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EDITORIAL

SHAPING THE FUTURE OF CANCER PREVENTION

"Hee is a better physician that keeps disease off us, than hee that cures them being on us. Prevention is so much better than healing, because it saves us the labor of being sick" (Thomas Adams 17th century). Importance of prevention is known from ages. Prevention works but takes time. Prevention is feasible. The good news is that cancer is preventable. Fortunately several types of evidence indicate that a major fraction (50-80%) of human cancer is potentially preventable, because its causation is largely exogenous. This evidence comes mainly from epidemiological studies including 1)time trends in cancer incidence and mortality 2) geographic variation and effect of migration 3) identification of specific causative factors like smoking, viruses, radiation etc 4) the fact that majority of human cancers don't show simple pattern of inheritance.

I should, of course, emphasize that genetic factors are probably very important in terms of influencing individual susceptibility and that in certain rare forms of human cancers, hereditary factors play a more decisive role. From the point of view of primary prevention, however, the external factors are probably the most operable variables in majority of human cancers. This is an optimistic message since it means that development of several forms of cancers are not inherent consequence of the aging process per se and that the human species is not inevitably destined to suffer a high incidence of cancer. In principle, majority of cancers are preventable if we can identify external causative factors. But major challenge is the precise identification of causative agent.

The second encouraging message is that early detection of atleast some forms of cancer saves lives. Therefore increased efforts in development of new diagnostic methods to detect early lesions and the development of mass methods of intervention including chemoprevention hold great promise. Recent studies have demonstrated the potential of using a genomic classifier to identify early lung cancer and of using precision medicines to reduce cancer risk in those who are at an elevated risk. Another emerging technology comes from determining your risk of cancer. A clinically validated test for sporadic breast cancer combines clinical risk factors with a genetic make up to determine risk of developing breast cancer. The test examines your DNA to look for the absence or presence of genetic markers that are associated with an increased risk of developing breast cancer (Prevention at molecular level).In future we will have better cancer screening i.e. detection of abnormal protein structures in blood before it gets detected clinically or on imaging. A low cost diagnostic DNA analyser of the size of smart phone is on its way.

New cancer vaccines train the immune system to use its antiviral fighting response to destroy cancer cells without harming healthy cells. Vaccines are already available in the market for preventing cervical cancer.

The third reason to be optimistic about prevention relates to the spectacular advances in basic research which are providing powerful new approaches to identify specific causes of human cancer. It seems likely that in coming decades the powerful and unifying themes will accelerate advances in both cancer prevention and treatment, thus leading to major reduction in both incidence and mortality of human cancer.

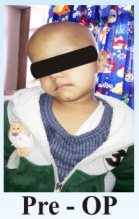
Unfortunately research on prevention is underfunded, yet vital to cancer control. Relatively little private sector interest is there in prevention research. Every cancer centre should spend part of its revenue in cancer prevention research. Govt. should also focus on independent policy relevant research in cancer prevention.

We have a duty to care to the patients of today and to the population of tomorrow.

Dr. A. K. Dewan
Director - Surgical Oncology

MANDIBULAR RECONSTRUCTION IN PAEDIATRIC PATIENT - A CASE STUDY

2 ½ years old boy from Arghakhanchi district of Nepal came to RGCIRC in September 2016 with left jaw swelling for last 2 months. He had seen several doctors in his home town where a biopsy from the mass revealed it to be cancerous. He was then referred to our institute for further management. He was seen in the Pediatric Hematology Oncology Department where the diagnosis of Ewing's sarcoma was confirmed and staging workup showed that the tumor was limited to the mandible on the left side coming upto the midline. 4 cycles of chemotherapy was given which led to reduction of tumour size. He was reassessed again for best modality of local control of the tumor.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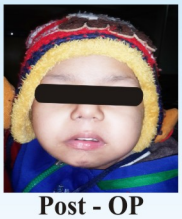
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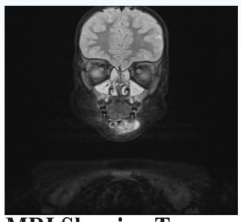
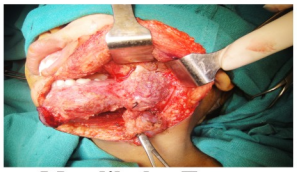
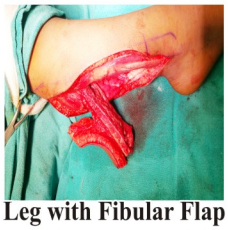
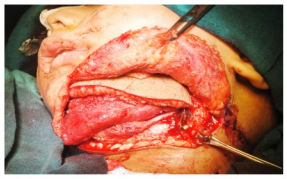

MRI Showing Tumor Left Side of Mandible

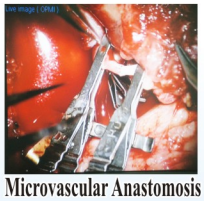
The surgical oncology team assessed him for feasibility of excision of more than half of the mandible. Radiation therapy as an alternative modality of treatment would result in long term side effects like growth disturbance and facial asymmetry. The parents opted for surgery. The biggest challenge was faced by the plastic and reconstructive surgeons who planned for a free fibular flap to reconstruct the mandible in such a small child after surgical removal of the tumor. Osteocutaneous free fibular flap was dissected with its vascular supply that is peroneal blood vessels. With the help of multiple osteotomies,with accurate measurements and calculations, fibula was given the shape of the part of the mandible removed. Fixation for the fibula was done using resorbable screws and plate to allow for growth potential of the remaining jaw bone. The artery and vein were anastomosed to the facial artery and common facial vein respectively in the neck using operating microscope. As the tumor was crossing the midline to the right side, there was a possibility of the child's tongue fall and blocking his breathing. Hence a tracheostomy was also done.


Mandibular Tumor

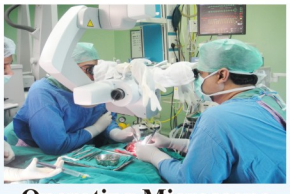

Leg with Fibular Flap

The 7 hours surgery was successfully performed in the last week of December 2016. The child tolerated the surgery well and did not require any blood transfusion during surgery. The team of surgeons from RGCIRC who managed this challenging case were Dr. A. K. Dewan and Dr. Surender Dabas from the Dept of Surgical Oncology, Head & Neck Unit; Dr. Shalini Mishra from the Department of Surgical Oncology, Pediatric Unit; and Dr. Rajan Arora and Dr. Rahul Kapoor from Plastic and Reconstructive Surgery Unit. He was put on ventilator in the Surgical Intensive Care Unit for 48 hours . With meticulous postoperative care he recovered fast and tracheostomy tube was removed on 10th day after surgery. The free flap was healthy and had a good blood supply. He was discharged 2 weeks after surgery, on Ryle's tube feedings. Histopathology showed 100% necrosis (Huvos Grade 4) with negative margins. Hence there was no need for radiation. Cosmetic appearance is excellent. He has been restarted on chemotherapy which will last almost a year. Feeding tube has been removed after one month and the child is able to take soft food by mouth.


Inset of Flap


Microvascular Anastomosis

He will need dental implants on the free fibula flap after 3-6 months and may also need bony corrective surgery (distraction osteotomy) later on in life when he grows up.


Operating Microscope

DISCUSSION:

Ewing's sarcoma is the second most common primary malignant tumor of bones in children and young adults. Its occurrence in the head and neck is rare comprising only 1-4% of all cases. Lesions in the jaw especially pose a distinct surgical challenge owing to the possibility of cosmetic inadequacy and functional impairment. After a thorough search of available English literature, to the best of our knowledge, this is the youngest child for whom a free fibular flap has been successfully performed for malignant disease. The 5 year disease free survival in non-metastatic Ewing's sarcoma is 60%.

Dr. Rajan Arora
Sr. Consultant Cosmetic, Plastic and Reconstructive Surgeon

IMMUNOTHERAPY IN HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS: BEGINNING OF A NEW ERA

Introduction

Head and neck cancer is a complex disease that historically has been associated with high recurrence rates and poor long-term outcomes, highlighting the critical need for new treatment options. No new drugs have been approved for HNSCC since the introduction of cetuximab more than 10 years ago. Squamous cell carcinoma of the head and neck that progresses after platinum-based therapy has a dismal prognosis, and there is no effective standard of care. No treatment has improved survival for this patient population, but this is about to change. Immune checkpoint inhibitors such as pembrolizumab or nivolumab, which target the interaction between programmed death receptor 1/programmed death ligand 1 (PD-1/PDL-1) and PDL-2, have been recently approved for the treatment of head and neck squamous cell carcinoma (HNSCC). Data available indicate substantial activity accompanied by a favourable safety and toxicity profile in this patient population.

Molecular Background

Immunosurveillance, i.e., the recognition and elimination of malignant cells by the immune system constantly occurs in humans. Immunoediting is a dynamic process consisting of tumor elimination, equilibrium, and tumor escape . Tumor elimination represents the successful eradication of the evolving tumor by the immune system. However, if the tumor is not completely destroyed, tumor cells might enter an equilibrium state, where the immune system controls tumor outgrowth . In recent years the introduction of immune checkpoint inhibitors for therapeutic purposes has revolutionized cancer treatment. T cell regulation, i.e., activation or inhibition is mediated via co-stimulatory or co-inhibitory signals. This interaction is exerted via ligand/receptor interaction. Hijacking these pathways by tumor cells contributes to their successful immune escape. For HNSCC tumors it has been reported that 45–80% express programmed death ligand 1 (PDL-1). In addition, exposure of HNSCC cells to therapy can result in tumor PDL-1 upregulation: It has been observed that HNSCC patients have elevated PDL-1 expression compared to healthy controls and that chemotherapy and radiation causes an PDL-1 upregulation in HNSCC patients.

Approved Molecules

Nivolumab (Opdivo), an anti–PDL-1 (programmed cell death protein 1) checkpoint inhibitor, improved survival in patients with squamous cell carcinoma of the head and neck who progressed within 6 months of platinum therapy as part of the initial treatment for recurrent or metastatic disease, according to the interim results of the phase III CheckMate-141 trial[1] reported at the 2016 Annual Meeting of the American Association for Cancer Research (AACR). Patients with squamous cell carcinoma of the head and neck that progresses after platinum-based therapy have an average survival of less than 6 months. In CheckMate-141, nivolumab reduced the risk of death by 30% compared with standard therapy using investigator's choice (P = .0101). One-year survival was 36% in the nivolumab arm vs 16.6% in the control arm, representing an absolute improvement of 20%. Median overall survival was 7.5 months for nivolumab vs 5.1 months for those assigned to investigator's choice. Patients in all subgroups had a survival benefit with nivolumab.

Overall, PD-L1–positive patients fared better than PD-L1–negative patients, but some PD-L1– negative patients did respond to this therapy, so PD-L1 expression is not a valid predictive marker for response in this population.

Pembrolizumab at 200 mg every 3 weeks was approved by FDA in patients with recurrent or metastatic head and neck quamous cell carcinoma (HNSCC) with disease progression during or after platinum-containing chemotherapy. The FDA granted an accelerated approval for this indication, The accelerated approval was based on results from the Keynote-012 trial[2], which showed an objective response rate (ORR) of 16%, complete response rate of 5%, and responses lasting for 6 months or onger observed in 82% (23/28) of the responding patients. The ORR and duration of response were similar regardless of uman papillomavirus (HPV) status. The ORR seen with pembrolizumab is double that of cetuximab , which is the only targeted therapy for these patients, The ORR with pembrolizumab was 27.2% in the 81 HPV-negative patients and 20.6% in the 34 HPV-positive patients. This is notable because there appears to be less efficacy with epidermal growth factor receptor inhibitors, such as cetuximab, in HPV-positive head and neck cancers

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Future

HNSCC responding to immunotherapy is the new ray of hope for these patients, and there are many ongoing research efforts to further enhance the effects of immunotherapy,. Current studies in HNSCC include those to discover and validate biomarkers that identify which patients are most likely to respond to checkpoint inhibition and how to best combine these agents with other therapies. With two approved molecules and multiple ones in pipeline, the prognosis of HNSCC patients is sure to change for better.

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2. Siewert et alLancet Oncol. 2016 Jul;17(7):956-65. doi: 10.1016/S1470-2045(16)30066-3. Epub 2016 May 27

Dr Mohit Agarwal
Consultant - Medical Oncology

ANNUAL CONVENTION OF IMA SOUTH DELHI

RGCIRC, Niti Bagh participated in 37th Annual Convention of IMA South Delhi on Sunday, 8th January 2017 at Hotel Eros, Nehru Place, New Delhi. Dr. Gauri Kapoor, Medical Director – RGCIRC, South Delhi Centre & Director Paediatric Haemato Oncology delivered a lecture on Approach to Child with Cervical Lymphnodes, Dr. Leena Dadhwal, Consultant - Surgical Oncology, RGCIRC delivered a lecture on When to Suspect a Cancer and Dr. Sajjan Rajpurohit, Consultant - Medical Oncology, RGCIRC spoke on Recent Advances in the Management of Cancer. The talks were well appreciated by doctors from South Delhi.


Architect's Impression of RGCIRC (post expansion)

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