 45% of the patients having treatment delays 16. On the other hand, a study reported from Kerala, India, suggested a much lesser rate of radiotherapy interruption with weekly concurrent chemotherapy (21% vs. 42%) 17. In the study by Gasparani et al who used three weekly cisplatin at a dose of 80 mg/m² the radiotherapy interruption rate was 34%. There are a number of studies which reveal that treatment interruption during RT decreases local control, although its effects on concurrent chemo RT are still not clear. As observed with weight loss, though statistically not significant, the data suggest a large decrease in the need for radiation treatment interruption in patients receiving PEG feeds.

Chemotherapy delays
Similar to the findings on compliance to radiotherapy, the compliance to three weekly chemotherapy was much better among the patients receiving PEG feeding. 86% of patients received their Day 22 chemotherapy on time, in comparison to only 44% in Arm B. Likewise, while 86% of Arm A patients successfully received the Day 43 chemotherapy on time, only 22% of the patients in arm B managed to do so. Again, the statistical significance for this difference was not reached, probably due to the small numbers of patients recruited. In concurrent chemo radiotherapy, a large number of patients fail to complete the prescribed treatment due to toxicities. A study by Al Sararraf et al evaluating 3 weekly concurrent chemotherapy reported only 58% chemotherapy completion rates. 18 In the study reported by Geetha et al., 36% of patients could not receive third course of CT with the three weekly schedule. 19 With only 2 cycles of Concurrent chemotherapy administered on Day 1 and Day 22, Harrison et al 20 reported a better completion rate of 87%. Thus, while a 77% chemotherapy completion rate with the three weekly regimen in our study is comparable with the other reports, in a large percentage of patients this could be achieved only because of PEG feeding.

In contrast to the 3 weekly regimens, the arm C receiving weekly chemotherapy fared much worse. 83% of the patients failed to complete the planned schedule of chemotherapy. The delays in administration were also much more in this group. In most of these patients, the cause of interruption was increased hematological toxicity, which is discussed later. Comparison of this data with other studies is complicated by the fact that different fractionation schedule and dosage of cisplatin were used in various studies. In the study by Bachaud et al 13 Phase II who used cisplatin 5-7 mg/m²/day none of the patients completed the chemotherapy. In the study reported from Kerala 66% of the patients received 6 cycles of chemotherapy for their weekly schedule. 17 In another study by Glaser et al 21 who used weekly cisplatin at a dose of 35 mg/m² about 86% of the patients were able to receive the full course of chemotherapy. The difference noticed may be due to the difference in dosage of cisplatin administered. It appears that dose of Cisplatin < 40 mg/m² weekly may be tolerated better.

Skin toxicities: In our study the grade 1 and grade 2 acute skin reactions predominated in all the arms. Only 5 patients had grade 3 toxicity. A higher degree of skin reactions were observed in patients receiving the three weekly regimen. PEG feeding did not seem to influence the skin reactions, with both the Arm A and Arm

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B having similar rates of grade 2 reactions (52% and 59%, respectively). On the other hand, most patients in the Arm C had only Grade 1 skin reactions at completion of the treatment. The difference noted in grade 2 skin reactions was statistically significant for between the three arms (p value 0.045). In the study from Kerala, 28% of the weekly chemotherapy, 35% of the 3 weekly chemotherapy patients had grade 2 skin reactions and grade 3 skin reactions were 16% and 8% respectively. But overall the difference in grade of toxicities between the arms was significant (p value 0.0008).

**Mucous membrane toxicity:** Grade 2 and grade 3 acute mucous membrane reactions predominate in all the three arms. Nearly half of the patients in all the arms had grade 3 reactions by the completion of treatment. 44.83% in Arm A, 48.15% in Arm B and 45.83% in Arm C had Grade 3 toxicity by the 6th week. Studies by Al Sararraf et al16 reported grade 3 mucositis in 31%. Harrison et al16 reported 100% (grade not mentioned), Cooper et al21 from the RTOG group 9501/intergroup reported mucositis 55%, and Bernier et al27 reported mucositis of 41%. In our study also the toxicities are comparable to the above mentioned studies. When weekly administration of chemotherapy is considered study by Arias et al15 reported mucositis 75% while Serin et al18 reported grade 3 toxicity 14%. The study from Kerala also reported more mucositis(28%) in the weekly arm compared to 4% in the 3weekly chemotherapy. In our study the grade 3 toxicity is 45.83% and grade 4 toxicity is 8.3% in Arm C. These data shows mucous membrane toxicity is more in the weekly chemotherapy arm. However for each grade of toxicities the difference noticed between the three arms was statistically insignificant.

**Pharyngeal toxicities:** In our study, the predominant pharyngeal toxicity was of grade 2 and grade3. Grade 3 toxicities were more in Arm B (59%) compared to Arm B (38%) and Arm C (46%). In the study by Cooper et Al20 RTOG the reported toxicity was 51%. In the study from Kerala grade 3 pharyngeal toxicities was 51% in patients on 3 weekly chemotherapy. Our study results are comparable to the above mentioned studies with respect to arm A and arm B (38% and 59% respectively) But the difference in pharyngeal toxicity between the arms in our study was statistically not significant for all the grades of toxicity. The pharyngeal toxicity in patients in Arm A was manageable with PEG feeding.

**Laryngeal Toxicity:** In our study grade 2 and grade 3 laryngeal toxicities predominate in all the three arms. Grade 4 laryngeal toxicity is noted only in one patient in Arm C. The differences noticed for all the grades of laryngeal toxicity between the three arms were not statistically significant.

**Hematological toxicity:** In the study by Bachaud et al17 hematological toxicity was the dose limiting factor and none of the patients completed the chemotherapy protocol. In our study it was observed that in Arm C there was a progressive increase in the grade 1 and grade 2 WBC toxicity in all the three arms, most noticeable in Arm C. At week 5 the wbc toxicity (grade 2) in Arm C is 37.5% vs. 3.45% in arm A vs. 7.4% in Arm B which was statistically significant (p value 0.008). At week 6 the grade 2 wbc toxicity in Arm C was 33.3% vs. 13.8% in Arm A vs. 3.7% in Arm B, which was also statistically significant (p value 0.05).

Hematological toxicity was in the order of 19% in the study by Al Sararraf et al16, 61% in the study by cooper et al17 RTOG and 13% in the study by Bernier et al17 EORTC 22931. In the study from Kerala the grade 3 neutropenia was 16% in the weekly chemotherapy compared to 8% in the 3 weekly arm. The grade 3 wbc toxicity in week 6 was 6.9% in Arm A and 7.4% in Arm B. These differences were not statistically significant. Grade 3 toxicities in Arm C were 4.1% at week 5 and week 6, though it was expected to be high. This may be due to the omission of chemotherapy in this arm due to progressive neutropenia and poor patient compliance.

Percentage of patients with Grade 1 Hb toxicity gradually increased for all the three arms as the treatment progressed. Grade 2 toxicity was noticed predominantly in the weekly arm in all weeks. At week 6 a higher percentage of patients on the weekly arm had grade 1 Hb toxicity (54%) as against 41.3% and 44.4% in arm A and arm B respectively. Although the difference for each grade was is statistically significant between the three arms, the data in percentages shows that the administration of weekly chemotherapy without PEG is not well tolerated.

**Conclusion**

1. Patients in Arm A tolerated concurrent chemoradiotherapy better, the treatment delays and interruptions being significantly less compared to Arm B. This highlights the importance of PEG feeding in patients being treated with concurrent chemoradiotherapy for head and neck cancer.
2. Substantial weight loss occurring in Arm A ascertains the need for early dietary intervention in the form of counseling and intensive nutrition support to these patients.
3. Weekly chemoradiotherapy without PEG feeding was not well tolerated by patients as delay in radiotherapy completion, chemotherapy administration and omission of chemotherapy was more.

**References :**

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16. Kean F, Ho, Ric Swindell, Caroline V. Brammer; Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: A retrospective comparison from New Cross Hospital, Wolverhampton, UK Acta Oncologica, 2008; 47: 1513-1518.
A Comparative Analysis of Concomitant Boost Radiotherapy vs. Conventional Fractionated Radiation in Carcinoma Larynx

Dr. Pranabandhu Das, Senior Resident, Dept. of Radiation Oncology, Regional Cancer Centre, JIPMER (CO-AUTH: Dr. S. Padhi, Dr. S. N. Senapati, Dept. of Radiation Oncology, A.H.R.C.C, Cuttack)

Introduction

The incidence of laryngeal cancer is 1-2% of all malignancies. However, a considerable body of literature on it reflects the perceived importance of this cancer relative to its potential impact on people's communication skills. Various schemes of altered fractionation schedule like hyperfractionation & accelerated fractionation developed to compare with conventional fractionated schedule aimed at better laryngeal preservation. The concomitant boost technique had been tried keeping in mind the radiobiological aspects of accelerated fractionation radiotherapy which gives beneficial results by decreasing the number of clonogenic cells to considerable extent and without doing much harm to normal cells.

Aim of the study

To compare the feasibility, tolerability, effectiveness of concomitant boost RT over conventional RT in treatment of carcinoma larynx.

Materials and Methods

50 patients of histologically proven squamous cell carcinoma of the larynx in Stage I-IV without distant metastasis with good performance status (KPS>60) and no significant co-morbidities were included in the study. All the patients were stratified into two arms, Control Arm A – Patients received conventional External Beam Radiotherapy (EBRT) of dose 60 Gy in 30#, 2Gy per fraction, 5# per week for 6 weeks. Study Arm B – Conventional EBRT of dose 60 Gy/6 weeks + concomitant boost RT of dose 1.2 Gy per #, 5# / week × 2 weeks during last 2 weeks of the 6 week period with a total dose of 72 Gy.

Results

All patients in Arm A (n=25) and Arm B (n=25) received complete treatment as per defined protocol. Response assessment done after 6 weeks of completion of treatment. Complete response (CR) seen in the study was 84% vs. 68%, the locoregional control after a median follow up of 12 months was 68% vs. 44% and the 2 year DFS was 67 % vs 43% in study arm (CBT) vs. control arm (Conv. EBRT) respectively. Acute toxicity including mucositis, dysphagia, dermatitis were increased but tolerable in the study arm but the significant late morbidity (persistent laryngeal edema) was comparable in both arms.

Conclusion

We conclude that the response to RT, locoregional control, 2 year DFS of CBT is better than Conv. EBRT in carcinoma of larynx with manageable local toxicities. Further analysis and follow-up are needed to evaluate if the benefit will translate into prolonged survival.
Editors' Picks:

1. Paradigm Shift in the Treatment of Head and Neck Cancer: The Role of Neoadjuvant Chemotherapy


Abstract

Chemotherapy is an integral component of the management of patients with locally advanced head and neck cancer, though the optimal use of chemotherapy remains to be defined. Approximately 50%–60% of patients with advanced disease have local disease recurrence within 2 years, and 20%–30% of patients develop metastatic disease. The combination of a platinum agent and 5-fluorouracil has been used as the standard neoadjuvant treatment and has been shown to permit organ preservation in operable patients and improve long-term survival outcomes in operable and inoperable patients. The largest and most detailed meta-analysis, performed by the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group, evaluated data from more than 10,000 patients enrolled in 63 clinical trials. In that analysis, concomitant chemoradiotherapy was associated with an absolute survival benefit of 8% at 5 years (p < .0001), while the survival benefit with neoadjuvant chemotherapy, 2% at 5 years, was not significant. A recent update of this analysis incorporated data from 24 additional studies, confirmed a survival benefit of 5% at 5 years with the addition of chemotherapy (p < .0001) and also significantly favored the use of concomitant chemoradiotherapy. In a subset analysis including only PF induction regimens, there was a significant 5% absolute survival benefit at 5 years (p < .01). The three-arm Intergroup 91-11 study compared induction chemotherapy, concurrent chemoradiotherapy, and radiation therapy alone in patients with operable, intermediate-stage laryngeal cancer. The rate of laryngeal preservation was highest with concurrent chemoradiotherapy, followed by induction chemotherapy and then radiation alone; but overall survival rates were similar for all three groups. Recently, the addition of a taxane, docetaxel or paclitaxel, to standard platinum plus 5-fluorouracil induction chemotherapy has been shown to further improve response rates and survival outcomes (TAX 323 Study). Phase III data have emerged to support combinations of docetaxel or paclitaxel with a platinum plus 5-fluorouracil as a new, more effective and less toxic standard for neoadjuvant chemotherapy. Sequential treatment regimens (TAX 324), incorporating a combination of induction chemotherapy and chemoradiation, have also under study in efforts to further improve long-term survival outcomes. Induction regimens incorporating docetaxel or paclitaxel with a platinum plus 5-fluorouracil are under evaluation in this setting. Randomized trials comparing a sequential treatment approach with standard therapies are also being undertaken and will likely define a new treatment paradigm for patients with locally advanced head and neck cancer.

2. Improved Results with Accelerated Hyperfractionated Radiotherapy of Advanced Head and Neck Cancer

Felix Leborgne, Eduardo Zubizarreta, Jack Fowler. 

Abstract

A retrospective study on local tumor control, survival, and complications of conventional irradiation vs. accelerated hyperfractionated irradiation in patients with selected head and neck cancer sites was undertaken. A total of 1,007 consecutive patients treated with radiation alone for cure from 1974–1997 were analyzed. Excluded were female patients, patients with T1 stage of the vocal cord, and patients who were also treated with brachytherapy implants. There were 637 patients treated with conventional fractionation once daily (QD) in 1974–1997, at a median 2.1 Gy/fraction, to a total median dose of 71.4 Gy in a median overall time of 54 days. As was common before the mid-1980s, 39% and 22% of patients had overall times exceeding 8 and 9 weeks, respectively; 370 patients were treated with accelerated hyperfractionation twice daily (BID) from 1987–1997, at a median 1.6 Gy/fraction, with an interfraction interval of 4–6 h, to a total median dose of 68 Gy in 40 days. Both schedules were well-balanced with respect to their pretreatment characteristics. Patients were not randomized into QD or BID. The 10-year actuarial probability of local control was 37% vs. 56% for QD and BID, respectively (P < .001), which reflects an increase of 19% or a 51% reduction in the local failure rate. Multivariate analysis revealed that T-stage, QD or BID schedule, and overall treatment time were significant independent factors for achieving local tumor control. The 10-year actuarial probability of cause-specific disease-free survival was 25% and 30% for QD and BID, respectively (P = 0.012). Acute morbidity was slightly higher with the BID schedule; patients requiring tube or parenteral feeding were 2.4% for BID and 0.5% for QD (P = 0.01). The 10-year actuarial probability of RTOG/EORTC Grades 3–5 late effects was 13% for both QD and BID. The lack of increase in late complications was most probably due to the lower total dose and dose per fraction in the BID schedule. This study has shown that accelerated hyperfractionated irradiation using two doses of 1.6 Gy each treatment day for less than 6 weeks in advanced head and neck cancer in male patients provides significantly better local tumor control and cause-specific disease-free survival, without increased late morbidity, than conventional fractionation delivered at the previously relaxed overall times of 7 weeks, but sometimes exceeding 8 or 9 weeks.
3. The role of human papillomavirus infection in head and neck cancers


S. Syrja¨nen.

Abstract
The link between head and neck squamous cell cancer (HNSCC) and HPV has become established with oro-pharyngeal carcinomas, tonsillar cancers in particular, show the strongest association with HPV, with some 60% being ascribed to HPV. A recent systematic review (Dayyani et al; Head and Neck Oncology 2010) showed an overall HPV prevalence of 25.9% in specimens obtained from 5046 patients with HNSCC, analysed in 60 separate studies. HPV16 is the most common genotype in these tumours but HPV6 and HPV11 can also be found in a minority of these cancers, implying that these low-risk HPV types are not entirely benign in the head and neck region. According to SEER data (US National Cancer Institute), also in the USA the incidence of HNSCC at the sites that are potentially related to HPV infection (base of tongue, lingual and palatine tonsil, pharynx) significantly increased between 1973 and 2004, with an annual increase of 0.8%. HPV status is also associated with p16 expression and HPV+ tumours are less likely to harbour p53 mutations. HPV DNA is closely associated with poorly differentiated cancers, positive lymph nodes and late-stage disease, which all indicate poor prognosis. Contradictory to this, patients with HPV+ HNSCC seem to have significantly improved response to chemotherapy and radiotherapy as compared with HPV-negative tumours. Interestingly, the risk factors of HNSCC are the same as for HPV, including the number of sexual partners, younger age at first sexual intercourse, practice of oral sex, history of genital warts and younger age.

4. Molecular targeted therapies in head and neck cancer - An update of recent developments

Head & Neck Oncology 2010, 2:8.

Martin Goerner, Tanguy YSeiwert, Holger Sudhoff.

Abstract
Targeted therapies have made their way into clinical practice during the past decade. They have caused a major impact on the survival of cancer patients in many areas of clinical oncology and hematology. Indeed, in some hematologic malignancies, such as chronic myelogenous leukemia or non-Hodgkin’s lymphomas, biologicals and antibodies specifically designed to target tumour-specific proteins have revolutionized treatment standards. In solid tumours, new drugs targeting EGF- or VEGF- receptors whether receptor blockers (Eg: Cetuximab, Panitumumab), or Tyrosine kinase inhibitors (Eg: Gefitinib, Erlotinib) are now approved and are entering clinical practise for treatment of colon, lung, kidney and other cancers, either alone or in combination with conventional treatment approaches. Recent data have now shown that molecular targeted therapy might display efficacy in patients with head and neck squamous cell carcinoma (HNSCC) also as seen in recently published results of the EXTREME study (Erbitux in First-line Treatment of Recurrent or Metastatic Head and Neck Cancer). In this controlled randomized phase III trial, data demonstrated addition of cetuximab prolonged OS from 7.4 months to 10.1 months and disease-free survival from 3.3 to 5.6 months. The evaluated biologicals are generally well tolerated from HNSCC patients, who usually have the burden of multiple co-morbidities that interfere with conventional systemic treatment options. Therefore, molecular targeted therapies offer new treatment options even for heavily pretreated and seriously ill patients usually unable to tolerate chemotherapy or radiation therapy. The two most promising and advanced strategies are the blockage of growth-factor based cellular signalling and interference with angiogenesis-related pathways (Eg: Sorefanib, Dasatanib). But inhibitors of alternative targets, such as Ser and proteasomes, have already been evaluated in early clinical trials with HNSCC patients.

5. The role of intercellular adhesion molecule-1 in Head and Neck Cancer.

Experimental Oncology 28, 270–274 (December 2006).

A. Georgolios, A. Batiatstou, N. Bonitsis, et al

Abstract
The interactions either among cells are mediated by adhesion molecules which are involved in the various processes like morphogenesis, normal growth and development, wound healing, in signal transduction, cancer invasion as well as metastasis. The intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin gene super-family of adhesion molecules mainly expressed in leukocytes, endothelial cells, in certain types of epithelial cells and fibroblasts. ICAM-1 is also known as a potent co-stimulatory molecule in T-cell mediated cytotoxicity and the derangement of the ICAM-1 expression could also be correlated to the cancerous process. Derangement in the architectural structure of the ICAM-1 or significant alterations in the concentration of its soluble form has been positively related to breast cancer, hematologic malignancies, gastrointestinal cancer and melanoma. ICAM-1 concentration shows a significant elevation in the sera of patients with nasopharyngeal carcinoma compared to healthy controls as well as patients suffering from the squamous origin laryngeal and oral cancers and was found to correlate with recurrence and poor prognosis of nasopharyngeal carcinoma. In another study (Xue F; J Oral Pathol Med 2005), the up-regulation of ICAM-1 displayed significant relationship to the squamous origin laryngeal and oral cancers and was found to correlate with recurrence and poor prognosis of nasopharyngeal carcinoma. In another study (Xue F; J Oral Pathol Med 2005), the up-regulation of ICAM-1 displayed significant relationship to the squamous origin laryngeal and oral cancers and was found to correlate with recurrence and poor prognosis of nasopharyngeal carcinoma.
6. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience

Head & Neck Oncology 2009, 1:17

T Gupta, J P Agarwal, S Ghosh-Laskar, P Parikh, AK D’Cruz and KADinshaw.

Abstract
The dominant pattern of failure for squamous cell carcinoma of head and neck remains loco-regional, although distant metastases are now being increasingly documented. Radical radiotherapy with concurrent chemotherapy is contemporary standard of care in the non-surgical management of these loco-regionally advanced cancers, based on large randomized controlled trials utilizing high-dose cisplatin (80–100 mg/m2) cycled every three-weekly during definitive radiotherapy. Although efficacious, this is associated with high acute morbidity necessitating intensive supportive care with attendant resource implications. The aim of this retrospective study was to assess the efficacy and acute toxicity of an alternative schedule i.e. concurrent weekly cisplatin-based radical radiotherapy and its potential to be an optimal regimen in advanced head and neck cancers. Outcome data of patients with Stage III & IV head and neck squamous cell carcinoma, excluding nasopharynx, planned for radical radiotherapy (66–70 Gy) with concurrent weekly cisplatin (30 mg/m2) treated in a single unit between 1996–2004 was
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Dr. Pooja Sethi, M.D. (Radiation Oncology)

Across

1. FDA approved monoclonal antibody against EGFR for squamous cell head and neck cancer (SCCHN) (9)
2. Oral infection with .......... DNA virus increases the risk of H&N cancer between 15-50 fold (5)
3. Major risk factor for H&N cancer (7)
4. Esthesioneuroblastoma is a locally aggressive tumor of .......... epithelium (9)
5. Technique of delivering highly conformal radiotherapy (abbreviation) (4)
6. Less than ..........Gy is the mean dose recommended to parotid glands by IMRT planning in H&N cancer (6)
7. Comprehensive neck dissection in which spinal accessory nerve, IJV & sternocleidomastoid muscle are preserved (8)
8. Most commonly used radiosensitizer in chemoradiotherapy setting in management of H&N cancer (abbreviation) (4)
9. Type of rash related to cetuximab administration (9)

Down

10. Tumor arising from paraganglionic tissue found in carotid body, middle ear and jugular bulb (12)
11. Technique of delivering higher dose of radiation to smaller subvolumes in the target in a shorter period of time (abbreviation) (3)
12. Functional imaging modality used for detection of occult primary in H&N cancer (abbreviation) (3)
13. Virus associated with nasopharyngeal cancer (abbreviation) (3)
14. Method used for detection of HPV DNA (abbreviation) (3)
15. HPV positive oropharyngeal cancers carry .......... prognosis compared to HPV negative cancers (6)
16. EGFR overexpression in H&N cancers is associated with .......... Prognosis (4)
17. In TPF chemotherapy regimen for H&N cancers, 'T' stands for .......... agent (9)
18. Side effect of radiotherapy, related to salivary gland dysfunction (10)