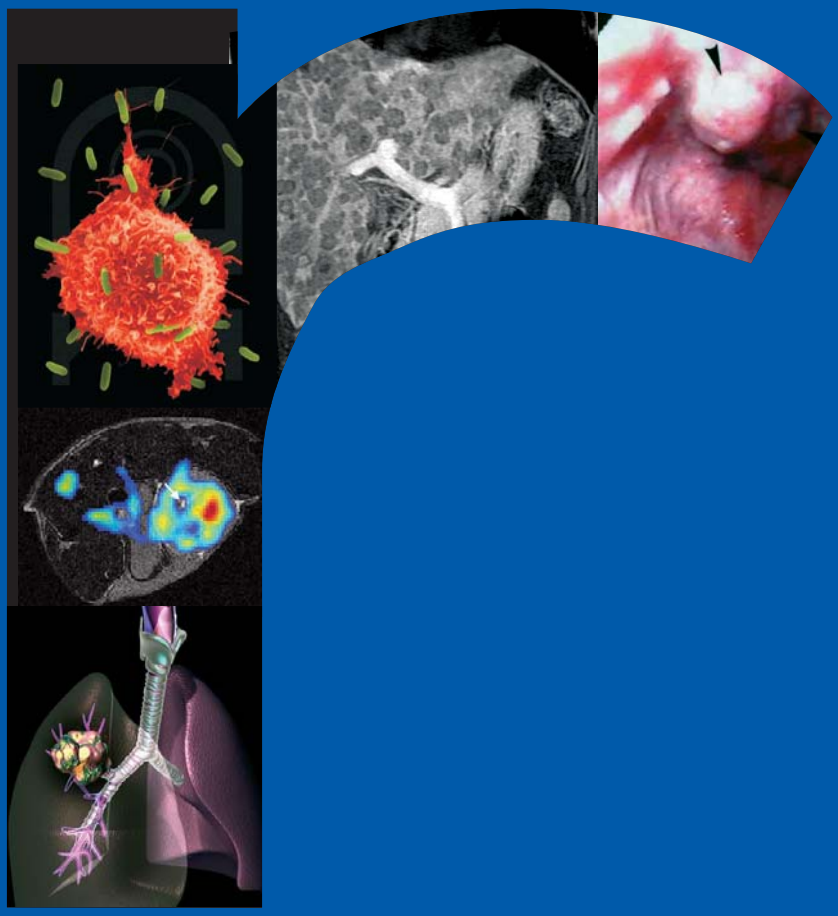
ISSN 0973-9653

CANCER NEWS

VOL 5 NO 2 JUNE 2011



RAJIV GANDHI CANCER INSTITUTE AND RESEARCH CENTRE

Website: www.rgci.org

Printed and Published by
Rajiv Gandhi Cancer Institute &
Research Centre, Sector - 5
Rohini, Delhi - 110 085, India

From the Desk of Director Research

Head and neck cancer remains a difficult cancer to treat as most patients have advanced disease on presentation and aggressive therapy is warranted to increase the chances of cure. Multidisciplinary approach is important in treating these patients, given the complexity of the treatment and the acute and long-term complications that result from chemotherapy, radiation therapy and surgery. Over the last decade tremendous achievements have been made in the management of patients with head & neck cancer. Advancements in the understanding of the pathogenesis of head & neck malignancies could rapidly lead to the elaboration of tailored treatment.

The present issue highlights the biology of head & neck cancer; recent advances in radiotherapy, robotic surgery and targeted therapy.

We are grateful to Dr Anil D'Cruz, Director, Professor & Surgeon, Head Neck Services, Tata Memorial Hospital, Mumbai, for providing the 'Guest Article' on "Understanding the Biology of Head Neck Cancer"

I would like to thank Merck Serono Oncology for supporting this issue of Cancer News. Views and suggestions from the readers are welcome.

Dr D C Doval

CONTENTS

Printed at
Sagar Printers &
Publishers,
1880 Udaichand Marg,
Kotla Mubarakpur,
New Delhi - 110 003

SPECIAL FEATURE

RECENT ADVANCES IN RADIOTHERAPY IN HEAD AND NECK CANCER

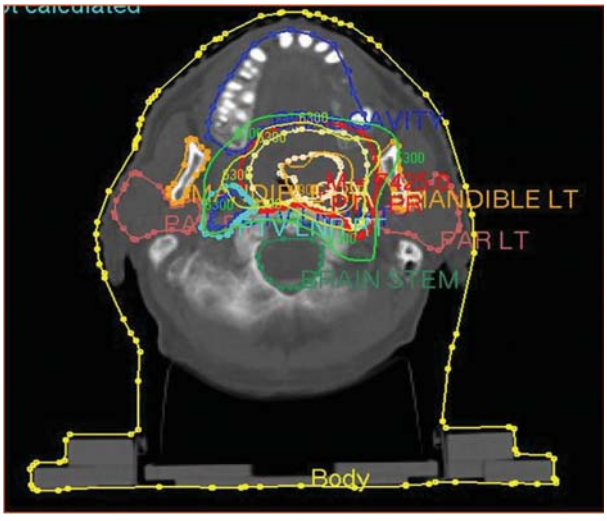
Introduction

The incidence of head and neck cancer is increasing globally and is now the fourth most common malignancy in the world, with more than 70% of all cases found in developing countries. Head and neck cancer remains a difficult cancer to treat; most patients have advanced disease on presentation and aggressive therapy is warranted to increase the chances of cure, but at the same time, this aggressive therapy can result in significant and permanent morbidity.

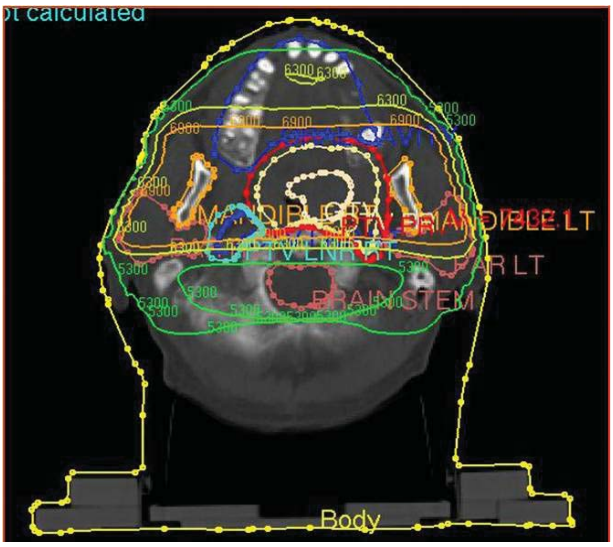
Advances are being made in head and neck cancer treatments. In addition to advances from the medical oncology side, decades of research in the field of radiation oncology for cancers of the head and neck has focused on increasing the therapeutic ratio of the radiation treatment. Efforts have been directed towards dose escalation to achieve higher tumor control probability while keeping the normal tissue complication rate at the minimum possible.

Evolution

Conventional techniques of radiation planning using mask immobilization and conventional simulation allowed only square or rectangular treatment portals associated with daily set up variations in the range of 3-6 mm. This required generous safety margins leading to irradiation of a large volume of normal tissues. With rapid advances in computer software for treatment planning, evaluation and dose delivery, dose sculpting around irregularly shaped tumors, dose escalation and reducing dose to the OARs (organ at risk) became a possibility.



Dose Distribution by IMRT Technique



Dose Distribution by Conventional Technique

The major acute toxicity during radiation treatment of head and neck cancers is mucositis, leading to pain and at times treatment interruptions. Long term morbidities include hearing loss, xerostomia (resulting in loss of taste and difficulty in speech), dental decay and dysphagia having a significant impact on patient's quality of life.

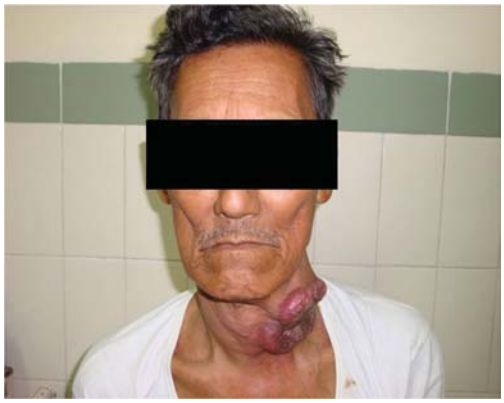
Intensity Modulated Radiotherapy (IMRT)

In IMRT, the radiation dose is designed to conform to the three-dimensional shape of the tumor by modulating the intensity of the radiation beam to focus a higher radiation dose to the tumor while limiting the dose delivered to defined normal structures, such as the salivary glands, auditory and optic apparatus, spinal cord and larynx.

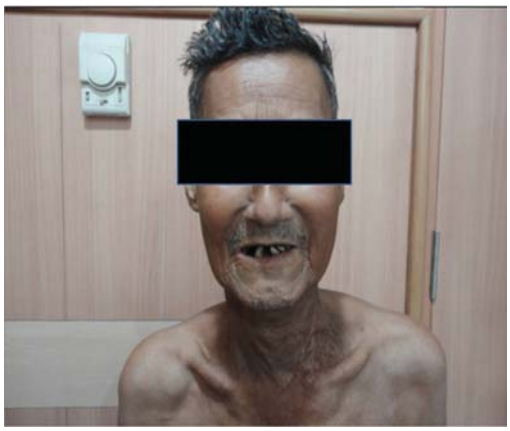
Several small single institutional studies with variable cohort of patients have reported excellent locoregional control rates in head and neck cancers with significant reduction in the rates of acute mucositis and long term xerostomia and dysphagia.

However, steep dose gradients achieved with multi-leaf collimation and intensity modulation could lead to geographical miss due to random and systematic errors, thereby requiring larger PTVs (planning target volumes).

These sophisticated techniques of radiation delivery allow the oncologist to treat elderly and pediatric population with acceptable toxicity. Here is an example of an 80 years old gentleman who was treated for Stage IV tumor of head and neck, who is presently on follow



Before Radiation



After Radiation

up in the Department of Radiation Oncology of Rajiv Gandhi Cancer Institute & Research Centre.

Image Guided Radiotherapy (IGRT)

Exquisitely sculpted dose distributions (increased geographical miss) with IMRT, plus tumor motion and anatomical changes during radiotherapy make IGRT an essential part of modern radiation delivery. Image guidance can be used for tumor delineation, reduction in PTV margin and treatment verification.

Image Guidance for Tumor Delineation: CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) of the head and neck region obtained in treatment position, followed by fusion of the two allows accurate delineation of the tumor volume, OARs and electron density data for dose calculation. Additional biological information from FDG-PET (Fluoro Deoxy Glucose Positron Emission Tomography) allows further dose escalation to the tumor. Radioresistant hypoxic regions within the tumor may be highlighted using 18F-FMISO (fluorine-18-labelled fluoromisonidazole)-PET. This technique is in investigational stages as of now.

Image Guidance for Reduction in PTV Margin: Reduction in size of the tumor, and shift in the position of the OARs (e.g. parotids), leads to interfraction variations in dose distribution. In room, images may be obtained using CT on rails, kilo voltage cone beam CT (kVCBCT), megavoltage cone beam CT (MVCBCT) or tomotherapy. These images are fused with the planning CT scan images using bony and soft tissue landmarks and corrections made in the patient's position or treatment plan, thus obviating the need for a large PTV. This concept may be furthered in the form of adaptive radiotherapy in which a patient with bulky nodal disease or tumor lying close to vital structures is planned for an interim scan and the tumor volumes and OARs are recontoured and replanned. This allows for better sparing of OARs and better dose distribution in target volumes in selected patients.

Image Guidance for Treatment Verification: Higher precision in radiation treatment plans and delivery systems necessitates treatment verification at regular intervals. EPID (Electronic Portal Imaging Device), kVCBCT and *in vivo* dosimetry are the tools available for minimising random and systematic errors.

Particle Therapy

There have been concerns of second malignancies arising in the regions receiving low dose radiation to a large volume of normal tissues (dose bath effect) in IMRT/IGRT. Particle therapy (protons, neutrons and heavy ions) attempts to minimize this effect. It has shown promise in skull based tumors and tumors in close proximity to the spinal cord. These particles deposit minimal energy in the beginning while depositing maximum energy in a small area towards the end of their range (Bragg peak). The position and fluence of the Bragg peak may be modified using intensity modulation (IMPT), thereby allowing further dose homogeneity and normal tissue sparing.

Chemotherapy and Radiation

Addition of chemotherapy to radiotherapy either in definite or post operative setting in patients with poor prognostic features has become the standard of care. It has led to better control rates, small but significant absolute survival gains (4%) but at the cost of increase in acute toxicities.

Cetuximab with Radiotherapy

Epidermal growth factor receptor (EGFR) plays a vital role in growth regulation of normal tissues. It also induces tumorigenesis and progression of malignancies.

It, therefore, forms an important tumor target. Monoclonal antibody, Cetuximab, targeted against epidermal growth factor receptor, enhances radiosensitivity of human squamous cell carcinoma cell lines by inducing cell cycle arrest at G1. A phase III, multicentre study has shown that addition of Cetuximab to high dose radiotherapy significantly improved locoregional disease control and survival compared with radiotherapy alone in patients with locoregionally advanced squamous cell carcinoma of head and neck.

CyberKnife

CyberKnife is a frameless robotic radiosurgery system that allows delivery of radiotherapy with the intention of targeting treatment more accurately than standard radiotherapy. The two main elements of the CyberKnife are: (1) the radiation produced from a small linear particle accelerator, and (2) a robotic arm which allows the energy to be directed at any part of the body from any direction.

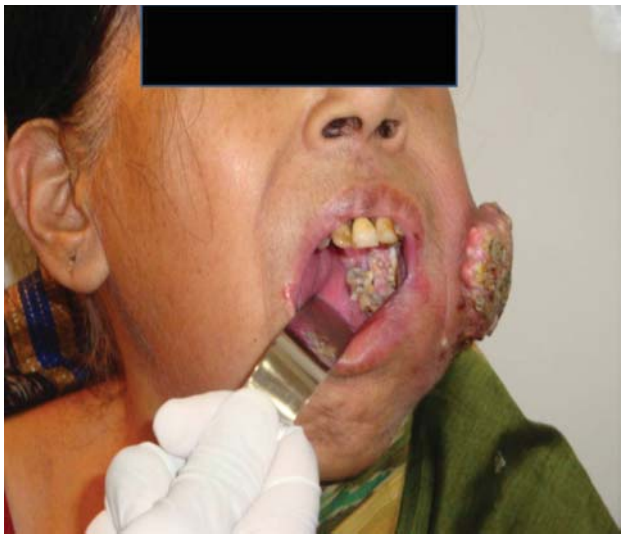
The radiation source is mounted on a general purpose industrial robot that allows near-complete freedom to position the source within a space around the patient. It allows very fast repositioning of the source, which enables the system to deliver radiation from many different directions without the need to move both the patient and source as required by current gantry configurations.

The image guidance system is the other essential item in the CyberKnife system. X-ray imaging cameras are located on supports around the patient, allowing instantaneous X-ray images to be obtained.

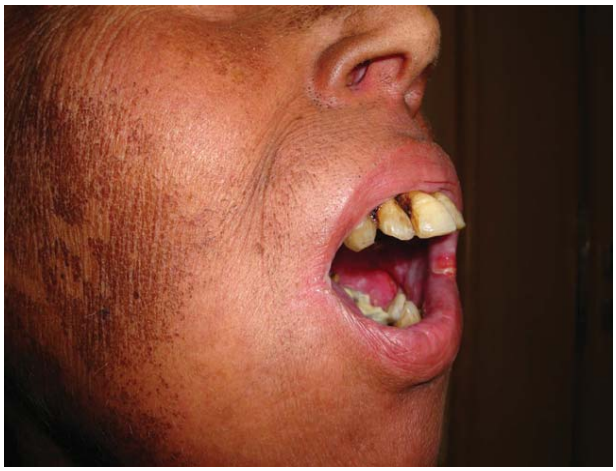
It has US FDA clearance for treatment of tumors in any location of the body. Some of the tumors treated include: pancreas, liver, prostate, spinal lesions, head and neck cancers, and benign tumors.

Conclusion

Advances in the field of radiation oncology have been possible because of new insights into the basic epidemiological and biological aspects of head and neck cancers. Improvements in techniques of radiotherapy planning and delivery are directed towards reducing toxicity, improving efficacy and functional preservation. A multidisciplinary approach combined with treatment individualisation after proper selection of patients will result in further reduction in comorbidities associated with radiation.



Locally Advanced Carcinoma Buccal Muccosa (Pretreatment)



Complete Response at Completion of Chemoradiation

(Dr Anjali Kakria, Clinical Assistant; Dr Sheh Rawat, Sr Consultant; Dr Manoj K Sharma, Associate Consultant; Dr Deepika Chauhan & Dr Gaurav Kumar, Senior Resident, Dept of Radiation Oncology)

GUEST ARTICLE

UNDERSTANDING THE BIOLOGY OF HEAD NECK CANCER

The tumor progression model for head neck squamous cell carcinoma is well defined. These cancers result from a combination of an individual's genetic predisposition in addition to exposure to environmental carcinogenesis. Despite advances in molecular biology detailing the multistep carcinogenesis of head neck tumors, there are still many unanswered questions. Head neck cancers exhibit very different biological behavioral patterns, despite similarity in clinical staging and histology. The TNM staging system is currently used to bring similarity between various head and neck cancers. However, this staging system is based on clinical findings and has its own limitations. Locally advanced stage III and IV cancers form a heterogeneous group comprising of 14 different TNM stage combinations. A stage T1N1 tumor would behave very differently from a T3N1 tumor, although both would be stage III. Similarly, T1N3 would be very different from T4N0 although both are staged as stage IV. The reason that different cancers in same stage behave differently is primarily because of different biology. From a clinician's point of view, it would be important to identify the subset of patients within these groups in order to tailor treatment to achieve highest locoregional control and survival balanced against preserving quality of life and the organ preservation.

A simple classification of biology of head neck cancers would be histological and molecular. The molecular biological parameters can be further classified into those that have defined targeted therapies and those that are still experimental.

Conventional Parameters

1. Tumor thickness: Tumor thickness is a highly significant prognostic factor, particularly for oral cancers. Studies by Spiro et al and Mohit-Tabatabai have proved that increasing tumor thickness is associated with increased chances of lymph node metastases as well as treatment failure and reduced survival[1,2]. Currently, the optimal tumor thickness cutoff point is taken as 4 mm[3].

2. Grade of differentiation: Broders in 1920 described four grades of differentiation depending upon the maturation of tumor cell population. However, this classification is of limited prognostic significance. Jakobsson et al in 1973 developed a multifactorial malignancy grading system, which included the morphologic parameters of tumor cell population "structure", "degree of keratinization", "nuclear polymorphism" and "number of mitoses" as well as the parameters of host tumor relationship "mode and stage of invasion", "vascular invasion" and "the degree of lymphoplasmocytic infiltration"[4]. This was further modified by Anneroth and Hansen omitting the parameter "vascular invasion". Recently, Bryne et al have described a multifactorial malignancy grading system of deep invasive margins at host tumor interface (Invasive Cell Grading = ICG)[5]. This system has been found to be of good prognostic significance. In the latest modification of Bryne et al grading system, the parameter "number of mitoses" has been excluded without resulting in any change in prognostic value.

3. Pattern of invasion: The histologic pattern of tumor invasion reflects the aggressiveness of tumor. Depending upon the pattern of invasion, tumor can be graded from 1 to 4 based on the criteria used by Anneroth et al. Grade 1 tumors have well delineated, 'pushing' borders. In Grade 2 lesions, the advancing edge of the tumor infiltrates in solid cords, bands, or strands. Grade 3 tumors have margins that contain small groups or cords of infiltrating cells. In Grade 4, the host/tumor interface shows marked cellular dissociation in small groups or in a single cell. Widespread association of tumor cells indicate aggressive disease with increased risk of lymph node and distant metastasis as opposed to tumor with pushing border.

4. Lymphovascular invasion: The high incidence of lymphovascular invasion identified at the primary site may predict the future cervical metastases.

5. Perineural invasion: Perineural invasion is a histological sign of biological aggressiveness independent of tumor size. Tumor may spread proximally or distally after entering into perineural space thus compromising otherwise adequate margins of resection. Presence of perineural invasion has been found to be associated with high incidence of local recurrences, regional lymph node metastasis and reduced survival[6].

6. Desmoplastic response: Desmoplastic response has been found to be associated with extracapsular tumor spread and almost a seven-fold increased risk of neck recurrence[7]. Increased desmoplastic response is associated with more radioresistant tumor ultimately affecting prognosis.

7. Extracapsular spread: Spread of tumor beyond the capsule of lymph node into the perinodal tissue, known as extracapsular spread (ECS), has been correlated with a high likelihood of regional recurrence as well as distant metastasis and poor long-term survival.

8. Margin status: Positive or close margins impart a poor prognosis in terms of recurrence at the primary site, disease-free survival and overall survival. Tumors with aggressive biology tend to have more positive/close margins despite adequate resection. Histologically tumor-free margins may contain small clusters of residual tumor cells known as minimal residual cancer (MRC), which may proliferate later leading to recurrence. Use of PCR in detecting residual tumor cells in histologically free margins is under investigation.

All these factors are indicators of aggressive tumor biology and hence, must be mentioned in the histopathology report which can influence further adjuvant treatment. To maintain uniformity, emphasis should be given to synoptic reporting of data.

Histological parameters, however, have their limitations. They may be unavailable at the time of initial decision making in many cases. Treatment response also varies among patients with these adverse factors. Therefore, there is a need to establish other parameters that could help to predict biological characteristics of head neck tumors. The recent past has seen a multitude of efforts towards the identification of new molecular and genetic markers to complement existing parameters in an effort to identify high risk patients. The significant molecular and genetic parameters are as follows:

Molecular Parameters

1. Oncogenes/proto-oncogenes: These are the DNA sequences that encode factors that drive the cell cycle and include growth factors, their ligands, internal signaling pathway protein kinases, cyclins, cyclin associated kinases, and DNA transcription factors.

Epidermal growth factor receptor (EGFR), critical for various cellular processes, is found to be upregulated in 90% of head neck cancers. Overexpression of EGFR is associated with aggressive disease, increased risk of recurrence and decreased survival. In a phase III trial by Bonner, Cetuximab, a monoclonal antibody against EGFR, has been found to be associated with increased disease-free survival when combined with radiotherapy[8]. Down-regulation of TGFâ receptors, an inhibitory growth factor pathway, is often found in head neck carcinomas. Decreased TGFâ signaling is linked to NF-êB activation which is a transcription factor involved in various phases of cell proliferation, apoptosis, angiogenesis and metastasis. Vascular endothelial growth factor (VEGF) acts as an inducer of angiogenesis by stimulating endothelial-cell proliferation and increasing vascular permeability. It has also been linked to poor prognosis and increased risk of development of lymph node metastasis. Cyclin D1 oncogene, a cell cycle regulator at G1-S interphase overexpression, correlates with poor prognosis, aggressive histology and increased chances of recurrence. Chemokine receptor 7 (CCR7), by activating integrin á vâ 3 has been shown to promote cell migration and adhesion in metastatic head neck carcinoma. Presence of microRNA-137 promoter methylation is associated with poorer overall survival[9]. The serine/threonine protein kinase Akt, a downstream target of phosphatidylinositol 3'kinase (PI3K) regulates various steps involved in cell differentiation and apoptotic pathways. Its overexpression is linked to the poor prognosis in head neck cancer.

2. Tumor suppressor genes: Tumor suppressor gene p53 plays a central role in cell cycle regulation and survival. Tumors carrying abnormal p53 gene as a result of loss of heterozygosity or mutations are associated with poor prognosis. Promoter hypermethylation of another tumor suppressor gene p16 is associated with less favorable outcomes.

3. Proliferating cell markers: Proliferating cell markers like PCNA (Proliferating cell nuclear antigen) and Ki67 may serve as valuable markers in predicting lymph node metastasis. They have also been found to be inversely related to degree of tumor differentiation. Overexpression of keratins 6/16 is associated with cell proliferation while keratins 1/10 are markers of cell differentiation.

4. DNA ploidy: Cellular DNA content can also aid in predicting the outcome. Tumors with aneuploidy, carry poor prognosis as compared to tumors with diploid DNA content.

5. Markers for treatment response: Molecular markers can also be used for prediction of treatment response. Expression of ERCC1, a rate limiting enzyme in NER (nucleotide excision repair) pathway, can be used as a predictive marker of cisplatin response. Tumors expressing this enzyme have been found to have worse survival after cisplatin based chemoradiotherapy as compared to ERCC1 negative patients[10]. Overexpression of hypoxia-inducible factor 1á (HIF-1á) and carbonic

anhydrase IX (CA IX) has been associated with poor response to radiotherapy.

Though molecular markers may prove to be of great utility in terms of predicting prognosis, treatment selection, screening and margin analysis in future, the value of their use in current routine practice is limited. Barring the use of EGFR, the routine use of other markers is still investigational. Further research is needed in this direction. Gene expression profiling techniques combined with proteomics could help to select useful genetic and biomarkers of progression which could be used in combination with the TNM staging system and histological factors. A better understanding of the molecular biology of head and neck cancer could also result in therapeutic improvements.

References

1. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the to ngue and floor of the mouth.Am J Surg 1986; 152: 345-50.
2. Mohit-Tabatabai MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 1986; 152: 351-53.
3. Huang SH, Hwang D, Lockwood G, et al. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity. Cancer 2009;115:1489-97.
4. Jakobsson PA, Eneroth CM, Killander D, et al. Histologic classification and grading of malignancy in carcinoma of the larynx (a pilot study). Acta Radiol Ther Phy Biol 1973; 12: 1-8.
5. Bryne M, Nielsen K, Koppang HS, Dabelsteen E. Reproducibility of two malignancy grading systems with reportedly prognostic value for oral cancer patients. J Oral Pathol Med 1991; 20: 369-72.
6. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998; 124: 637-40.
7. Olsen KD, Caruso M, Foote RL, et al. Histopathological predictors of recurrence after neck dissection in patients with lymph node involvement. Arch Otolaryngol Head Neck Surg 1994; 120(12):1370-74.
8. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354: 567-78.
9. Langevin SM, Stone RA, Bunker CH, et al. MicroRNA-137 promoter methylation is associated with poorer overall survival in patients with squamous cell carcinoma of the head and neck. Cancer 2010 (Epub ahead of print)
10. Jun H, Ahn M, Kim H, et al. Clinical significance of ERCC1 expression in advanced squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent chemoradiation. Proc Am Soc Clin Oncol 2007; 25: 6061.

(Dr Shilpi Sharma, Fellow; Dr Anil D'Cruz, Director, Professor & Surgeon, Head Neck Services, Tata Memorial Hospital, Mumbai)

NOTABLE ADVANCES IN HEAD & NECK CANCER - 2010

Survival is Better with HPV-Related Oropharyngeal Tumors: In large randomized clinical trials, researchers have found that stage III or IV patients with HPV-positive oropharyngeal cancer had significantly better overall survival than those with HPV-negative tumors. Future HPV-positive trials would focus on treatment de-intensification to improve quality of life in those patients who are likely to have a better prognosis; whereas HPV-negative trials would focus on intensifying treatment to improve survival in this patient group that appears to have a poorer prognosis.

Accelerated Radiotherapy Schedule is More Effective in Head & Neck Cancer in Resource-Poor Countries: Several large, randomized studies in Western countries have shown that accelerated fractionated radiotherapy, which shortens the overall radiation course without compromising the total dose, can improve local and regional tumor control in patients with locally advanced head & neck cancer. A large, multicenter, randomized trial in nine centers located in countries with limited resources showed that this treatment was more effective than conventional fractionation and can be feasibly delivered to a large number of patients without requiring additional resources.

Sentinel Node Biopsy Shows Potential for Early Stage Oral Cancer: A prospective, multicenter trial found that sentinel node biopsy could serve as a useful tool for staging oral cavity cancer, rather than performing a larger, more invasive neck surgery to determine if the cancer has spread. These findings are important because such neck surgery can be disfiguring and also associated with swallowing and shoulder dysfunction. It is too early to call for the routine use of such testing, and more research is needed.

Radiotherapy Quality and Protocol Compliance are Keys to Head & Neck Cancer Survival: In the context of an international phase III clinical trial of radiotherapy and chemotherapy in patients with locally advanced head and neck cancer, researchers for the first time showed that radiation quality and adherence to radiotherapy guidelines impact tumor control and translate into a survival difference.

(J Clin Oncol, Dec 20, 2010)

PERSPECTIVE

ROBOTIC SURGERY IN HEAD AND NECK CANCER

Introduction

Robotic surgical devices have been developed beyond the investigational stage and are now being routinely used in minimally invasive general surgery, pediatric surgery, gynecology, urology, cardiothoracic surgery and otorhinolaryngology. Transoral robotic surgery allows surgeon to completely remove tumors of the head & neck region while preserving speech, swallowing and other key quality of life issues such as eating.

History

The use of surgical robots in otorhinolaryngology started only recently in 2003 in animal models and cadaveric studies. In 2005, the first ENT robotic surgery was done for excision of a **vallecular cyst**.

The world's first Transoral Robotic Surgery (TORS) program was developed at the University of Pennsylvania. They researched the role of robotic surgical approaches for a variety of malignant and benign tumors of the mouth, voice box, tonsil, tongue and other parts of the throat. In 2006 O'Malley and colleagues were the first to operate on three patients with tumors of the **base tongue**. Complete resection was achieved with negative surgical margins, good haemostasis with no complications. In 2007, Solares and Strome described transoral carbon dioxide laser robot-assisted **supraglottic laryngectomy** in a 74-year old woman with a large supraglottic tumor. In the same year, Weinstein and colleagues described **robot-assisted supraglottic partial laryngectomy** on three patients and **radical tonsillectomy** on 27 patients with squamous carcinomas of the tonsillar region. This technique provided excellent surgical exposure, which allowed for complete tumor resection with minimum morbidity and good functional outcomes.

Principles of Robotic Surgery

The da Vinci system has been utilized for almost all surgical procedures performed in the head and neck region. It comprises of three components: (i) a surgeon's console, (ii) a patient-side robotic cart, and (iii) high-definition 3D vision system. Articulating surgical instruments are mounted on the robotic arms and introduced into the mouth and throat for access to the tumor. It helps to avoid incision in an aesthetically important area (the neck) while still being able to safely and fully remove the tumor with minimum complications, better cosmesis and good functional outcome.

The manipulator unit is equipped with a camera system and up to three manipulating arms, which can be fitted with various instrument tips to operate on the patient. The surgeon controls the unit from the console and an assistant can be positioned near the manipulator unit to either retract or provide suction as needed. This setup allows for the manipulation of tissues in small spaces and provides greater access to regions that might not be reachable by conventional techniques. As such, there have been several studies on its feasibility, safety, and outcomes compared with conventional procedures.

Specific Applications

Rhinology: The approach to sinus surgery has drastically changed with the advent of robotics and endoscopic sinus surgery. Today, FESS (Functional Endoscopic Sinus Surgery), as it is commonly called, is widely practiced with minimal surgical complicaltions.

Robot Assisted Skull Base Surgery: Robot assisted surgery is best suited for excising well circumscribed benign lesions, such as cyst, adenomas, schwanomas and selected malignant tumors involving the skull base and paranasal sinuses. Anterior and middle cranial fossa

Advantages and Disadvantages of Robotic Surgery

Advantages	Disdvantages
• Increased ranges of motion of surgical instruments • Image guidance and stereotactic orientation • Instrument stabilization and tremor control • Binocular endoscopic vision • Multiplanner dissection	• Bulky instrumentation requires considerable space and additional time and personnels for setup • Cost barrier • Lack of tactile feedback

lesions may be approached using robot assisted transantral endoscopic approach for lesions of the nasopharynx (nasopharyngeal angiofibromas and carcinomas) and tumors of clivus, sphenoid, pitutary sella and suprasellar region.

Robot assisted endoscopic surgery for selected cases of paranasal sinuses and skull base tumors has become the procedure of choice at several centres around the world. It offers the technical advantage of resection of tumors of sinonasal tract, especially those which have breached the skull base without the need for craniofacial resection.

When compared to conventional open surgery, robot assisted skull base surgery offers the advantage of being minimally invasive, has reduced morbidity and provides similar disease free and overall survival in selected cases. It also allows for shorter hospital stay and better cosmetic outcomes. Contraindications include extremely vascular tumors, extensive tumors with facial soft tissue involvement or involvement of orbital contents. Generally it is believed that if the tumor is inoperable by traditional methods, it is usually not a candidate for curative resection by endoscopic surgery.

Laryngology: Laryngology has been benefited tremendously with the introduction of operating microscope, microscopic instrumentation and CO_2 laser. The advent of TORLS (Transoral Robotic Laser Surgery) has recently helped to overcome the various limitations of laser surgery.

Robotic surgery provides unique advantage by introducing optics and instrumentation with multiple degrees of rotation that allows for access to entire pharyngeal surface and specific areas of the endolarynx. It also allows the three dimensional camera to be placed close to the tumor with excellent view of the surgical bed.

In general, the lack of tactile sensation is well compensated by superior optics. It is especially indicated for early cases of carcinoma larynx, including vocal cords, hypopharynx, selected cases of posterior pharyngeal wall and base tongue lesions. For early stage cancers, preliminary reports have suggested results comparable with standard organ conservation protocols with chemoradiation.

Functional evaluation suggests better preservation of swallowing and airway function without long term dependence on enteral feeding and tracheostomy. Other advantages include less blood loss, shorter hospital stay and limited post-operative complications.

Otology: The precise and delicate nature of surgery involved in treating middle ear lesions has changed with the advent of endosopic surgery. Three potential otologic applications of robotic surgery are mastoidectomy/ antrostomy, stapes footplate micropick fenestration and cochlear implant well drilling. However, its role still needs to be explored in more difficult temporal bone dissections. Robotic assistance could also improve identification of superior semicircular canal and internal auditory canal during middle cranial fossa surgery.

Head & Neck Surgery: Endoscopic robot assisted thymectomy, submandibular gland excision, parotidectomy and neck dissections have also been described in literature.

Minimally invasive thyroid surgery may be done by endoscopic approach by either cervical or a transaxillary access. It helps to avoid incision in an aesthetically important area (the neck) while still being able to safely and fully remove the thyroid gland. Although there are no established guidelines, endoscopic thyroidectomy is especially suited for nodules less than 3 cm in size and total ultrasonic estimated thyroid volume of 20 ml. Contraindications include prior history of irradiation to neck, previous neck surgery, previous thyroiditis and aggressive tumors with either extracapsular spread or extensive nodal disease.

A more recent study has suggested the role of robot assisted surgery in microvascular free tissue transfer. The flexibility of the robotic arms may allow for suture placement transorally in areas of decreased visibility and access (eg. reconstruction of base tongue and lateral pharyngeal wall defects).

Conclusion

Robotic surgey in head and neck cancer is an exciting innovation that provides significant advantages in terms of en-bloc removal of tumor using minimal invasive technique without a traditional cervical incision, while preserving function and potentially avoiding long term sequelae of chemoradiation. Long term oncologic and functional data are needed to fully validate its use, however, early results seem to be promising.

(Dr Ashish Goel, Consultant, Dr AK Dewan, Sr Consultant Surgical Oncology & Medical Director)

RESEARCH & DEVELOPMENT

Radiotherapy for HIV-Positive Cancer Patients

Radiation therapy (RT) constitutes a current standard treatment for head and neck cancer. Traditionally, aggressive RT has been used sparingly in human immunodeficiency virus (HIV)- positive head and neck cancer patients due to concerns regarding acute and late complications. The newly presented research had sought to determine the feasibility of RT and the likelihood of cure for HIV-positive head and neck cancer patients. The researchers found that three-year estimates of overall survival and local-regional control were 78 percent and 92 percent, respectively. Grade 3+ toxicity was reported by 58 percent of patients but this did not appear worse than the standard rate seen in HIV-negative patients. Of patients studied, 75 percent were receiving highly active antiretroviral therapy at the time of RT. All patients underwent dental prophylaxis and gastrostomy tube placement before beginning therapy, which may have played a role in the toxicity levels remaining comparable to HIV-negative patients.

(ASTRO, Jan 9, 2011)

Smoking During Radiotherapy

Researchers have found that patients who continue to smoke while undergoing radiation treatments for head and cancer fare significantly worse than those who quit smoking. 23% of 101 patients who continued to smoke were still alive five years after treatment, compared with 55% of matched patients in a control group who quit smoking before they began radiation therapy. In addition, 53 of the patients who continued to smoke suffered cancer recurrence, compared with 40 patients in the control group. The patients who kept smoking also had more treatment-related complications, such as the development of scar tissue, hoarseness and difficulty in eating. Poorer outcomes for persistent smokers were found both in patients who had radiation alone and in those who had surgery prior to radiation. Continued smoking contributed to negative outcomes with regard to curability, overall survival and tolerability of treatment. Further research is needed because actual cause of death was not determined for each patient, and the study did not establish a cause and effect relationship between smoking during treatment and worse outcomes.

(HealthDay News, Feb 18, 2011)

Targeting UROD Enzyme Boosts Treatment

Researchers at Princess Margaret Hospital have discovered that targeting uroporphyrinogen decarboxylase (UROD) enzyme can sensitize disease tissue to radiation and chemotherapy, which could mean fewer side effects for individuals with head and neck cancer. This enzyme is involved in the production of a heme molecule, which is vital to all body organs. Targeting UROD exploits the heme synthesis pathway, which disrupts the equilibrium of iron and free radical levels in cells and in turn kills cancer cells. The findings of the study are significant because the researchers have suggested that targeting UROD–identified for the first time as a key player in human cancers–can selectively boost the effect of radiotherapy and chemotherapy in head and neck tumors, while minimizing toxicity to normal tissues. UROD levels were significantly higher in tumor tissues versus normal tissues and cancer patients with lower UROD levels prior to radiation treatment had improved clinical outcome, suggesting that UROD could potentially be used to predict patients' response to radiation therapy.

(Princess Margaret Hospital, Jan 27, 2011)

Voice-Saver: Photodynamic Therapy

Photodynamic therapy uses a powerful laser and a nontoxic, light-activated drug photofrin. Laser activates the drug, causing a reaction in the cancer cells to destroy deadly cancer cells without harming the surrounding healthy tissue. According to a recent study , photodynamic therapy is an effective treatment for early laryngeal squamous cell carcinomas, offering patients a less invasive option with fewer side effects than other therapies, while preserving the voice. During the first five weeks following treatment, researchers noted a significant worsening in the non-vibrating portion of the affected vocal cords. Ten weeks following treatment, there was noticeable improvement, a consistent trend towards normal vocal cord vibration. Photodynamic therapy is a good alternative to radiation and surgery for early stage lesions. It can preserve function and allow to reserve use of radiation therapy and surgery, both known to have more functional improvement of vocal cord function, should the cancer recur following photodynamic therapy. Future studies are aimed at a prospective comparison of photodynamic therapy with surgery and radiation and subsequent voice production results.

(Science Daily, Jan 29, 2011)

NEW TECHNOLOGIES

DIAGNOSTICS

Detection of Circulating Tumor Cells

Polymer-coated and dye-studded gold particles, directly linked to a growth factor peptide rather than an antibody, can detect circulating tumor cells (CTC) in the blood of patients with head and neck cancer by laser spectroscopy. This technology has led to a major improvement in discriminating tumor cells from non-tumor cells in the blood and the CTCs could be detected without separating the tumor cells from normal blood cells. The researchers used nanoparticles to test for CTCs in blood samples from 19 patients with head and neck cancer. Of these, 17 had positive signals for CTCs in their blood. The two with low signals were verified to have no circulating cells by different technique. They demonstrated that one tumor cell out of approximately one to ten million normal cells can be detected and measuring CTC levels may be sensitive enough to distinguish patients with localized disease from those with metastatic disease. This technology could be faster and lower in costs than other detection methods. There is need to validate this study.

(Science Daily, Feb 12, 2011)

Intraoperative qRT-PCR in Head & Neck Cancer

Researchers have developed a rapid automated and quantitative PCR (qRT-PCR) assay for detection of lymph node metastasis in head and neck cancer. It showed high accuracy compared to pathological analysis and may be more accurate than intraoperative pathology. This assay was used to analyse 103 lymph nodes in an intraoperative timeframe. Concordance of qRT-PCR for individual markers with final pathology ranged from 93% to 98%. The best marker combination was TACSTD1 and PVA. A rapid multiplex assay for TACSTD1 and PVA was developed which demonstrated excellent reproducibility and linearity. Analysis of 103 lymph nodes demonstrated 94.2% accuracy of this assay for identifying positive and negative nodes. Average time for each assay was 35 minutes. It was concluded that combined sentinel node biopsy and rapid qRT-PCR could more appropriately guide surgical treatment of patients with head and neck cancer.

(Clinical Cancer Res, Feb 25, 2011)

DRUGS

Multikine in Head and Neck Cancer

Multikine is CEL-SCI Corporation's flagship immunotherapy developed as a first-line standard of care in treating head and neck cancer. Nine countries, including India, are to participate in global Phase III trial, which would be conducted in approximately 48 clinical centres to determine if Multikine administered prior to current standard of care (surgery plus radiotherapy or surgery plus concurrent chemo-radiotherapy) in previously untreated subjects with advanced primary squamous cell carcinoma of the oral cavity/soft palate (head and neck cancer) will result in an increased overall rate of survival as compared with subjects treated with standard of care only. Phase II clinical trials demonstrated that the product was safe and well-tolerated and eliminated tumors in 12% of the subjects less than a month into treatment. It showed a 33% improvement in the survival rate of those treated with Multikine at a median of three and a half years following surgery. The US Food and Drug Administration granted orphan drug status to Multikine in the neoadjuvant therapy of patients with squamous cell carcinoma of the head and neck.

(CEL-SCI Corporation, Apr 8, 2011)

Reolysin

Reolysin (wild-type reovirus) is a formulation of reovirus that Oncolytics Biotech is developing for the treatment of various cancers and cell proliferative disorders and is classified as a oncolytic virus, a virus that preferentially lyses cancer cells. Reovirus was noted to be a potential cancer therapeutic when early studies on it suggested it reproduces well in certain cancer cell lines. It has successfully completed a number of Phases I and II clinical trials across a variety of cancer types and currently a Phase III trial is being conducted in multiple jurisdictions to examine Reolysin in combination with paclitaxel and carboplatin in patients with platinum-refractory head and neck cancers. US Phase II clinical trial (REO 015) is using intravenous administration of Reolysin in combination with paclitaxel and carboplatin in patients with advanced head and neck cancers, in part to confirm the results of UK Phase II study, which enrolled a slightly different patient population, and to support ongoing Phase III study. This US study examined a greater proportion of patients with prior taxane exposure.

(Oncolytics Biotech Inc, Mar 25, 2011)

TECHNIQUES

Boron Neutron Capture Therapy

After years of work done on developing and clinically testing of Boron Neutron Capture Therapy (BNCT), the therapy has been successfully used to treat patients with advanced head and neck cancer who have not responded to previous treatments and generally have poor prognosis. This treatment is based on producing radiation inside a tumor using boron-10 and thermal neutrons. Boron-10 is introduced into cancer cells with the help of phenylalanine, after which the tumor is irradiated with low energy neutrons. The latter react with the boron to generate high-LET radiation, which may destroy the cancer cells. One to two BNCT treatment sessions may be sufficient to destroy a tumor, while keeping the impact of radiation on surrounding healthy tissue to minimum. Helsinki University Central Hospital (HUCH) is the world's only provider of radiation safety audited BNCT treatment. Clinical trial results showed that out of 30 patients with locally recurrent head and neck cancer, 76% responded well to the treatment and 30% were still alive two years after treatment, although only one patient has survived 55 months. As BNCT saves healthy tissue, it promises to make a good choice as a first-line therapy for patients with large head and neck tumors, avoiding the need for extensive surgery. Further studies would be needed.

(Biocompare News, Mar 6, 2011)

Narrow-Band Imaging for Head and Neck Cancer

New diagnostic tools for malignancies of the upper aerodigestive tract are developed all the time, and narrow band imaging (NBI) is one of these new options for early diagnostics. Narrow-band imaging relies on the principle of depth of penetration of light, with the narrow-band blue light having a short wavelength penetrating into the mucosa and highlighting the superficial vasculature. Superficial mucosal lesions that would be missed by regular white light endoscopy, are identified, in view of their neoangoingenetic pattern of vasculature, using the blue light of the narrow-band imaging. Irjala H et al from University Hospital of Louvain at Mont Godinne, Belgium, has described the implementation of NBI technique in their institution. During the first 6 weeks, they used NBI to examine 73 patients with different types of pharyngeal or laryngeal problems. They found that NBI is useful in the diagnosis of malignancies of the upper aerodigestive tract. This is a useful tool in improving the accuracy of the diagnostics. However, it still takes an experienced clinician and a learning curve can be expected.

(Eur Arch Otorhinolaryngol, Feb 15, 2011)

Reconstruction of Trachea

Reconstruction of trachea is challenging, due to the structural complexity and unique properties of the airway. The surgical team at Henry Ford Hospital has used a novel surgical approach to rebuild the trachea and preserve a patient's voice after removing an invasive throat cancer. Patient had a malignant immature teratoma, a cancerous tumor that had spread to the trachea, thyroid gland, muscles around the thyroid gland and nerves in the area. By adopting the approach of removing trachea and voice box and give the tumor's proximity to the larynx and other surrounding structures, the patient would no longer have been able to speak or swallow normally. Surgeons first removed the tumor and about half of the patient's airway, just below the voice box. They used bone and skin from the patient's arm and two titanium plates to reconstruct the airway, providing it with full coverage and allowing it to be fully functional. Currently, the patient is using a tracheostomy tube, but the surgeons do not expect it to be permanent. The patient, however, is able to speak and swallow normally.

(Henry Ford Health System, Jan 29, 2011)

Volumetric Modulated Arc Therapy

Volumetric Modulated Arc Therapy (VMAT) is a next generation therapeutic technique that establishes new standards for radiation therapy treatment speed and dose reduction to the patient. Single or multiple radiation beams sweep in uninterrupted arc(s) around the patient, with complete or partial arc(s) to reduce treatment times from the usual eight to twelve minutes required for "conventional" radiation therapy to only two minutes. 3D volumetric imaging integration enables to visualize the tumor target at the time of treatment and to guide therapy. Compared to other techniques, VMAT provides the greatest freedom to optimise dose to be delivered, and the unique flexibility to simultaneously apply digital control to all treatment parameters, allowing doctors to manipulate the radiation dose and the imaging dose. Both advantages mean patients receive the lowest possible dose outside of the targeted area with their VMAT treatment.

(Elekta Medical Systems, Mar 25, 2011)

CLINICAL TRIALS

Benefits of Intensity Modulated Radiotherapy

According to the results of "Parotid-Sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT)": a Phase III multicentric randomized controlled trial, sparing the parotid glands with intensity modulated radiotherapy (IMRT) significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life. It strongly supports the role of IMRT in squamous-cell carcinoma of the head and neck. At 12 months after treatment, grade 2 or worse dry mouth was reported by 74% of patients receiving conventional radiotherapy compared with 38% given IMRT, and at 24 months, their respective percentages were 83% and 29%. At 12 and 24 months, significant benefits seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomized groups in non-xerostomia late toxicities, locoregional control or overall survival.

(The Lancet Oncology, Feb 2011)

Chemoradiotherapy in Head and Neck Cancer

Long term follow up of randomized Phase III trial of concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer, conducted by Swiss Group for Clinical Cancer Research, showed that combined-treatment with cisplatin and hyperfractionated radiotherapy maintained improved rates of loco-regional control, distant metastasis-free survival, and cancer-specific survival compared to that of hyperfractionated radiotherapy alone, with no difference in major late toxicity. From July 1994 to July 2000, a total of 224 patients with squamous cell carcinoma of the head and neck were randomized to receive either hyperfractionated radiotherapy alone (median total dose 74.4 Gy; 1.2 Gy twice daily; 5 days per week) or the same radiotherapy combined with 2 cycles of cisplatin (20 mg/m^2 on 5 days of weeks 1 and 5). Median follow-up was 9.5 years. Rates of locoregional failure-free survival (hazard ratio [HR], 1.5), distant metastasis-free survival (HR, 1.6) and cancer-specific survival (HR, 1.6) were significantly improved in the combined-treatment arm, with no difference in major late toxicity between treatment arms. However, overall survival was not significantly different (HR, 1.3).

(Int. J Radiat Oncol Bio Phys., Feb 16, 2011)

Survival and HPV in Oropharynx Cancer

The association between survival and human papillomavirus (HPV) in oropharynx cancer (OPC) was retrospectively examined in TAX 324, a Phase III trial of sequential therapy for locally advanced head and neck cancer. Of 264 patients with OPC, 111 (42%) had evaluable biopsies; 56 (50%) were HPV+ and 55 (50%) were HPV-. HPV+ patients were significantly younger, had T1/T2 primary cancers and had performance status of zero. Overall survival (OS)and progression free survival (PFS) were better for HPV+ patients. Loco-regional failure was less in HPV+ patients at 5 years, 82% of HPV+ patients were alive compared with 35% of HPV-patients. The results of the study showed that HPV+ OPC has a different biology compared with HPV-; 5-year OS, PFS, and loco-regional control are unprecedented. These results support the possibility of selectively reducing therapy and long-term morbidity in HPV+OPC while preserving survival and approaching HPV- disease with more aggressive disease.

(Ann Oncol, Feb 11, 2011)

Zalutumumab for Head and Neck Cancer

The first randomized trial of zalutumumab, in patients with recurrent or metastatic squamous cell carcinoma of the head and neck after failure of platinum chemotherapy, showed that the patients who were given zalutumumab, survived significantly longer without the disease progressing than patients receiving best supportive care (BSC). Zalutumumab is a human Ig G1 monoclonal antibody that targets the epidermal growth factor receptor (EGFR). In a Phase III open-label trial, involving 286 patients in three countries, the patients were randomly assigned to zalutumumab plus BSC (191 patients) or to BSC which could include methotraxate (95 patients). Zalutumumab dosing was titrated according to the apperance or absence of rash. Zalutumumab treatment was associated with longer progression free survival (PES) but did not significantly increase overall survival (OS) (median OS: 6.7 vs 5.2 months). PFS and OS seemed to be longer in patients with high EGFR expression compared with low EGFR expression. Zalutumumab dose titration on the basis of rash was safe.

(Medpage Today, Mar 7, 2011)

WATCH-OUT

Lead Cancer Compound Sym004

Sym 004 is a novel drug candidate in oncology, based on a 1:1 mixture of two anti-epidermal growth factor receptor (EGFR) monoclonal antibodies directed against distinct non-overlapping epitopes in EGFR extracellular domain III. Symphogen, a private biopharmaceutical company has been granted US patent for Sym 004 as well as other antibody compositions containing at least two distinct anti-EGFR antibodies having certain binding characteristics. The United States Patent and Trademark Office issued the patent (No. 7,887,805) entitled "Recombinant anti-epidermal growth factor receptor antibody compositions" on February 15, 2011. In preclinical studies, Sym 004 was significantly more effective than the two marketed EGFR inhibitors, cetuximab and panitumumab, and has the potential to treat tumors with acquired resistance to other EGFR targeted agents, including both monoclonal antibodies and small molecule tyrosine kinase inhibitors.

(Symphogen, Mar 8, 2011)

Molecular Detection of Head and Neck Cancer

Univ Johns Hopkins [US] has been assigned Patent No. EP 2271942 (A1), entitled "Detection of Head and Neck Cancer Using Hypermethylated Gene Detection" on January 12, 2011. Molecular detection could be useful to predict tumor recurrence before clinical symptoms or appearance of lesions having the potential to change treatment and follow-up approach. An epigenetic pathway of transcriptional inactivation for many tumor suppressor genes includes CpG island hypermethylation within promoter regions. The present invention is based on the discovery of a panel of markers that detect epigenetic changes associated with head and neck squamous cell carcinoma (HNSCC) in salivary rinses and serum from patients with HNSCC. Further, this panel of promoter hypermethylation markers can be used to anticipate the diagnosis of tumor recurrence by detecting the epigenetic changes associated with HNSCC. Methods and kits used for diagnosing, or evaluating a subject having or at risk of developing head and neck cancer by determining the methylation state of a gene or the regulatory region of at least one gene in a nucleic acid sample from the subject, and wherein at least one gene or regulatory region is hypermethylated as compared to the same region in a corresponding normal cell, have also been described.

(www.patentlens.net, Mar 26, 2011)

Molecule for Prognosing Tumor Grade

The present invention bearing Patent No US2011008821 (A1), and published on January 13, 2011, provides a labeled molecule for prognosing the tumor grade of head and neck cancer and a method for the same, wherein a 78-kDA glucose regulated protein (GRP78) is used to estimate the tumor grade of head and neck cancer, whereby physicians can adopt proper measures to promote the therapeutic effect of head and neck cancer. GRP78, a functional protein, is a member of the heat shock protein 70 family. The invention is based on the facts that GRP78 expression in head and neck cancer cells is much higher than the expression in non-cancer cells and that GRP78 expression correlates with clinical malignant indications, such as tumor size, tumor depth, lymph metastasis, etc, wherein the above mentioned facts are obtained via analyzing the relative GRP78 expression in head and neck cancer tissue and normal tissue. Thus, the present invention adopts GRP78 as a labeled molecule for prognosing the tumor grade of head and neck cancer.

(esp@cenet, Mar 21, 2011)

Vaccines for Head and Neck Cancer

In order to improve both survival and quality of life for patients with unresectable disease, new therapeutic alternatives are mandated.Mayo Foundation; Univ Maryland has been assigned Patent No US2011070252(A1) entitled "Mage-A3/Hpv 16 Peptide Vaccines for Head and Neck Cancer" on March 24, 2011. The invention provides novel Trojan antigen-based compositions and method for their use in the treatment of HNSCC, which include an isolated polypeptide comprising amino acids 1-35 of SEQ ID NO:15, an isolated polypeptide comprising amino acids 1-47 of SEQ ID NO:17, an isolated polypeptide comprising amino acids 1-21 of SEQ ID NO:19, and an isolated polypeptide comprising amino acids 1-43 of SEQ ID NO:22. The invention also provides MAGE-A3 and HPV 16-based Trojan antigen compositions, each composed of 1-2 HLA-A2.1 restricted CTL epitopes, HLA-DR helper epitopes joined together with furin-cleavable linkers and HIV TAT translocating region.

(European Patent Office, Apr 11, 2011)

GLOBE SCAN

HPV-Associated Oropharyngeal Cancers

Hocking JS et al from Australia analysed oropharyngeal and oral cavity cancer rates in Australia in 1982-2005. They found that potentially human papillomavirus (HPV)-associated oropharyngeal cancer in Australia is increasing. Cancers from the oropharynx (base of tongue, tonsil and other specific oropharyngeal sites) were classified as potentially HPV associated (n=8844); cancers in other oral cavity and oropharyngeal sites not previously associated with HPV were classified as comparison (n = 28379). In 2000-2005, an average of 219, 159 and 110 cancers of the tonsil, base of tongue and other oropharyngeal sites were diagnosed annually, with incidences of 1.09, 0.79 and 0.55 per 100000, respectively. An average of 1242 comparison cancers were diagnosed annually (6.17 per 100000). In 1982-2005, there were significant annual increases in tonsil (1.39%) and base of tongue cancers in males (3.02%) and base of tongue cancer in females (3.45%). There was a significant decrease in comparison cancers in men (-1.69%) but not in females. It has been suggested to monitor the impact of HPV vaccination on HPV-associated oropharyngeal cancer.

(Australia: Br J Cancer, Mar 1, 2011)

World Record for DNA Analysis

Researchers at the Royal Institute of Technology (KTH) in Stockholm, Sweden, have invented the new method, which means that DNA sequencing analysis can be performed both in record time and at a very low cost. Today, the great majority of samples are run ten at a time. This costs SEK 10,000 per sample. New method allows 5000 samples to be run at the same time at a cost of SEK 100000. This computes to SEK 20 per sample. This constitutes a world record for the number of tests run in a single DNA sequencing analysis. Each test result can be distinguished, because each sample is marked in an ingenious way with an ID. There are several areas where this new method can have great impact. One of them is cancer research, where there is a great need to scan numerous cell samples from many individuals. This is to see which cells and genes are involved in the cancer. Many DNA analyses are required to create a database for matching organ donors with transplant recipients. New method can be of huge importance in organ transplants.

(Sweden: Science Daily, Mar 8, 2011)

New Tobacco Control Plan

'Healthy Lives, Healthy People: A Tobacco Control Plan for England', published by UK Government in March 2011 aims at reducing smoking rates and helping tackle the damage caused by tobacco. By the end of 2015, the government wants to reduce smoking rates in England from 21.2% to 18.5% or less among adults; from 15% to 12% or less among 15-year-olds; and from 14% to 11% or less among pregnant women. Regulations to put tobacco out of sight in shops in England will come into force for large stores such as supermarkets on April 6, 2012, but the deadline for smaller shops to comply has been pushed back from the previous Labour government's original date in October 2013 to April 2015. For banning cigarette vending machines in October this year and removing tobacco displays in shops, the government will hold a consultation on the possibility of introducing plain packaging for cigarettes and other tobacco products.

(UK: Cancer Research UK, March 9, 2011)

Oral Tongue Cancer in Young, White Females

A team of researchers has found increasing incidence of squamous cell carcinoma of the oral tongue in young white females in the United States over the last three decades. They analyzed incidence and survival data from the Surveillance, Epidemiology and End Results (SEER) program from 1975 to 2007 for oral tongue squamous cell carcinoma (OTSCC) and oral cavity squamous cell carcinoma (OCSCC). They found that overall incidence of OCSCC was decreasing for all ages. However, incidence was increasing for young white women (percentage change [PC], 34.8). Incidence of OTSCC was decreasing for all ages except for age 18 to 44 years group (PC, 28.8). Young white individuals had increasing incidence of OTSCC (white women: PC, 111.3; young white men: PC, 43.7). The annual percentage change of OTSCC was significantly greater in young white women compared with that in young white men. Incidence of SCC in all other subsites of the oral cavity was decreasing. Non-whites had a decreasing incidence of OCSCC and OTSCC. Young white women of age 18 to 44 years may be a new, emerging head and neck cancer patient population.

(USA: J Clin Oncol, Mar 7, 2011)

IN FOCUS

TARGETED THERAPIES IN SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents the 4th leading cause of cancer in the world by incidence with more than 70% of all cases found in developing countries. The five-year survival rates of SCCHN patients (about 50% at 5 years) have not improved significantly despite advancements in multimodality therapy, including surgery, radiation and chemotherapy. Major thrust is being laid on development of molecular targeted therapies for SCCHN. Weak activity with these agents as monotherapies, suggests that combinations of targeted agents and conventional therapy will be necessary to achieve improved outcomes. Cetuximab (Erbitux), a monoclonal antibody (MoAb) has been approved by US FDA. Trials are ongoing in all stages of disease and with a variety of modalities and agents, and those trials should provide critical insight into the best way to use these agents to improve patient outcomes.

Treatment Approaches

SCCHN falls into 4 stages: (1) early-stage disease, (2) locally advanced (LA) disease, (3) recurrent and metastatic (RM) disease, and (4) platinum-refractory disease. For patients with early-stage SCCHN (stage I and most stage II), cure is achieved readily with single-modality radiotherapy and/or surgery. For LA SCCHN (stages III-IVB), a combination of local therapy (radiotherapy and/or surgery) and systemic chemotherapy usually is used. Combined modality therapy (i.e, induction and/or concurrent) has emerged over the last decade as the standard therapy for LA SCCHN. Despite much progress, toxicity has impeded advances with current approaches so the targeted agents have been the subject of great clinical interest.

Targeting the Epidermal Growth Factor Receptor

Two classes of epidermal growth factor receptor (EGFR) antagonists have been successfully tested in phase 3 trials and are now in clinical use: anti-EGFR MoAb and small-molecule EGFR tyrosine kinase inhibitors. Anti-EGFR monoclonal antibodies, such as cetuximab, bind to the extracellular domain of EGFR

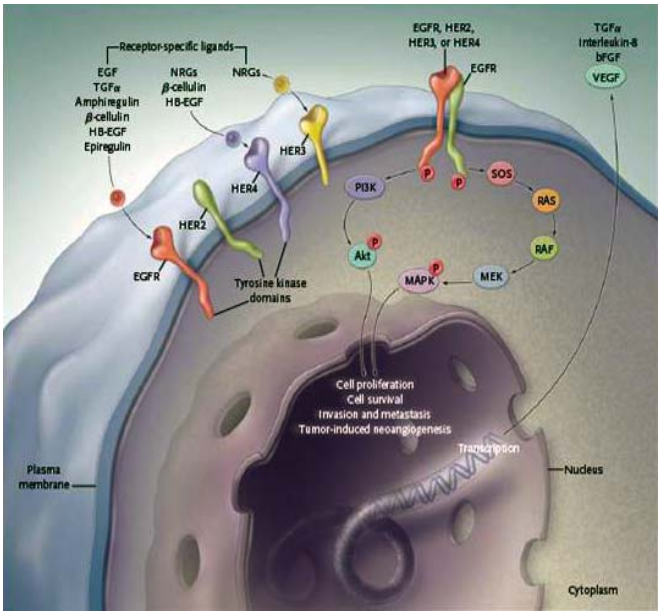


Fig 1: Molecular Pathway Involved in Head & Neck Cancer

when it is in the inactive configuration, compete for receptor binding by occluding the ligand-binding region, and thereby block ligand-induced EGFR tyrosine kinase activation (Fig 1). Small-molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR tyrosine kinase and, thus, inhibit EGFR autophosphorylation and downstream signaling. In addition, various small-molecule EGFR tyrosine kinase inhibitors can block different growth factor receptor tyrosine kinases, including other members of the EGFR family, or the vascular endothelial growth factor receptor.

The combination of cetuximab and radiotherapy was initially tested in patients with previously untreated, locally advanced squamous-cell carcinoma of the head and neck. In a randomized, multicenter, phase 3 clinical trial, patients were treated with radiotherapy alone or in combination with cetuximab (Table 1). Radiotherapy plus cetuximab significantly prolonged progression-free survival, duration of locoregional control, and overall survival. A randomized phase 3 trial of cisplatin plus cetuximab as compared with placebo in patients with previously untreated, metastatic squamous-cell carcinoma of the head and neck showed a significantly higher response rate in the group that received cisplatin plus cetuximab. However, no significant difference in overall survival was observed, possibly because of the relatively small study sample. A recent larger, randomized, multicenter phase 3 trial showed that the addition of cetuximab to platinum- and fluorouracil-based chemotherapy in the first-line treatment of recurrent or

Table 1: Efficacy of Cetuximab in Efficacy of Squamous Cell Carcinoma of Head and Neck Cancer

Study BONNER et al	Radiotherapy (N-213)	Radiotherapy Plus Cetuximab (N-211)	Hazard Ratio (95% C1)	P Value	Chemotherapy (N-220)	Chemotherapy Plus Cetuximab (N-222)	Hazard Ratio (95% C1)	P Value
Overall response rate (%)	64	74	0.57 (0.36-0.90)	0.02				
Median locoregional control	14.9	24.4	0.68 (0.52-0.89)	<0.005				
Median progression-free survival (mo)	12.4	17.1	0.70 (0.54-0.90)	<0.006				
Median overall survival (mo)	29.3	49.0	0.74 (57-0.97)	<0.03				
EXTREME TRIAL								
Overall response rate (%)					19.5	35.6		0.001
Median progression-free survival (mo)					3.3	5.6	0.54 (0.43-0.67)	<0.001
Median overall survival (mo)					7.4	10.1	0.80 (0.64-0.98)	0.04

metastatic squamous-cell carcinoma of the head and neck may be helpful, since progression-free survival and overall survival were significantly prolonged (Table 1). This phase 3 study is unique in showing a survival benefit for a novel treatment as compared with platinum-based chemotherapy in the treatment of this disease. Several phase 2 studies evaluated cetuximab alone or in combination with cisplatin in the treatment of platinum-resistant squamous-cell carcinoma of the head and neck, a cancer in which no specific therapy has been effective; such patients have a very short life expectancy. The overall response rate with cetuximab monotherapy was 10 to 13%, with a disease-control rate of approximately 40 to 46%.Cetuximab was approved by the US FDA in February 2006 for use in combination with radiotherapy to treat patients with locally advanced, unresectable squamous cell carcinoma of the head and neck. It was also approved as monotherapy for metastatic disease in patients who have not had a response to chemotherapy. In March 2006, the EMEA approved cetuximab in combination with radiotherapy for the treatment of locally advanced disease.

Other Anti–EGFR MoAbs: Panitumumab (Vectibix) and zalutumumab (HuMax-EGFR) are fully human MoAbs that, similar to cetuximab, bind to the extracellular domain of EGFR. Ongoing late-stage clinical trials with these MoAbs should answer question of whether either provides a clinical advantage over cetuximab in SCCHN.

Other Potential Targets

Tyrosine Kinase Inhibitors (TKIs): Studies are evaluating gefitinib and erlotinib in combination with more aggressive chemotherapy regimens, such as platinum or docetaxel, and either with or without concurrent radiotherapy. 'Erlotinib Prevention of Oral Cancer Trial' is the only late-stage prevention trial ongoing in SCCHN, being studied in the high-risk setting of oral leukoplakia.

Dual Kinase Inhibitors: Lapatinib, a dual kinase inhibitor that targets both EGFR and HER-2, has been tested in SCCHN and reportedly has a favorable safety profile but little activity as a single agent in RM SCCHN.

Multitargeted Kinase Inhibitors: Oral kinase inhibitors sorafenib, sunitinib, and vandetanib agents, are in clinical development that affect multiple pathways and may provide a simpler approach to blocking multiple targets. Promising early clinical results were obtained in RM SCCHN with sorafenib in the treatment naive patients.

Future Directions

The development of new biological agents should focus on inhibitors that are likely to hit multiple targets. Combination of different agents that target distinct specific pathways is likely to inhibit the escape of tumor cells by alternate mechanisms leading to more effective disease control. But the success of future clinical trials will depend upon (i) patient population and (ii) study design for assessment of response to therapy. Further, to evaluate the efficacy of these biological agents, there is urgent need to identify novel biomarkers that can be used to accurately assess and individualize therapy.

Conclusion

Molecular targeted therapies are promising novel treatment options for patients with SCCHN. Profound clinical data are available for cetuximab, both in the adjuvant and palliative setting and the others are currently being evaluated. 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 SCCHN in the near future.

(Dr Deni Gupta, DNB Student; Dr DC Doval, Director Medical Oncology & Director Research)

HEAD & NECK CANCER FACTS

1. Head and neck represents the 5th leading cause of cancer by incidence and the 6th leading cause of cancer mortality in the world.
2. Head and neck cancers constitute 25-30% of all malignancies in India.
3. Most head and neck cancers occur in the 5th decade, except salivary gland and nasopharynx which may occur at a younger age group.
4. Patients who have a first degree relative suffering from head and neck squamous cell cancer are at a 3.5-3.8 fold higher risk of developing the same.
5. Certain genetic mutations are inherited which predispose a patient to the carcinogenic effects of tobacco and alcohol.
6. Tobacco is responsible for nearly 1/3rd of all cancer deaths worldwide. Besides causing cancer in the upper aerodigestive tract, it has been implicated in cancers of the lung, bladder, kidney, pancreas and cervix. The overall risk of developing head and neck cancer is related to the total lifetime exposure which includes the amount of tobacco a person smokes each day, age at which smoking is started, number of years a person has smoked and years of passive smoking. Majority of the malignancies occur with tobacco pack years exceeding '40' a year.
7. Tobacco smoke contains 4000 different chemicals, of which 60 are known carcinogens. The major carcinogen are the tobacco specific N-nitrosamines. Following metabolism, they cause DNA alkylation, which can induce mutations. These mutations in the key target genes initiate cancer development.
8. Smoking has strongest association with laryngeal cancer. Cigar and pipe smoking have strong correlation with oral cancer. Reverse smoking is particularly associated with hard palate carcinoma.
9. Smokeless tobacco, implicated in the causation of oral cavity cancer, is known to contain 28 carcinogens.
10. The second most important cause of head and neck cancer is alcohol.
11. The risk of developing head and neck cancer is 15.5 folds higher in patients who consume both tobacco and alcohol.
12. Human papilloma virus (HPV) type 16 is a risk factor for cancer of the oropharynx (45-67%), oral cavity (10-18%) and nasopharynx (2-5%). Vaccination strategies are being tested as a potential means for preventing HPV induced head and neck cancers.
13. The majority of patients with head and neck cancers present with locally advanced, stage III / IV (55-65%) disease that requires multimodality treatment entailing chemotherapy, radiotherapy, or surgery.
14. Second primary tumors occur in head and neck cancers due to field cancerization in 30% of the cases. The risk of developing second primary post radiotherapy is 4-6% per year.
15. Individuals who continue to smoke and drink alcohol post treatment have a 20-40% risk of developing second primary malignancy.

(Dr Shamim Akhtar, DNB Student; Dr Tapaswini Pradhan, Consultant, Dr AK Dewan, Sr Consultant, Surgical Oncology & Medical Director)

GUTKA/ PAN MASALA MENACE

Serious concerns over the growing smokeless tobacco products, including gutka/ pan masala menace, have been raised by anti-cancer campaigners and the Government has been urged to take urgent action to stop their sale through stringent measures. India has the highest prevalence of oral cancer globally, with 75,000 to 80,000 new cases of oral cancers being detected in a year. Smokeless tobacco comes in various forms like gutka, khaini, zarda, mishri, mawa, pan masala and is sold cheap in small sachets. Due to its flavoured taste, easy availability, low price and attractive marketing by the companies, it is becoming increasingly popular amongst youth, women and children. A recent report prepared by experts shows that India alone accounts for 86% of total oral cancer figures across the world. Chewing tobacco and gutka contributes to 90% of oral cancer cases in the country. Nearly one-third of Indian population use smokeless tobacco. 34.6% adults (47.9% males & 20.3% females) currently consume some form of tobacco in India. Around 25.9% adults (32.9% males & 18.4% females) in India use smokeless tobacco, among daily tobacco users, 60.2% consume tobacco within half an hour of waking up.

ERBITUX® (Cetuximab) Abbreviated Prescribing Information (Summarized Specific Information): ERBITUX® NOTE: Before prescribing ERBITUX®, please consult the full product information for health care professionals ERBITUX® 5mg/ml solution for infusion (Cetuximab is a chimeric monoclonal IgG1 antibody produced by recombinant DNA technology). **Quantitative composition:** Each ml of solution for infusion contains 5 mg Cetuximab. Each 20 ml vial contains 100 mg Cetuximab and 100 ml vial contains 500 mg Cetuximab. **Therapeutic indications:** 1] ERBITUX® is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild type metastatic colorectal cancer (i) in combination with chemotherapy (ii) as a single agent in patients who have failed oxaliplatin - and irinotecan-based therapy and who are intolerant to irinotecan. 2] ERBITUX® is indicated for the treatment of patients with squamous cell cancer of the head and neck (i) in combination with radiation therapy for locally advanced disease (ii) in combination with platinum-based chemotherapy for recurrent and/or metastatic disease. **Posology and method of administration:** Administration must be supervised by a physician experienced in antineoplastic medicinal products. Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. ERBITUX® is administered once a week. Adults: The initial dose is 400 mg/m^2 of body surface area, infused over 120 min. The subsequent weekly doses are 250 mg/m^2 each infused over 60 min. Maximum infusion rate must not exceed 10 mg/min. Elderly: No dose adjustment required, but experience limited in patients older than 75 years. Children: Safety and efficacy have not been established. ERBITUX® is administered intravenously with an infusion pump, gravity drip or a syringe pump. Closely monitor the patient throughout the infusion and for at least 1 hour afterwards. Resuscitation equipment must be available. Colorectal cancer: In patients with metastatic colorectal cancer, ERBITUX® is used in combination with chemotherapy or as a single agent. Chemotherapy must not be administered earlier than 1 hour after the end of the ERBITUX® infusion. Continuation of ERBITUX® treatment until disease progression is recommended. Squamous cell cancer of the head and neck: In patients with locally advanced squamous cell cancer of the head and neck, ERBITUX® is used concomitantly with radiation therapy. It is recommended to start ERBITUX® therapy one week before radiation therapy and to continue ERBITUX® therapy until the end of the radiation therapy period. In patients with recurrent and/or metastatic squamous cell cancer of the head and neck, ERBITUX® is used in combination with platinum-based chemotherapy followed by ERBITUX® as maintenance therapy until disease progression. Chemotherapy must not be administered earlier than 1 hour after the end of the ERBITUX® infusion. Continuation of ERBITUX® treatment until disease progression is recommended. **Contraindications:** ERBITUX® is contraindicated in patients with known severe hypersensitivity reactions to Cetuximab. **Special warnings and precautions for use:** Severe hypersensitivity reactions have been reported in patients treated with Cetuximab. Symptoms usually occurred during the initial infusion and up to 1 hour after the end of infusion, but patients should be warned that they may occur after several hours or with subsequent infusions. Occurrence of a severe hypersensitivity reaction requires immediate and permanent discontinuation of Cetuximab therapy and may necessitate emergency treatment. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease. **Skin reactions:** If a patient experiences a severe skin reaction (grade 3 or 4), Cetuximab therapy must be interrupted. Treatment may only be resumed, if the reaction has resolved to grade 2. With the second and third occurrences of severe skin reactions, Cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m^2 after the second occurrence and 150 mg/m^2 after the third occurrence), if the reaction has resolved to grade 2. If severe skin reactions occurs a fourth time or do not resolve to grade 2 during interruption of treatment, permanent discontinuation of Cetuximab treatment is required. **Respiratory disorders:** If interstitial lung disease is diagnosed, ERBITUX® must be discontinued and the patient be treated appropriately. **Electrolyte disturbances:** Hypomagnesaemia has been reported, which is reversible following discontinuation of ERBITUX®. In addition, hypokalaemia may develop as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular in combination with platinum-based chemotherapy; the frequency of severe hypocalcaemia may be increased. Electrolyte repletion is recommended, as appropriate. **Neutropenia and related infectious complications:** Patients who receive Cetuximab in combination with platinum-based chemotherapy are at an increased risk for the occurrence of severe neutropenia, which may lead to febrile neutropenia, pneumonia or sepsis. Careful monitoring is recommended in such patients, in particular in those who experience skin lesions, mucositis or diarrhoea that may facilitate the occurrence of infections. **Cardiovascular Disorders:** An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths have been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. When prescribing Cetuximab, the cardiovascular status of the patients and concomitant administration of the cardiotoxic compounds should be considered. Colorectal cancer patients with KRAS mutated tumours: Cetuximab should not be used in the treatment of colorectal cancer patients whose tumours have KRAS mutations or for whom KRAS tumour status is unknown. **Pregnancy and lactation:** Only use in pregnancy if potential benefit justifies potential risk to foetus. Breast-feeding during treatment with ERBITUX® and for 2 months after the last dose is not recommended. **Undesirable effects:** In combination with local radiation therapy of the head and neck area, additional adverse effects were for radiation therapy (such as mucositis, radiation dermatitis, dysphagia or leucopenia, mainly presenting as lymphocytopenia). In a randomized controlled clinical study, severe acute radiation dermatitis, mucositis and late radiation-therapy-related events were highly reported in patients receiving radiation therapy in combination with ERBITUX® than those receiving radiation therapy alone. Very common ($\geq$ 1/10): Mild or moderate infusion-related reactions (fever, chills, dizziness, or dyspnoea); Mild to moderate mucositis leading to epistaxis; Increase in liver enzyme levels; Hypomagnesaemia; Skin reactions (acne-like rash, pruritus, dry skin, desquamation, hypertrichosis, or nail disorders, skin necrosis) Common ($\geq$ 1/100 to < 1/10): Diarrhoea; Nausea; Vomiting; Headache; Fatigue, Conjunctivitis, Dehydration, Anorexia followed by weight loss; Hypocalcemia, Severe infusion-related reactions (bronchospasm, urticaria, blood pressure, loss of consciousness or shock); Uncommon($\geq$ 1/1000 to < 1/100): Blepharitis, keratitis, Pulmonary embolism; Deep vein thrombosis; Rare ($\geq$ 1/10,000 to < 1/1,000): Angina pectoris; Myocardial infarction; Cardiac arrest; Frequency not known: Aseptic meningitis, Superinfection of skin lesions leading to subsequent complications, e.g. cellulitis, erysipelas, or potentially with fatal outcome, staphylococcal scalded skin syndrome or sepsis. **Storage:** Store in a refrigerator (2°C - 8°C). **Date of revision:** Februaury 2011; version 1.8

CRC, colorectal cancer; KRAS, a gene encoding a small GTPase that passes on a growth signal in the epidermal growth factor receptor signaling pathway; PFS, progression-free survival; SCCHN, squamous cell carcinoma of the head and neck

1. Van Cutsem E et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer – the influence of KRAS and BRAF biomarkers on outcome : Updated data from the CRYSTAL trial. ASCO GI 2010, Abstract No. 281.
2. Vermorken et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Eng J Med 2008; 359:1116-27.

Merck Serono

Merck Serono is a division of Merck

MERCK