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You say the sooner the better, when you think something should be done as soon as possible. It holds true not only for early detection of cancer to improve survivorship, it also holds true for starting palliative care in cancer patients, which can improve Quality of Life (QoL) of patients!

Model of palliative care delivery has been evolved in last couple of decades. The earlier concept of palliative care towards the end of active or curative treatment has been replaced by more practical model of integrating palliative care right at the diagnosis of life limiting illnesses. The disease focused care and comfort focus care, covered under umbrella of psycho-social and spiritual care has better outcome. The World Health Organization (WHO) and American society of clinical oncology have recommended early integration of specialist palliative care in patients with cancer.

Improved Quality of Life

As per WHO definition palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. This definitely shows the importance of early reference and intervention of palliative care, aimed at improving QoL of patients and caregivers.

Palliative care improves Health Related Quality of Life (HRQOL) of cancer patients. HRQOL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning. It goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life. In adult oncology, there is evidence to suggest early specialist palliative care improves HRQOL, mood, treatment decision making, health care utilization, advanced care planning, patient satisfaction, and end-of-life care.

A very important RCT by Zimmermann et al. of early palliative care for patients with advanced cancer shows favorable outcome of patients at the end of four months of intervention with palliative care. This study suggests that early palliative care might improve QoL and increase satisfaction with their care for patients with a large range of advanced solid tumor malignancies.

Early involvement of specialized palliative care is becoming a quality standard for patients with cancer but it is currently underutilized. When a person is suffering from life limiting illness, he or she has many physical, psychological, social, spiritual and financial issues. These issues are at their pick when the end is nearer. Palliative care is specialty care in which all these issues are given attention by multidisciplinary team of physician, psychologist, nurse, social worker, and may be spiritual expert. Early reference to this team helps patient and caregiver to address these issues, gives them enough time to seek for a solution, and helps them to cope up with the situation.

A qualitative study by Yoong et al. shows early palliative care clinic visits emphasize managing symptoms, strengthening coping, and cultivating illness understanding and prognostic awareness in a responsive and time-sensitive model. A similar study on newly diagnosed incurable lung or non-colorectal GI cancer to receive either early integrated palliative care and oncology care or usual care concluded that for patients with newly diagnosed incurable cancers; early integrated palliative care improved QoL and other salient outcomes, with differential effects by cancer type. Early integrated PC may be most effective if targeted to the specific needs of each patient population. (Figure. 1)

Improved survival

Palliative care is holistic care given to patient and family members. Early diagnosis of symptoms, in-depth assessment of pain and its etiology, providing this care with understanding of disease and other psychosocial and spiritual issues, helps patients to leave longer. Palliative care has effect on improved survival of patients.

In a well-designed study of Temel et al. on “early palliative care for patients with metastatic non–small-cell lung cancer”, total 151 patients were randomly
allocated to two groups. One group received standard oncologic treatment and another group received standard oncologic treatment integrated with palliative care. Findings in palliative care group showed median survival 2.7 months longer, there was improved QoL and mood of patients and they received less aggressive end-of-life care, but survived longer.

Research has demonstrated that palliative care is associated with better QoL and mood, improved symptom control, more appropriate health resource use, increased patient and caregiver satisfaction, health care savings, and possibly even survival. 1

Palliative care and chemotherapy
All prolonged illness requires to be treated with various therapeutic approaches. In cancer patients it can be chemotherapy or radiation therapy or surgery. It is very much essential that patient adhere to these treatments and comply with various drug regimens. Early palliative care helps patients and caregiver understand the importance of these therapies by better understanding of disease. It addresses the side effects and helps them to adhere to treatment protocols, which may improve survival. One plausible hypothesis for this survival benefit is that early palliative care enhances the management of adverse effects and complications from treatment, allowing patients to receive more regimens of chemotherapy. 10

Similarly it also helps to discontinue chemotherapy when it doesn’t work. In addition, the integrated model of care may facilitate the cessation of anticancertherapy at the end of life for patients who could suffer adverse outcomes from aggressive treatment.

Palliative care reduces healthcare cost
Impact of palliative care on financial aspect of treatment has been addressed by many studies in cancer patients. Early palliative care in oncology patients reduces overall cost of treatment. Palliative care is known for its “Low Tech, High Care” approach. The cost of care towards end of life is highest. Many of our patients leave against medical advice from ICU because of lack of finances. Early intervention of palliative care will prepare patient and family for the inevitable end of life, decrease emergency ICU admissions and emotional stress to caregivers. Smith et al. 11 studied the impact of the palliative care unit on the cost of care. The results showed that, daily charges were 59% lower, direct costs was 56% lower, and total costs was 57% lower in patients receiving palliative care.

Similarly, outpatient palliative care services have been estimated to reduce overall treatment costs for seriously ill patients by up to 33% per patient. 12 Early outpatient palliative care achieves these savings by decreasing the need for acute care services, leading to fewer hospital admissions and emergency department visits. 13 The site of death may be another mediator of savings, because patients receiving early specialized palliative care are more likely to forgo costly inpatient than other patients at the end of life. 14

Earlier integration of palliative care in oncology patients, not only improves QoL, but it has impact on survival and reduction in cost of treatment.

References:
Cancer immunotherapy has recently achieved remarkable success in treating late stage tumors but a substantial fraction of patients failed to respond. A detailed understanding of how cellular and molecular interactions within the tumor micro environment sculpt the activities of innate and antigen specific immune cells is therefore important. Tumor-infiltrating lymphocytes are key mediators of tumor immune surveillance and are important prognostic indicators in cancer progression. Among the various lymphocyte subsets implicated in protection against cancer are γδ T lymphocytes, which can kill tumor cells and secrete potent antitumor cytokines. By contrast, recent reports from our lab have revealed an unexpected series of protumor functions for these cells. Gall bladder cancer (GBC) is the most common malignancy of the biliary tract. 70-80% of GBC patients are associated with inflammatory condition of cholelithiasis. The tumor environment in GBC complements chronic inflammation and may modulate immune surveillance. The immune microenvironment in GBC is not well investigated. The present study aimed at understanding the dynamics and functions of proinflammatory (Th17, Tγδ17, Tc17) and anti-inflammatory (Regulatory T cells; Tregs) immune cells in GBC. Our data unravelled novel protumorigenic functions of Tγδ17 cells in GBC, opening new avenues for targeted therapies.
Ablation uses extreme micro-environmental conditions to destroy tumor cells and alleviate patient symptoms. Ablative therapies include chemical (ethanol, acetic acid), thermal (RFA, HIFU, microwave, LASER, cryoablation) and non-chemical and non-thermal methods (Irreversible electroporation, light-activated drug therapy). Ablation procedures are minimally invasive treatments in which a thin, needle-like probe is inserted through the skin into the tumor. This probe comes in direct contact with the lesion and kills tumor cells through disruption of the membranes. The access can be obtained by means of various guidance modalities like ultrasound, CT or MRI.

Radiofrequency ablation (RFA) is the most commonly used method which uses high frequency alternating current for cellular heating. It is widely used for treating liver tumors (HCC, metastases), renal cell carcinoma, osteoid osteoma, etc (Figure 1). Microwaves achieve similar results by heating achieved by electromagnetic waves with a frequency >900kHz. It can be employed for all indications in which RFA is being used. Cryoablation uses probe cooled with argon or liquid nitrogen placed into the tumor. Cyclical repetition of freezing and thawing results in ice ball formation in the target tissue resulting in cell destruction through ice crystal formation, cellular dehydration and protein denaturation.

High Intensity Focused ultrasound (HIFU) delivers mechanical energy to target volume resulting in local heat-induced tissue necrosis.

Irreversible electroporation (IRE) is one of the latest technique in the ablative armamentarium. It Increases cell membrane permeability by changing transmembrane potential and subsequently disrupting the lipid bilayer integrity. This allows transportation of molecules across the cell membrane via nanosize pores and results in tissue death in micro to milliseconds (Figure 2).

The benefits of these treatments include their minimally invasive nature, less morbidity, excellent pain relief, shorter hospital stay and possibility of repetition, if new lesions develop over time. These can also be used in conjunction with other cancer treatments.
A Preliminary Study Evaluating IKAROS Protein Expression and IKZF1 mRNA Transcripts in B-Cell Acute Lymphoblastic Leukemia

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Summary
IKAROS, a zinc finger transcription factor protein encoded by the IKZF1 gene is crucial for hematopoiesis in humans. Loss of function mutations in IKZF1 have been implicated in adult and pediatric B cell Acute Lymphoblastic Leukemia (B-ALL). Our aim is to evaluate the incidence of IKAROS protein expression and IKZF1 mRNA transcripts in B-ALL patients. IKAROS protein expression was evaluated in total 34 patients diagnosed as de-novo B-ALL using flow cytometry and IKZF1 mRNA Transcripts were detected using reverse transcriptase - polymerase chain reaction (RT-PCR) method in 13 patients. The expression levels of the IKAROS protein and IKZF1 isoforms were analysed and correlated with clinical and hematological parameters. B-ALL patients with presence of only IK-6 isoform were associated with high WBC count, blast count (>85%) as well as progenitor cell markers CD34 and Tdt positivity. Also there was a significant correlation of low hemoglobin and CD19 positivity with IKAROS protein over expression. In one of the patient we found only 99% of IKAROS protein, having two dominant negative isoforms IK-4 and IK-6 with absence of normal isoforms, which might suggest disease aggressiveness. However, IKAROS protein evaluation by flow cytometry method should be correlated with IKZF1 isoforms in more number of B-ALL patients so that the clinical relevance of IKAROS protein could be established. Correlation with conventional prognostic markers suggests that the patients showing the presence of IK-6 isoform can be considered as high risk patients.

Keywords: B-ALL, IKAROS, IKZF1 isoforms

Introduction
Alterations of the transcriptional regulation of lymphoid development is a hallmark of B cell Acute Lymphoblastic Leukemia (B-ALL), with deletion, sequence mutations, or rearrangements of the transcription factors PAX5, IKZF1, and EBF1 present in more than two-thirds of patients. Relatively few of the novel genetic alterations have been found to be reproducibly associated with outcome, with the notable exception of alterations of the lymphoid transcription factor gene IKZF1 (IKAROS) in B-ALL which is associated with a high risk of treatment failure in B-ALL.

IKZF1 encodes IKAROS, the founding member of a family of zinc finger transcription factors that is required for the development of all lymphoid lineages. Loss of function mutations in IKZF1, the gene encoding IKAROS, have been implicated in adult and pediatric B-ALL. These mutations result in haploinsufficiency of the IKAROS gene in approximately half of the cases. The remaining cases contain more severe or compound mutations that lead to the generation of dominant-negative proteins or complete loss of function. All IKZF1 mutations are associated with a poor prognosis.

The IKAROS protein expression has been studied by western blot or immunofluorescence but not by flow cytometry. The present study was aimed to analyze the protein expression by flow cytometry in B-ALL patients and correlate it with the clinical and hematological parameters. Further, IKAROS isoforms were also analyzed in the same B-ALL patients. The study was intended to evaluate the clinical significance of IKAROS protein as well as isoforms in B-ALL patients.

Flow Cytometry analysis
Bone marrow (BM) or peripheral blood (PB) samples were used for Flow Cytometry study. The number of cells were quantified and adjusted 1x10⁶ in each tube. The intracellular IKAROS protein expression was analyzed using phycoerythrin (PE) conjugated anti-IKAROS monoclonal antibody (R32-1149). The peridinin-chlorophyll protein (PerCp)-conjugated CD45 monoclonal antibody was added to each tube for gating lymphoblasts. The surface and intracellular antigens related to leukemia associated phenotype (LAP) were analyzed using reagents procured from BD Bioscience (San Jose, CA, USA) and the manufacture’s protocol was followed. For lineage assignment the following combination of monoclonal antibodies were used as the primary panel: CD22/CD34/CD45/CD5/CD10/CD19, CD7/CD13/CD45/CD33/CD117/HLADR and MPO/CD79a/CD45/CDS/Tdt. The negative controls for surface and cytoplasmic antigens were simultaneously stained with omission of antibodies except CD45 to gate lymphoblast cells.

To study the intracellular IKAROS expression, 2 mL lysing solution (1:10 dilution, BD Biosciences) was added to 1 x 10⁶ mononuclear cells (100 µL) and incubated for 15 min. Then samples were centrifuged at 400 g for 5 minutes. The supernatant was discarded and 1 mL Perm/Wash buffer (1:10 dilution, BD Biosciences) was added followed by 20 minutes incubation. The samples were centrifuged at 400 g for 5 minutes and the supernatant was discarded. Antibodies [10 µl (CD45) and 5 µl (IKAROS)] were added to the pellet and incubated for 15 minutes. Two washes of 2 mL PBS...
were given with centrifugation at 400 g for 5 minutes and supernatant was discarded. The pellet was resuspended in 500 µl PBS.

**Data acquisition and analysis**

A FACSCanto II flow cytometer with FACSDiva software (BD Biosciences) was used for the acquisition and analysis of the samples. At least 30,000 events /tube were acquired. For analysis, lymphoblasts were gated on dot plot of side scatter vs. CD45 PerCp. If the percentage of positive events was more than 20%, the leukemic samples was considered to be positive for that surface or intracellular marker.

**Isoform analysis**

IKZF1 isoforms were analyzed by RNA extraction followed by cDNA synthesis and polymerase chain reaction (PCR). RNA was extracted from fresh BM or PB samples using QIAamp RNA mini kit (Qiagen, Germany) according to manufacturer’s protocol. cDNA synthesis was done using first strand cDNA synthesis kit (Fermentas, Canada). The procedure was divided in two steps. In step 1, approximately 3 µg was used as starting sample with addition of 1 µl oligo (dT)$_n$ primer and nuclease free water to make the volume upto 11 µl. Centrifuged briefly and incubated at 65°C for 5 minutes. Spinned down and chilled on ice. In step 2, 4 µl (5X) reaction buffer, 1 µl ribolock RNase inhibitor, 2 µl 10 mM dNTP were mixed and 2 µl M-MuLV RT was added in sequence to the mix from step 1. The final volume in each tube was made upto 20 µl. Mixed and centrifuged. cDNA synthesis was carried out in Mastercycler gradient (Eppendorf, Germany) with conditions consisting of 37°C for 60 minutes followed by 70°C for 5 minutes and holding at 4°C for 5 minutes. cDNA was amplified by PCR using IKZF1specific primer sets [exon 2 forward (F) 5’-CACATAACCTGAGGACCATG – 3’ and exon 8 reverse (R) 5’– AGGGCTTTAGCTCATGTGGA – 3’] (Sigma, India). Approximately 100 ng of cDNA was added to PCR mix containing 5 µl (10X) PCR buffer, 10 µl (5X) Q solution, 2 µl 25 mM MgCl2, 1.5 µl dNTP (10mM each) and 0.5 µl Taq DNA polymerase of PCR core kit (Qiagen, Germany) and 5 µl (0.8 µM final concentration) each of forward as well as reverse primers, to make a final volume of 50 µl. PCR was carried out with conditions consisting of initial denaturation step at 95°C for 2 minutes followed by 40 cycles each of denaturation at 95°C for 30 seconds, annealing at 56.6°C for 1 minute and extension at 72°C for 1 minute and final extension step at 72°C for 10 minutes. Amplified products were resolved on 2% agarose gels stained with ethidium bromide and visualized on Gel Documentation System (Alpha Innotech Corp., USA). The IKAROS isoforms obtained were IK1 at 1400 bp, IK2 at 1200 bp, IK4 at 1050 bp and IK6 at 900 bp.

**Statistical analysis**

Statistical analysis was carried out using SPSS statistical software version 19 (SPSS Inc., USA). Mean, standard error (SE) of mean and median were calculated and Pearson’s Chi-square test with Pearson’s correlation coefficient (r) was used to assess correlation and significance between the two parameters. In case of patient number less than 5 in the cells of 2 x 2 tables, Yates’ continuity correction value along with its significance was taken into consideration. P values ≤0.05 were considered significant.

**Results**

IKAROS protein was evaluated in 34 de novo B-ALL patients. Of these patients, 13 patients were further evaluated for IKZF1 mRNA transcripts. The IKAROS parameters were further correlated with clinical parameters, hematological parameters and LAP.

**IKAROS Protein in B-ALL Incidence :** IKAROS protein expression was evaluated in 34 de novo B-ALL patients and 8 healthy controls. The IKAROS protein expression ranged from 9 to 99% in blasts of B-ALL patients while it ranged from 97 to 100% in normal lymphocytes of healthy control. In 34 de novo B-ALL patients, 85% (29/34) of patients had IKAROS protein levels lower than 97% while only 6% (02/34) of patients had protein levels lower than 20% (Figure 1). Thereafter, mean ± standard error of mean for IKAROS protein expression obtained was 78.26 ± 4.014 and median was 86. For statistical correlation, IKAROS protein expression was sub grouped into high and low groups keeping mean as cutoff (Table 1).

**Correlation of IKAROS Protein with Clinical Parameters**

With clinical parameters, a trend of high incidence of decreased IKAROS protein was noted in pediatric group (<15 years, 39%, 07/18) as compared to adult group (≥15 years; 19%, 03/16) and in female patients (45%, 05/11) as compared to male patients (22%, 05/23) (Table 1).
Table 1: Correlation of IKAROS Protein and Isoforms with Clinical and Hematological Parameters

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>Total Patients</th>
<th>IKAROS protein expression (mean) [N(%)]</th>
<th>Total Patients</th>
<th>IK-Isosforms [N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Low (&lt;78%)</td>
<td>N (%)</td>
<td>Ik-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High (≥78%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (100)</td>
<td>10 (29)</td>
<td>24 (71)</td>
<td>12 (100)</td>
</tr>
</tbody>
</table>

### Clinical Parameters

<table>
<thead>
<tr>
<th>Age</th>
<th>N (%)</th>
<th>Low (&lt;78%)</th>
<th>High (≥78%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric (&lt;15 years)</td>
<td>18 (53)</td>
<td>07 (39)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Adult (≥15 years)</td>
<td>16 (47)</td>
<td>03 (19)</td>
<td>13 (81)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.83, p = 0.36, r = 0.22 \]

<table>
<thead>
<tr>
<th>Gender</th>
<th>N (%)</th>
<th>Low (&lt;78%)</th>
<th>High (≥78%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (68)</td>
<td>05 (22)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (32)</td>
<td>05 (45)</td>
<td>06 (55)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 2.02, p = 0.16, r = -0.24 \]

### Hematological Parameters

<table>
<thead>
<tr>
<th>Blast (Median = 85%)</th>
<th>N=31</th>
<th>09 (29)</th>
<th>22 (71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest through 84 %</td>
<td>15 (44)</td>
<td>03 (20)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>85% Through Highest</td>
<td>19 (56)</td>
<td>07 (37)</td>
<td>12 (63)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.48, p = 0.49, r = -0.18 \]

<table>
<thead>
<tr>
<th>WBC Count</th>
<th>N=11</th>
<th>04 (36)</th>
<th>07 (64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.9 x 10^7/µL</td>
<td>06 (19)</td>
<td>02 (33)</td>
<td>04 (67)</td>
</tr>
<tr>
<td>4-11 x 10^7/µL</td>
<td>03 (10)</td>
<td>01 (33)</td>
<td>02 (67)</td>
</tr>
<tr>
<td>&gt;11 x 10^7/µL</td>
<td>22 (71)</td>
<td>06 (27)</td>
<td>16 (73)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.11, p = 0.94, r = 0.06 \]

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8g/dL</td>
<td>19 (61)</td>
<td>07 (37)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>&gt; 8g/dL</td>
<td>12 (39)</td>
<td>02 (17)</td>
<td>10 (83)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.64, p = 0.42, r = 0.21 \]

<table>
<thead>
<tr>
<th>Platelet Count</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5 x 10^11/µL</td>
<td>30 (97)</td>
<td>09 (30)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>1.5 - 4.5 x 10^11/µL</td>
<td>01 (03)</td>
<td>00 (00)</td>
<td>01 (100)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.00, p = 1.00, r = 0.12 \]

<table>
<thead>
<tr>
<th>RBC count</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.8 x 10^12/µL</td>
<td>24 (77)</td>
<td>07 (29)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>3.8 – 4.8 x 10^12/µL</td>
<td>05 (16)</td>
<td>01 (20)</td>
<td>04 (80)</td>
</tr>
<tr>
<td>&gt;4.8 x 10^12/µL</td>
<td>02 (07)</td>
<td>01 (50)</td>
<td>01 (50)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.62, p = 0.73, r = -0.05 \]

<table>
<thead>
<tr>
<th>Myeloid: Erythroid Ratio</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(2:1 - 4:1) Normal</td>
<td>00 (00)</td>
<td>00 (00)</td>
<td>00 (00)</td>
</tr>
<tr>
<td>Altered</td>
<td>31 (100)</td>
<td>09 (29)</td>
<td>22 (71)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.23, p = 0.63, r = 0.41 \]

<table>
<thead>
<tr>
<th>Philadelphia chromosome (Ph)</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>26 (79)</td>
<td>08 (31)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>Positive</td>
<td>07 (21)</td>
<td>02 (29)</td>
<td>05 (71)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.000, p = 1.00, r = 0.02 \]

\[ \chi^2 = 0.006, p = 0.94, r = 0.29 \]

p value ≤ 0.05 is significant, a= Yates continuity correction for cell volume <5
Correlation of IKAROS Protein with Hematological Parameters

In case of hematological parameters, data of WBC count, hemoglobin levels, platelet counts, RBC counts and Myeloid:Erythroid (M:E) ratio at diagnosis for 3 patients was not available in their respective medical records. Hence, statistical correlation for these parameters was done in 31 patients only. The incidence of decreased IKAROS protein tended to be higher in high blast count (≥85%; 37%, 07/19) as compared to low blast (<84%; 20%, 03/15) and in low hemoglobin level (<8g/dL; 37%, 07/19) as compared to high hemoglobin level (≥8g/dL;17%, 02/12). All the patients with decreased IKAROS protein had platelet count (<1.5x10^11/µL; 30%, 09/30) and altered M:E ratio (29%, 09/31). No significant correlation was noted within the subgroups of WBC count (<3.9x10^9/µL; 33%, 02/06) (4-11x10^9/µL; 33%, 01/03) (>11x10^9/µL; 27%, 06/22)], RBC count [(<3.8x10^12/µL; 29%, 07/24) (3.8-4.8x10^12/µL; 20%, 01/05) (>4.8x10^12/µL; 50%, 01/02)] (Table 1).

Correlation of IKAROS Protein with Philadelphia (Ph) Chromosome

Data related to Ph chromosome was available for 33 patients. The incidence of decreased IKAROS protein was similar in the subgroups of Ph chromosome [negative (31%, 08/26); positive (29%, 02/07) (Table 1).

Correlation of IKAROS Protein with B-ALL Subtypes

The incidence of decreased IKAROS protein was similar in the B-ALL subtypes [Pro B (33%, 01/03); Pre Pre B (28%, 05/18); Pre B (33%, 04/12)]. One patient with Burkitt’s ALL did not show decreased IKAROS protein (0/01) (Table 2).

Correlation of IKAROS Protein with LAP

IKAROS protein was correlated with CD34, a progenitor cell marker, where incidence of decreased IKAROS protein was similar in subgroups of CD34 [negative (25%, 04/16); positive (33%, 06/18)] (Table 2).

Correlating with B cell Markers

Further, IKAROS protein expression was correlated with B cell markers (CD19, CD22, and CD79a). A trend of high incidence of decreased IKAROS protein was noted in CD19 negative (67%, 02/03) as compared to CD19 positive patients (26%, 08/31) and in CD79a negative (50%, 01/02) as compared to CD79a positive patients (28%, 09/32). No significant difference was noted in the subgroups of CD22 [negative (25%, 04/16); positive (33%, 06/18)] (Table 2).

Correlating with Non-Lineage Markers

With non-lineage markers (TdT, HLA-DR and CD10), a trend of high incidence of decreased IKAROS protein was noted in TdT positive (31%, 09/29) as compared to TdT negative patients (20%, 01/05). No significant difference was noted in the subgroups of HLA-DR [negative (33%, 01/03), positive (29%, 09/31)] and CD10 [negative (25%, 01/04), positive (30%, 09/30)] (Table 2).

Correlating with Aberrant Myeloid and T cell Markers

IKAROS protein was then correlated with the aberrant marker expression of myeloid lineage (CD13, CD33, CD117 and MPO). CD13 and CD33 were aberrantly expressed in 07 and 06 patients, respectively. However, no significant correlation was noted in subgroups of CD13 [negative (30%, 08/27); positive (29%, 02/07)] while the incidence of decreased IKAROS protein was higher in aberrantly expressed CD33 (50%, 03/06) as compared to CD33 negative patients (25%, 07/28) (Table 2).

Similarly, IKAROS protein was then correlated with the aberrant marker expression of T cell lineage (CD3, CD5 and CD7). CD5 was aberrantly expressed in 01 patient where decreased IKAROS protein was noted (100%, 01/01) (Table 2).

IKZF1 mRNA Transcript in B-ALL

Incidence

IKZF1/IKAROS mRNA transcript expression was evaluated in 13 B-ALL patients. These patients showed mRNA expression with different isoforms. Four different IKZF1 isoforms were identified and they were IK1, IK2, IK4 and IK6 (Figure 2).

IKZF1 Isoforms

The predominately observed IKZF1 isoform was IK-6. All four isoforms (IK-1, IK-2, IK-4 and IK-6) were noted in 05 (38%) patients. Single IK-6 isoform was noted in 04 (31%) patients. IK-6 isoform in combination of IK-1, IK-2 or IK-4 isoforms was noted in 03 (23%) patients while single IK-2 isoform was noted in 01 (08%) patient (Table 3).

For statistical analysis, the patient with single IK-2 isoform was not taken into consideration. Therefore the total of 12 patients was then divided into two isoform groups: first group of patients had single IK-6 isoform while second group of patients had either all or combination of different isoforms (Table 3).
Table 2: Correlation of IKAROS Protein and Isoforms with B-ALL Subtypes and LAP

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>Total Patients</th>
<th>IKAROS protein expression (mean[N(%)])</th>
<th>Total Patients</th>
<th>IK-Isosforms [N (%)]</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Low (&lt;78%)</td>
<td>High (≥78%)</td>
<td>N (%)</td>
<td>IK-6</td>
</tr>
<tr>
<td>B ALL Subtypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pro B ALL</td>
<td>34 (100)</td>
<td>10 (29)</td>
<td>24 (71)</td>
<td>12 (100)</td>
<td>04 (30)</td>
</tr>
<tr>
<td>Pre Pre B ALL</td>
<td>18 (53)</td>
<td>05 (28)</td>
<td>13 (72)</td>
<td>09 (75)</td>
<td>02 (22)</td>
</tr>
<tr>
<td>Pre B ALL</td>
<td>12 (35)</td>
<td>04 (33)</td>
<td>08 (67)</td>
<td>02 (17)</td>
<td>01 (50)</td>
</tr>
<tr>
<td>ALL Burkitt</td>
<td>01 (03)</td>
<td>00 (00)</td>
<td>01 (100)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>χ² = 0.55, p = 0.91, r = 0.02</td>
<td></td>
<td>χ² = 2.75, p = 0.25, r = 0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Progenitor cell marker:CD 34 | Negative | 16 (47) | 04 (25) | 12 (75) | 04 (33) | 01 (25) | 03 (75) |
|                            | positive  | 18 (53) | 06 (33) | 12 (67) | 08 (67) | 03 (37) | 05 (63) |
| χ² = 0.02, p = 0.88, r = -0.09 | | χ² = 0.00, p = 1.00, r = -0.12 |

| Leukemia Associated Immunophenotype (LAP) | Progenitor cell marker:CD 34 | Negative | 03 (09) | 02 (67) | 01 (33) | 03 (25) | 00 (00) | 03 (100) |
|                                           | positive  | 31 (91) | 08 (26) | 23 (74) | 09 (75) | 04 (44) | 05 (56) |
| χ² = 0.67, p = 0.41, r = 0.25 | | χ² = 0.30, p = 0.48, r = -0.41 |

| Cell markers | CD 19 | Negative | 16 (47) | 04 (25) | 12 (75) | 04 (33) | 01 (25) | 03 (75) |
|              | positive | 18 (53) | 06 (33) | 12 (67) | 08 (67) | 03 (37) | 05 (63) |
| χ² = 0.02, p = 0.88, r = -0.09 | | χ² = 0.00, p = 1.00, r = -0.12 |

| CD 22 | Negative | 16 (47) | 03 (25) | 12 (75) | 07 (58) | 02 (29) | 05 (71) |
| positive | 18 (53) | 06 (33) | 12 (67) | 05 (42) | 02 (40) | 03 (60) |
| χ² = 0.02, p = 0.88, r = -0.09 | | χ² = 0.00, p = 1.00, r = -0.12 |

| CD 79a | Negative | 02 (06) | 01 (50) | 01 (50) | 01 (08) | 00 (00) | 01 (100) |
| positive | 32 (94) | 09 (28) | 23 (72) | 11 (92) | 04 (36) | 07 (64) |
| χ² = 0.00, p = 1.00, r = 0.11 | | χ² = 0.00, p = 1.00, r = -0.23 |

| Non-lineage markers | TdT | Negative | 05 (15) | 01 (20) | 04 (80) | 01 (08) | 00 (00) | 01 (100) |
|                     | positive | 29 (85) | 09 (31) | 20 (69) | 11 (92) | 04 (36) | 07 (64) |
| χ² = 0.00, p = 1.00, r = -0.09 | | χ² = 0.00, p = 1.00, r = -0.21 |

| CD 19 | Negative | 03 (09) | 01 (33) | 02 (67) | 01 (25) | 00 (00) | 03 (100) |
| positive | 31 (91) | 08 (26) | 23 (74) | 09 (75) | 04 (44) | 05 (56) |
| χ² = 0.67, p = 0.41, r = 0.25 | | χ² = 0.30, p = 0.48, r = -0.41 |

| HLA-DR | Negative | 03 (09) | 01 (33) | 02 (67) | 01 (25) | 00 (00) | 03 (100) |
| positive | 31 (91) | 08 (26) | 23 (74) | 09 (75) | 04 (44) | 05 (56) |
| χ² = 0.00, p = 1.00, r = 0.11 | | χ² = 0.00, p = 1.00, r = -0.23 |

| CD 18 | Negative | 04 (12) | 01 (25) | 03 (75) | 01 (08) | 01 (100) | 00 (00) |
| positive | 30 (88) | 09 (30) | 21 (70) | 11 (92) | 03 (27) | 08 (73) |
| χ² = 0.00, p = 1.00, r = -0.03 | | χ² = 0.14, p = 0.71, r = 0.43 |

| Myeloid markers | CD 13 | Negative | 27 (79) | 08 (30) | 19 (70) | 08 (67) | 02 (25) | 06 (75) |
|                | positive | 07 (21) | 02 (29) | 05 (71) | 04 (33) | 02 (50) | 02 (50) |
| χ² = 0.00, p = 1.00, r = 0.009 | | χ² = 0.04, p = 0.83, r = -0.25 |

| CD 33 | Negative | 28 (82) | 07 (25) | 21 (75) | 10 (83) | 03 (30) | 07 (70) |
| positive | 06 (18) | 03 (50) | 03 (50) | 02 (17) | 01 (50) | 01 (50) |
| χ² = 0.53, p = 0.47, r = -0.21 | | χ² = 0.00, p = 1.00, r = -0.16 |

| CD 117 | Negative | 34 (100) | 10 (29) | 24 (71) | 12 (100) | 04 (33) | 08 (67) |
| positive | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) |
| χ² = 0.00, p = 1.00, r = 0.16 |

| MPO | Negative | 34 (100) | 10 (29) | 24 (71) | 12 (100) | 04 (33) | 08 (67) |
| positive | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) |

| T cell markers | CD 3 | Negative | 34 (100) | 10 (29) | 24 (71) | 12 (100) | 04 (33) | 08 (67) |
|               | positive | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) |
| χ² = 0.21, p = 0.65, r = -0.27 |

| CD 7 | Negative | 34 (100) | 10 (29) | 24 (71) | 12 (100) | 04 (33) | 08 (67) |
| positive | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) | 00 (00) |
| χ² = 0.00, p = 1.00, r = 0.21 |

p value ≤ 0.05 is significant, a= Yates continuity correction for cell volume <5
Correlation of IKZF1 Isoforms with B-ALL Subtypes

In relation to B-ALL subtypes, Pre Pre B ALL showed higher incidence of combined isoforms (78%, 07/09) than IK-6 isoform (22%, 02/09). One patient having Pro B ALL showed IK-6 isform while two patients having Pre B ALL showed similar incidences of IK-6 isoform (50%, 01/02) and combined isoforms (50%, 01/02) (Table 2).

Correlation of IKZF1 Isoforms with LAP

IKZF1 isoforms were correlated with CD34, a progenitor cell marker, and CD34 positive patients showed high incidence of combined isoforms (63%, 05/08) as compared to IK-6 isoform (37%, 03/08) (Table 2).

Correlating with B cell Markers

Further, IKZF1 isoforms were correlated with B cell markers (CD19, CD22, and CD79a). Incidence of combined isoforms was higher in CD19 positive (56%, 05/09), CD79a positive (64%, 07/11) and CD22 positive patients (60%, 03/05) as compared to IK-6 isoform (50%, 01/02) (Table 2).

Correlation of IKZF1 Isoforms with Clinical Parameters

In relation to clinical parameters, IKZF1 isoforms were correlated with age and gender. The pediatric patients (<15 years) showed a trend of high incidence of combined isoform (86%, 06/07) as compared to IK-6 isoform (14%, 01/07) while adult patients (≥15 years) showed a trend of high incidence of IK-6 isoform (60%, 03/05) as compared to combined isoform (40%, 02/05). However, in case of gender, incidences of combined isoforms in both male (67%, 06/09) and female patients (67%, 02/03) were higher than IK-6 isoform in male (33%, 03/09) and female patients (33%, 01/03) (Table 1).

Correlation of IKZF1 Isoforms with Hematological Parameters

In case of hematological parameters, data of WBC count, hemoglobin levels, platelet counts, RBC counts and Myeloid:Erythroid (M:E) ratio at diagnosis for 1 patient was not available in the respective medical record. Hence, statistical correlation for these parameters was done in 11 patients. The incidence of combined isoform (71%, 05/07) was higher in high blast count (≥85%) as compared to IK-6 isoform (29%, 02/07). Similarly, combined isoform (56%, 05/09) was higher in low platelet count as compared to IK-6 isoform (44%, 04/09). However, the incidence of IK-6 isoform was higher in high WBC count (57%, 04/07) as compared to combined isoforms (43%, 03/07). Low hemoglobin and low RBC count both showed similar incidences of combined isoforms (50%, 04/08) and IK-6 isoform (50%, 04/08). All patients had altered M:E ratio where incidence of combined isoforms (64%, 07/11) was higher than IK-6 isoform (36%, 04/11) (Table 1).

Correlation of IKZF1 Isoforms with Ph chromosome

Data related to Ph chromosome was available for 11 patients. The Ph- patients showed high incidence of combined isoforms (67%, 06/09) as compared to IK-6 isoform (33%, 03/09) while two Ph+ patients showed combined isoforms (100%, 02/02) (Table 1).

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expressed in 01 patient in whom combined isoforms were present (100%, 01/01) (Table 2).

Correlation of IKAROS Protein with the Subgroups of IKZF1 Isoforms

In relation with IKZF1 isoform subgroups, the incidence of decreased IKAROS protein tended to be higher in IK-6 (50%, 02/04) as compared to combined isoforms (37%, 03/08) (Table 4).

Discussion

IKZF1 gene encoding IKAROS protein, the member of a family of zinc finger transcription factors, is required for the development of all lymphoid lineages. The IKZF1 alterations observed in ALL include focal or broad deletions that result in loss of function.1 The present study was designed to evaluate the incidence of IKAROS protein in 34 B-ALL by flowcytometry method. A majority of patients 94% (32/34) showed over expression of IKAROS protein. A previous study found high expression of dominant-negative isoforms of IKAROS with abnormal subcellular compartmentalization patterns while only wild-type Ik-1 and Ik-2 isoforms with normal nuclear localization were noted.7 In present study, the localization of protein was not known hence the patients were further evaluated for IKZF1 isoforms. Out of 34 patients, 13 patients were studied for IKZF1 isoforms by RT–PCR method. The IKAROS parameters were further correlated with clinical parameters, hematological parameters and LAP.

Very few studies have evaluated protein and none by flowcytometric method. The methodology used has been western blot and immunofluorescence or immunohistochemistry to quantitate and observe the subcellular localization, respectively.4 A study that has evaluated IKZF1 isoform/mutations along with protein expression observed that approximately 55% of B-ALL with IKZF1 mutations showed reduced protein levels.5 Also, approximately 33% of IKZF1 mutations lead to IK-6 isoforms and the protein is localized in cytoplasm due to loss of DNA binding domain.7 About 12% of B ALL with IKZF1 mutations has biallelic deletions corresponding to 2 null alleles and that leads to complete absence of IKAROS protein.10

The IKAROS protein subgroups that were based on mean as cutoff were correlated with the clinical parameters, age and gender. In the present study, IKAROS protein was analyzed in 18 pediatric and 16 adult out of 34 B-ALL patients. High incidence of decreased protein was noted in pediatric (39%, 07/18) and in female patients (45%, 05/11) as compared to their respective counterparts. Further, when protein expression was correlated with hematological parameters, high incidence of decreased protein was noted in high blast count (37%, 07/19) and low hemoglobin levels (37%, 07/19) as compared to their respective counterparts. No study till now has shown correlation of IKAROS protein with clinical and hematological parameters. However, data from other studies have established that IKAROS acts as a highly clinically-relevant tumor suppressor in B cell ALL.11 Hence in the present study, decreased IKAROS protein is probably due to the presence of dominant negative isoforms and the low protein level is associated with high blast count and low hemoglobin that are conventional prognostic markers for acute lymphoblastic leukemia.

Further, IKAROS protein was correlated with the leukemia associated immunophenotype, where no significant correlation was noted with immature marker CD34, B-cell markers, non-lineage markers and aberrantly expressed myeloid and T cell markers except a trend of low IKAROS protein associated with CD19 and CD79a negativity. CD19 and CD79a (part of B cell receptor complex) are required for the full activation and maturation of the B cell.7 Since IKAROS plays vital role in early B cell differentiation, the above mentioned correlation suggests clinical significance of low IKAROS protein. Further, the incidence of decreased protein tended to be high in TdT positive patients where TdT is immature progenitor cell marker however, no significant correlation of IKAROS protein was noted with B cell subtypes.

Further to evaluate the presence of IKZF1 isoforms and correlate them with the Ikaros protein over expression, IKZF1 mRNA expression was studied in 13 out of 34 patients. Four different IKZF1 isoforms were identified and they were IK1, IK2, IK4 and IK6. The predominantly observed IKZF1 isoform was IK-6. All four isoforms (IK-1, IK-2, IK-4, and IK-6) were noted in 05 (38%) patients. Single IK-6 isoform was noted in 04 (31%) patients. IK-6 isoform in combination of IK-1, IK-2 or IK-4 isoforms was noted in 03 (23%) patients while single IK-2 isoform was noted in 01 (08%) patient. There are studies that show variable results on the incidence of IKZF1 isoforms. Some of the initial reports have proposed that genomic IKZF1 deletions are the cause of expression of dominant-negative isoforms.10,13 Mullighan et al reported deletions of IKZF1 in 84% of Ph+ B precursor Acute Lymphoblastic Leukemia (BPL), including 76% of pediatric and 91% of adult Ph+ BPL cases.10 The same authors also reported >25% frequency of IKZF1 deletions in Ph-high risk BPL patients.11 In both studies, IKZF1 deletions included homozygous/biallelic as well as heterozygous / monoallelic deletion of the entire gene locus as well as intragenic deletions.10,11 Subsequently, Volejnikova et al (2012) reported discordant results in 206 children with Ph−ALL. In that study, out of 24 patients with over expression of dominant-negative isoforms other than IK6, only one patient had a deletion within the IKZF1 locus and only half of the IK6+ cases were found to have monoallelic IKZF1 deletions. The overall incidence of IKZF1 deletions was only 7% and no patient had homozygous IKZF1 deletions and no patient had evidence of decreased IKAROS protein expression even in the presence of monoallelic IKZF1 deletions.14 In their most recent paper, Palmi et al (2013)
documented no homozygous IKZF1 deletions and heterozygous IKZF1 deletions were detected in only ~13% of their Ph+ BPL patient population. In approximately half of the cases with deletions (7.1%), the deletion involved the entire IKZF1 locus and in the other half a portion of the IKZF1 gene.17 IKZF1 deletions (and sequence mutations) are less common, being present in approximately 15% of childhood ALL cases and are hallmark of high-risk ALL.18

For statistical analysis, the patient with IK-2 isoform was not taken into consideration. The patients were then divided into two isoform groups: first group of patients had only IK-6 isoform while second group of patients had either all or combination of different isoforms. In relation to clinical parameters, IKZF1 isoforms were correlated with age and gender. The IK-6 isoform was higher in adult patients while combined isoforms were higher in pediatric patients. However, the incidences of combined isoforms were similar in both male and female patients but higher as compared to IK-6 isoform. Similar to our results, a study that focused on the expression of dominant negative isoforms found that these isoforms were associated with adult B cell ALL.19 Further, when IKZF1 isoforms were correlated with hematological parameters, a trend of high incidence of IK-6 was noted in high WBC count while combined isoforms were found to be higher in high blast count and low platelet count. Low hemoglobin and low RBC count showed similar incidences of combined isoforms and IK-6 isoform. Similar to our study, Liu et al (2016) showed correlation of IKZF1 deletions with high WBC count. Abnormal WBC count is the major clinical feature of prognostic significance in acute leukemias and therefore association of IK-6 isoform with the abnormal WBC might suggest prognostic significance of the isoform.

Further, IKZF1 isoforms were correlated with the LAP, where no significant correlation was noted with immature marker CD34, B-cell markers, non-lineage markers and aberrantly expressed myeloid and T cell markers. However, combined isoforms tended to be higher in B cell markers CD19, CD79a and CD22. Combined isoforms were also found to be higher in CD34 positive along with TdT and HLADR positive patients. These immature progenitor cell markers are common aberrations with uniform positive expression in lymphoblasts of B-ALL.15

As discussed earlier, IKAROS gene abnormality is very frequent in Ph chromosome-positive ALL (about 80%)20 and therefore associated to poor prognosis. However, in the present study, the incidence of decreased IKAROS protein showed no difference in Ph- and Ph+ patients while combined isoforms were higher in both Ph+ and Ph- patients as compared to IK-6 isoform. Also, conventional RT-PCR method has been used in the present study which might not be sufficient to detect the variants and other intragenic mutations that might be present over and above the common deletions associated with isoforms generated by alternative splicing. IKAROS protein was then correlated to the individual isoforms wherein, no significant correlation was noted. In one of the patient we found only 09% of IKAROS protein expression and having two dominant negative isoforms IK-4 and IK-6 with absence of normal isoforms. Further, IKAROS protein was correlated with the combined isoforms and IK-6 wherein, a trend of high incidence of decreased IKAROS protein was noted in IK-6 isoform as compared to the combined isoforms. However, these findings need to be confirmed on larger patient series.

In conclusion, the present study showed that B-ALL patients with decreased IKAROS protein was associated with high blast count, low hemoglobin and TdT. These being the conventional prognostic markers, the patients showing decreased IKAROS protein can be considered as high risk patients. Also, when IKAROS protein was compared with isoforms, decrease in protein expression was noted in patients having dominant negative isoforms. However, to confirm clinical relevance of IKAROS more number of patients needs to be enrolled.

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Extracorporeal Irradiation in Management of Primary Bone Tumors- An Institutional Experience

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Summary:
Primary bone tumor, which has made limb salvage possible. It consists of en-bloc removal of the tumor bearing bone segment, removal of the tumor from the bone, irradiation and re-implantation of the Extracorporeal Irradiation (ECI) is a relatively newer method of delivering radiation in patients of bone. We report our preliminary experience of using ECI for management of Primary bone tumors at our institute. From year 2014 to 2016, Six patients with primary bone tumor were enrolled. Four patients were of Ewing's sarcoma (ES) and two of Osteosarcoma (OS). The eligibility criteria included histopathological proof of malignancy, no evidence of distant metastases at the time of surgery, and suitability for limb preservation therapy. Surgery was performed about 4 weeks after completion of neoadjuvant chemotherapy. The affected bone segment was resected, irradiated extracorporeally with a dose of 50 Gray and re-implanted. Local control and complications was studied. Out of the six patients treated so far, none of them developed local recurrence at the median follow up of 11 months. One patient developed systemic metastasis and one developed chemotherapy related complications during adjuvant chemotherapy. Results of our study suggest that ECI is technically feasible in the management of Primary bone tumors and provides decent local control with no complications. A larger study with more number of patients and longer follow up is required to draw further conclusions.

Keywords: Extracorporeal irradiation, Limb preservation, Primary bone tumors

Introduction
Primary bone tumors are relatively rare. They are more common in children and adolescents. Surgery followed by local radiation therapy is not sufficient for local control as the bone tumours require relatively higher dose of radiation which is technically challenging to deliver. Hence, amputation was the only option until last two decades. With the advent of modern imaging and surgical techniques, newer chemotherapy drugs, surgical advancements and radiotherapy techniques, the treatment of primary bone tumors has evolved a great deal from amputation to limb salvage. These modern strategies have made limb preservation possible.

Limb salvage is now an established option in primary bone tumours, without compromising local control and disease free survival. The aim of limb preservation is to achieve local control by completely resecting the tumor and to maintain the limb function by performing a reconstruction procedure using either prosthesis or a bone graft. Reconstruction using biological options like autografts, allografts, and bone transport have shown good functional results. A newer idea of re-implanting the patient's own tumor bone after it has been sterilized was conceived in the last decade. The various methods of sterilization reported in the literature are boiling, autoclaving, irradiation, microwave, pasteurization and the use of liquid nitrogen. Extracorporeal irradiation (ECI) and re-implantation is one method of sterilizing the bone. The principle of ECI is, the tumor-bearing bone is excised en-bloc, all soft tissues and macroscopic tumor is removed, the bone segment is irradiated and re-implanted back.

Literature survey indicates very few studies pertaining to ECI and also the number of patients treated by this modality is not high, the results so far are encouraging. Hence, we intend to report our preliminary experience with ECI at our institute.

Methods and Materials
From year 2014 to 2016, 6 patients with primary bone tumour were enrolled. Four patients were of Ewing's sarcoma (ES) and 2 of Osteosarcoma (OS). The eligibility criteria included histopathological proof of malignancy, no evidence of distant metastases at the time of surgery, and suitability for limb preservation which includes no history of pathological fracture and diaphyseal tumor. Consent was obtained from every patient. The initial pre-treatment workup of the patients consisted of clinical examination which was done by the orthopaedic surgeon and the radiation oncologist. All the investigations required for diagnosis, surgical procedures and metastatic work up were done for all the patients which included routine hematological tests like hemogram, liver and kidney function tests, coagulation profile, tumour markers where required. Magnetic resonance imaging (MRI) of the affected limb was done to assess the local extent of disease and X-ray chest and bone scan were performed to rule out distant metastases. Figure 1 shows the MRI of the affected bone. Computed tomography (CT) scan chest and positron emission tomography scan were done if necessary. Bone marrow examination was done for patients of Ewing's sarcoma family of tumors. The treatment approach and sequence of treatment
modalities were decided by the multidisciplinary team of orthopaedic surgeon, radiation oncologist and medical oncologist. The treatment policy contemplated for OS and ES was neoadjuvant chemotherapy (NACT) followed by surgery and further treatment according to pathological findings. The chemotherapy regimens were used as per our institutional protocol. The ES group received the HR protocol and the OS group received platin, adriamycin based regimens along with high dose methotrexate.

**Surgery**

Pre and post chemotherapy imaging was done to assess response to chemotherapy. Surgery was performed about 4 weeks after the completion of NACT. It consisted of en-bloc resection of the tumor and the involved bone (pre-chemotherapy volume) along with soft-tissues. The bone specimen was lavaged with normal saline and wrapped in vancomycin-soaked mops. It was tightly wrapped in wet sterile drape and then sealed in two plastic bags before it was sent for extra-corporeal radiotherapy. Figure 2 shows the resected bone segment and the method by which it is draped and prepared for ECI. The wrapping material was 3.0 cm thick, so that it can act as a bolus for megavoltage radiation. During the ECI, the operative site was prepared for re-implantation, and biopsy was performed at all osteotomy sites to assess the status of resection margins. The resection margins are usually kept at 2 cm all around.

**Technique of ECI**

The sealed bone segment was irradiated on a 6MV linear accelerator. The bone segment was placed on the treatment couch. The wrapped bone segment was surrounded on all sides by water pouches as water acts as tissue equivalent material for megavoltage radiation as shown in Figure 3. The bone segment was irradiated with a single session dose of 50 Gray prescribed at mid plane using 6 MV X-rays. Two parallel opposed Antero posterior-Posteroanterior (AP-PA) fields were used. Radiation field size was chosen which adequately covered the entire bone segment. Figure 4 shows the radiation treatment plan. After the completion of ECI, the sealed package containing the bone was opened in the operation theatre and the bone was re-implanted with fixation device. Figure 5 shows the re-implantation of the irradiated bone and the post treatment MRI of the implanted bone.

**Follow-up**

During the post-operative period, immobilization was advised till the imaging showed the evidence of complete union. Full weight bearing was allowed according to the clinical and radiological progress. Patients were followed-up every three months for one year and then every 6 months in the next 2 years. Plain X-ray and MRI of the local part were performed every 3 months and 6 months respectively. For detecting lung metastases, plain chest X-ray was done on and chest CT scan was done whenever required. Local recurrence free survival (LRFS) was calculated.

**Results**

The patient details and the clinical characteristics are enlisted in Table 1. All patients (6), of primary bone tumors had been treated by ECI at our institute. The median age of the patients was 11 years. There were 4 males and 2 female patients. Four patients had Ewings sarcoma and 2 patients had osteosarcoma which was histopathologically confirmed. The primary site was femur in 4 patients, humerus in one patient and tibia in one patients. In all patients, the radiotherapy dose delivered was 50 Gray. The median follow up period was 11 months (range 3-16 months). No patient had developed local recurrence. One patient developed lung metastasis and subsequently succumbed to brain metastasis with no evidence of local recurrence. The local control rate

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Site</th>
<th>Resected length (cm)</th>
<th>ECI dose (Gray)</th>
<th>Follow up (months)</th>
<th>Local disease status</th>
<th>Distant metastasis</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>F</td>
<td>ES</td>
<td>Femur</td>
<td>16</td>
<td>50</td>
<td>3</td>
<td>CR</td>
<td>Lung and brain</td>
<td>Died due to brain mets</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>OS</td>
<td>Humerus</td>
<td>15</td>
<td>50</td>
<td>9</td>
<td>CR</td>
<td>Nil</td>
<td>Died due to chemotherapy induced neutropenia</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>ES</td>
<td>Femur</td>
<td>14</td>
<td>50</td>
<td>16</td>
<td>CR</td>
<td>Nil</td>
<td>Alive</td>
</tr>
<tr>
<td>09</td>
<td>F</td>
<td>ES</td>
<td>Femur</td>
<td>17</td>
<td>50</td>
<td>15</td>
<td>CR</td>
<td>Nil</td>
<td>Alive</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>OS</td>
<td>Tibia</td>
<td>12</td>
<td>50</td>
<td>13</td>
<td>CR</td>
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<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>ES</td>
<td>Femur</td>
<td>16</td>
<td>50</td>
<td>8</td>
<td>CR</td>
<td>Nil</td>
<td>Alive</td>
</tr>
</tbody>
</table>
was 100% at median follow up 11 months and it needs longer follow up to assess local recurrence rate with 50 Gray radiation dose. Only one patient out of the six, developed systemic failure in the form of lung and brain metastasis after three months of ECI and died due to complications of brain metastasis though the patient had local control.

Peri-operative complication was not observed in any of the patients. All the patients completed their scheduled course of chemotherapy after the surgery. There was no other surgery or ECI related complication in any of the patient.

Discussion
Reconstruction of large defects after tumour resection is challenging in patients who are on chemotherapy as it renders them immunocompromised. Although artificial implants provide the option of immediate weight bearing and mobility, they are expensive and have the risk of wear and tear, physical damage etc. Biological reconstruction provides more durability at lesser cost. Reimplanting the sterilized tumor bone after ECI offers this option for reconstructing these defects.

ECI has a number of advantages which are as follows:
(1) The delivery of very high dose of radiation to tumor bearing bone which is otherwise not possible by conventional techniques
(2) No radiation injury to the un-irradiated bone, muscles, joint, and other healthy tissues of the body.
(3) An anatomically size-matched graft for biological reconstruction.
(4) It is cost effective as compared to the prosthetic devices
(5) It has psychological advantage to the patients as the patient does not have to go either for amputation or for prosthesis.
ECI has few limitations like infection, failure of the graft etc which should be taken care of. Though the infection rate in our case series was not very high, multiple case series have reported infection rate as high as 17%. Infection can result in delay in the subsequent chemotherapy which in turn can lead to systemic failure. Other complications of infection are delayed union/non-union and graft failure.

As most of the studies done so far, have limited number of patients and the malignancies are heterogeneous i.e. OS, ES etc, so a direct comparison cannot be done as these tumours have different biology and they respond differently to chemotherapy and radiotherapy. However, there have been two large studies with 50 patients each, so far which have shown promising results. In a study by Davidson et al in 50 bone tumors patients, mainly ES (21 patients) and OS (16 patients) with mean follow-up period of 38 months, were treated with en bloc resection and ECI of 50 Gray. They observed that 84% patients were disease free and 8% had developed local recurrence. Poffyn et al did a retrospective analysis of 107 patients with malignant bone tumor treated by ECI with 300 Gray, and re-implantation of the bone as an orthotopic autograft. At 5 year follow-up, there was no local recurrence and 64% of patients had well healed graft. The 0% local recurrence rate could be attributed to the very high dose of ECI (300 Gray) used in their study. Hence, it was concluded that a higher radiation dose can provide better local control. In 2013, Sharma et al presented a case series of 14 patients where the radiation dose used was 50 Gray with 73% local recurrence free survival at the end of 2 years. Puri et al reported their experience of treating 12 patients of ES employing ECI dose of 50 Gray. Although, the authors have concluded that ECI dose of 50 Gray avoids graft factures but 50% of the patients died due to disease. This again suggests that a higher dose of ECI needs to be tried in future trials.

As bone tumours are relatively radioresistant, a higher dose may warrant better local control which calls for studies with a higher ECI dose. As ours is a preliminary study, it is difficult to draw conclusions due to small sample size and short follow-up period but it suggests that ECI is technically feasible in our setup and provides optimum local control and short-term survival rates. We suggest that a higher dose of ECI needs to be explored in future trials in order to further improve the local control rates.

References
How often are you faced with a situation where your patient equates you with God while thanking you. In India this situation is not rare. It is an embarrassing situation for most, irritating for some due to the over exaggerated display of emotions but always it is a humbling experience. We thank God for giving us the opportunity to do His work and take credit.

A doctor always believes in God because doctors have the unique opportunity to see innumerable miracles that are going on in human body at every moment. If we read and understand anatomy and physiology of human body, with a different vision, we will realize all the wonderful mechanisms that God has put in our body so that we can survive in a hostile World. The deeper we go from enzyme level to molecular level we have to marvel at the intricate design and functioning of our body.

No doctor is disillusioned by the fact that we cure the patient, we merely provide appropriate physical action while it is God who cures the patients. A surgeon can suture a wound but it is God who heals it. The in-built protective and healing mechanisms of our body are mainly responsible for majority of cures, we just provide conducive environment. Yet! How often do we thank God during our day to day practice?

Patients and their families, on the other hand are greatly benefited by discussion of spirituality, it helps them cope with advanced disease and difficult choices. There is plethora of scholarly articles, research papers and accredited courses dealing with this aspect of doctor patient relationship. Positive effects of spirituality on health and psychological wellbeing have been amply documented.

In many western cultures a discussion about spirituality with the patients and their relatives may be considered as impinging your religious beliefs on the patient when he is most vulnerable hence a discussion on spirituality and faith in God is often avoided. The doctors should be taught how to take spiritual history from a patient, so it can be determined how a person’s religion may affect their medical care.

Various tools can be used for this purpose such as HOPE Questions:  
1. sources of Hope, strength, comfort, meaning, peace, love, and connection;  
2. role of Organized religion;  
3. Personal spirituality and religious practices  
4. what Effects does the patient's religious/spiritual perspective have upon medical care and end-of-life decisions?

Similarly, there is FICA:

| Faith/belief; Importance to you; to which spiritual Community do you belong; and how would you like the physician to Address or include your beliefs? The purpose of these approaches is to respect a patient's spiritual or faith perspective within the context of traditional medical practice. |

However in India, in spite of diversity of religious practices; a discussion about spirituality is always welcome and everyone is willing to participate.

As doctors we encourage our patients to strengthen their belief in God and pray for speedy recovery, we may also join them in praying for their health but coming back to the first question – how often do we pray to God and ask for His help so that we may become better physicians and a better person?

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Rising Tobacco Related Cancers !!! – Issues and our Role

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Current cancer scenario:
World: Every year around 14 million new cancer cases are diagnosed across the globe. Among 8.2 million cancer related deaths occurred in 2012. And it is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades. Globally, tobacco use killed 100 million people in the 20th century. Tobacco-related deaths will number around 1 billion in the 21st century if current smoking patterns continue. Among middle-aged persons, tobacco use is estimated to be the most important risk factor for premature death in men and the second most important risk factor in women (following high blood pressure) in 2010–2025.7

India: Recent report from National Cancer Registry Programme estimates almost 14 lakh new cancer cases every year in India. It is estimated that there are nearly 25 lakh cancer cases at any given point of time. In India, more than 6.8 lakh deaths occur annually due to cancer. Tobacco harms the health, the treasury, and the spirit of India. Every year more than 9,81,100 of country’s people are killed by tobacco-caused disease, while more than 25,42,000 children and more than 12,00,00,000 adult continue to use tobacco each day. On an average about 10,60,00,000 men smoke cigarettes each day which is 23.2% of total males of the country.7

Ahmedabad: Incidence of cancer among male and female is 99 and 76.5 cases per one lakh population respectively in 2013. The most common cancer among male is oral cavity, tongue, lung, oesophagus and larynx while among female it is breast, cervical, tongue and oral cavity cancer.3

Issues
Increased level of tobacco consumption leads to increased rate of Tobacco Related Cancers (TRC). As shown in Table 1, from all the cancers in male, as many as 56.34% cancers are tobacco related cancers and in females this proportion is 19.87%. This shows that majority of cancers are tobacco related cancers in Ahmedabad Urban Agglomeration area. Tobacco related cancers include cancer of lip, tongue, mouth, oropharynx, hypopharynx, pharynx, oesophagus, larynx, lung and urinary bladder.

Table 1: Proportion of Tobacco Related Cancers (TRC) for 2012 and 2013 combined of PBCR Ahmedabad urban

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Proportion of TRC</td>
</tr>
<tr>
<td>TRC Total</td>
<td>3086</td>
<td>56.34</td>
</tr>
<tr>
<td>All Sites</td>
<td>5477</td>
<td>100</td>
</tr>
</tbody>
</table>

Cancer age pyramid is shifting towards the wrong side which leads to higher cancer incidence among young population and we are losing our precious youth to cancer. Figure 1 shows comparison between overall population pyramid and age wise distribution of cancer cases. Overall male population in 35-64 years age group is around 32% while from total cancer cases in male around 62% cases are from this age group. It clearly shows that cancer incidence is higher in 35-64 years age group compared to overall population proportion of that age group both in male and female. This age group is the most productive and socially responsible age group. Losing a person at this age can affect whole family.

All class, gender, age and education level are involved in tobacco chewing and other addiction. This makes difficult for policy makers to focus on a particular group.

Figure 1: Comparison of General population distribution and Cancer Age distribution
In spite of knowledge, more and more people are involving in one or the other kind of addiction. So it creates a dilemma between primary prevention and secondary prevention.

Why people are reluctant to quit tobacco consumption?

Not/ Partially aware: Due to lack of awareness about the ill effects of tobacco and other related products, they continue to consume that. But this group is easiest group to convince just by awareness and follow up.

Aware but ignoring: Most of the consumers are in this group. They are aware about the hazardous effects of tobacco but they are ignoring it. They make various excuses for continuing their tobacco consumption. This group is most difficult group to convince. They may also need psychological intervention.

Do not get support: Most of the people who consume tobacco want to quit it and majority of them have tried to quit but due to lack of support from family and society, they can not stick to it.

Do not know where to go: Most of the lay people do not know where to go for de-addiction or whose help should be sought to get rid of the habit. Government de-addiction centers should be established in educational institutes, workplace and health institutes and they should be promoted as well.

Without being harmed currently, they don’t feel to quit: Cancer is a chronic disease and it does not show immediate effect on health. So tobacco consumer not harmed currently thinks that it will not harm them throughout life. So they do not feel to change the habit currently. For this, we need to change their perception by spreading awareness.

Peer pressure: Peer pressure is considered one of the major factors since years and it is still continuing as one of the major factor for any kind of addiction. Tobacco and its ill effects should be added in the formal education and school teachers have major role to play in this matter.

Working environment: Many consumers argue that their work force them to take various substances which can keep them alert. e.g. Drivers, while many workers who do heavy work throughout the day takes alcohol to relieve their tiredness and for peaceful sleep.

Withdrawal symptoms and actually dependent (addicted) – vicious cycle: These are the people who are actually dependent of various substances and who may develop withdrawal symptoms. This leads to more consumption of the substance which ultimately makes them more dependent and thus it forms a vicious cycle.

Awareness and advocacy in cancer:

Responsibility to only one centre/ department:

Is cancer control or de-addiction activity is the responsibility of cancer hospital only? Can we succeed just by going alone? No. we should adopt multipronged approach where other hospitals apart from cancer hospitals, education centers like schools and colleges, finance department to allocate optimal and timely funds and all the other responsible departments should get together for working towards achieving common objectives.

Financial allocation to health:

India’s financial allocation to the health sector is very less compared to western countries and other developing countries as well. And spending after prevention and awareness activities are not planned properly. Least priority is given to these activities.

Tobacco control programme:

Is there any National or State Tobacco Control Programme existing? If yes, is it functioning towards right direction and is it achieving its objectives? Tobacco control Programme needs to be strengthened and focus should be given to primary prevention by educating people.

Training of manpower:

Are we getting qualified manpower who can work for de-addiction? Or do we value manpower who works for de-addiction? The prevalence of tobacco consumers is so high; we should have many de-addiction centers and many more counselors who can do this work. Such manpower should be valued, developed and trained in a proper way.

Superficial level- can not penetrate deep:

Awareness and advocacy activities in cancer are going on, but it is just at the superficial level. Why we can not penetrate deep to the roots of cause? We should seriously think about the reasons of not penetrating it deep?

Role of ….

Role of each and every citizen: It is not a fight of an individual. Each and every citizen of the nation has to put some efforts individually or collectively. Creating a supportive environment, spreading awareness, speaking out against the tobacco at public places, obeying the legislation are few of the actions which can make our society better at long run. But the question is, are we ready to do all these?

Role of school teachers: At young tender age, children are influenced by their school teachers. If this opportunity is grabbed properly and if these children are counseled properly, the effect will be everlasting in their mind. School teachers need to understand their role in society building.

Role of celebrities: In a country like India where cricketers and actors are worshipped like god, their role is significant in awareness of the mass. Youngsters follow what they see from their role
models, so these celebrities should be cautious before selecting anything which may affect the mass.

Role of religious leaders: Religious leaders should come up against the use of substances like tobacco, alcohol etc. Many religious leaders are currently doing this activity but it needs to be intensified and to be started at a larger scale.

Role of Non Government Organizations (NGO): In our country, where we always face scarcity of resources of almost every kind like manpower, money, material etc., role of NGO has been increased. Integrated and well directed actions are needed from all NGOs with the directions from the Government.

Our role in de-addiction, as a clinician:

Patients and their relatives hear of doctors attentively. Sometimes they catch each and every word of doctors, and even spread the message to their relatives which is given by the doctors.

As a doctor, we should

Treat the person rather than treating the disease: If a patient comes to the doctor for any disease, that is an opportunity to counsel him/her. If we miss this chance, we never know the next time the person may come in front of you diagnosed with cancer. So if a patient has come for any disease, it is our duty to counsel them if he/she is addicted.

Spend some time in counseling: In a set up like GCRI where heavy patient load and long queue of the patient is there, it is difficult to spend much time only in counseling but we will have to start at some point in time. Just saying “Quit tobacco” will not work, we need to give them time and concern.

Try to save life of patient’s relatives: Not only the patients, but sometimes patients’ relatives are also in need of counseling. So if we find patients relatives having any kind of addiction, we should send them to de-addiction centre.

Spread this message to maximum and wherever possible: As a reputed member of the society, the doctors should spread the awareness message wherever they get chance. This will help in spreading the message and by this we can raise this issue in our society.

What we should make them aware of?

“Tobacco and other addictions are harmful.” all consumers know this fact. So we should make them aware in detail along with emotional touch.

Most of the tobacco consumers want to quit that or they have tried unsuccessfully before. So we need to give them ways about how to quit it, what effects will be there initially and how to overcome that.

No one is worried of their own life or health. Men are earning and living for their family while women are more worried about their children and family then their own life. So we should make them visualize the condition of their family if they suffer from cancer. This visualization can baffle them.

Make them realize their importance and role in their own family, society, workplace etc.

“Cancer Control Committee” should be formed for Ahmedabad which should include representatives from government health officials, private and corporate hospitals, education sector, legal expert, policy makers and all the other stakeholders. This committee should meet regularly and set their goals and objectives. By this, we can act through multipronged approach which is needed to fight the cancer menace. One thing is very clear that cancer cannot be controlled by the effort of an individual, an institute or a department. If we want to control the disease, we will have to get to gather to fight against it.

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Methotrexate Induced Toxic Epidermolysis Necrosis
Stevens-Johnson Syndrome in a Child with Acute
Lymphoblastic Leukemia

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DM Resident2, Professor2, Professor and Head1
Department of Medical and Pediatric Oncology

Summary
Methotrexate is an antineoplastic drug commonly used in the treatment of acute lymphoblastic leukemia (ALL). There are only few studies in the literature about Stevens-Johnson syndrome (SJS), occurring in two patients with acute lymphocytic leukemia and non-Hodgkin lymphoma after receiving high doses of methotrexate and leucovorin. We report a two-year-child with ALL, developed SJS after the administration of high dose of methotrexate. Early recognition and prompt supportive treatment is crucial to reduce the treatment related morbidity and mortality.

Keywords: Methotrexate, Stevens-Johnson syndrome, Toxic epidermolysis necrosis, Acute lymphoblastic leukemia

Introduction
Childhood Acute lymphoblastic in is a highly curable malignancy. It is treated with combination of chemotherapy regimens. The Stevens-Johnson syndrome (SJS) is characterized by severe erythema multiforme associated with orogenital mucosal ulceration and may be complicated by severe systemic upset and hepatic, renal and neurological disturbances. Methotrexate has increasingly been used in combination with chemotherapeutic regimens for the treatment of acute lymphocytic leukemia (ALL). Its principal toxic effects are bone marrow suppression, gastrointestinal mucositis, hepatitis, renal impairment, and erythematous rashes. In this study, we have reported a case of Stevens-Johnson syndrome-like exanthema following high dose methotrexate (HDMTX) treatment in a child receiving chemotherapy for treatment of ALL.

Case Report
A two year male child diagnosed with pre-B cell acute lymphoblastic leukemia – moderate risk group. He is on BFM-90 protocol treatment and completed the induction phase. Post induction bone marrow was in remission. We started the consolidation treatment with high dose methotrexate (5gm/m²) with adequate hydration (3L/m²/day) and soda bicarbonate in the intravenous fluid to alkalinize the urine to achieve pH >7.5. Methotrexate was started as 24 hours continuous intravenous infusion. Eighteen hours after the completion of methotrexate infusion, leucovorin (15 mg, intravenous) rescue was initiated every six hourly for three days. On day three, i.e twenty four hours after the completion of methotrexate infusion, child developed fever with bilateral erythematous macular blanchable rashes over the lower limbs. The methotrexate levels at twenty four hours after the completion (day three) was zero micromol/L. On day fourth, he developed redness of lips and oral mucosa, blackish pigmentation of the skin over the upper limbs, trunk and lower limbs. Further on examination, child was conscious, alert, febrile, oral mucositis and stomatitis was present, hyperpigmentation of both upper limb and lower limb (Figure 1a,b), peeling of the skin over the limbs including palms and soles, (Figure 1b,c) single blister like lesion over the foot (Figure 1d). The systemic examination was normal. The lesions rapidly spread and involved the whole body within 3 days. Clinically it was diagnosed as toxic epidermal necrolysis (TEN) or SJS, likely drug induced. Thus methotrexate induced cutaneous toxicity was suspected after ruling out all other causes including drugs, infections etc causing TEN/SJS.

Blood and radiological investigations revealed low Hb (6.8gm/dl), WBC (2000/mm³), absolute neutrophil count (1300/mm³), with normal platelet count (2 lakh/mm³). The liver and renal function tests were normal. The blood cultures were negative. The chest x ray was normal.

Supportive treatment like maintenance of hydration with I.V. fluids, nutritional supplements and daily dressings of the skin lesions was started. Drugs that can precipitate the skin lesions were avoided. Broad broad-spectrum antibiotics and barrier nursing in high dependency unit was given. He was kept under observation for ten days. During this period, exfoliation of the skin over the limbs was slow and gradual. Stomatitis and mucositis gradually resolved. Patient was non toxic during the admission. The broad spectrum antibiotics were tapered by seventh day. Child showed recovery signs like resolvement of mucositis, disappearance of hyperpigmentation and bullae, peeling of skin with appearance of new skin. Symptoms and signs resolved within two weeks follow up as shown in the Figure 2a-d.
Figure 1: Stomatitis, hyperpigmentation of both upper and lower limb (a,b), peeling of the skin over the limbs including palms and soles (b,c), single blister like lesion over the foot (d).

Figure 2 a-d resolvement of mucositis, disappearance of hyperpigmentation and bullae, appearance of new skin.
Discussion

High doses of methotrexate (>1 g/m²) is an important drug in acute lymphoblastic leukemia (ALL) management. About 90% of methotrexate is excreted in an unchanged form within 24 hrs through the kidneys; despite high doses of the drug, it gets excreted from the system within 72 hrs. Rarely, the drug may have altered excretion, resulting in toxic levels of drug, which may result in severe mucositis and renal failure. Mucositis, urticaria, angioedema, photosensitivity, alopecia, maculopapular eruption, erythema, desquamation and erosion of psoriatic plaques, including skin necrosis, have been reported as adverse cutaneous reactions to methotrexate. TEN has been reported with methotrexate in patients of psoriasis, but its occurrence without an underlying skin disease is extremely rare.

Whilst awareness of important potential adverse events such as hepatotoxicity, myelosuppression, and pulmonary fibrosis are reflected in robust guidelines for dosing and monitoring of treatment, other adverse events including cutaneous ulceration remain rarely reported and poorly characterized. Cutaneous ulceration may play a crucial role as an early clinical sign of impending systemic toxicity.

Cutaneous Toxicity of Methotrexate

A key cause of toxicity is the concurrent treatment with interacting agents that decrease protein binding or reduce renal clearance. Some interactions (proton-pump inhibitors) have been reported mainly during high-dose methotrexate regimens while others [such as trimethoprim, non-steroidal anti-inflammatory drugs (NSAIDs), and salicylates] have also been reported in patients on low-dose methotrexate. In our patient, none of these drugs were used concurrently with methotrexate.

A number of cutaneous adverse events have also been described, including: mucositis, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, photosensitivity, ‘recall reactions’ of previous photodermatoses, exfoliative dermatitis, and ulceration/skin necrosis. Of these, mucositis and photosensitivity are usually dose-related and more commonly associated with high-dose regimens used in chemotherapy than in low-dose therapy used in dermatology. Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis are idiosyncratic immune reactions where the full mechanism is not yet understood. Drug interactions and genetic predisposition are felt to influence the risk of development of severe adverse drug reactions, but are not present in all cases.

There are two previous reports of lymphoma/leukemia patients developing TEN on day 4 after the first dose of methotrexate and in the fourth month after initiation of methotrexate, respectively. In our case, the child presented with an extensive skin necrolysis on day 3 after first high-dose methotrexate administration. Concomitant medication, including non-steroidal anti-inflammatory drugs (NSAIDs), sulfonamides and salicylates, may compete with methotrexate for albumin binding sites, causing an increase in free active methotrexate in serum. Our patient did not receive any of the drugs that could have causes methotrexate toxicity. Methotrexate levels are usually undetectable at 72 h after its administration. In our case, methotrexate levels at 24 hours post completion (or at 48 hours of infusion) was 0 (zero) micromol/L. This indicates that this was an idiosyncratic reaction to the methotrexate drug irrespective of the serum levels. Hence the most likely etiology for TEN/SJS in this case was methotrexate. Blood cultures were negative, hence sepsis was ruled out. Intravenous immunoglobulins have been used in TEN, although there is no strong evidence to support the use in many retrospective and prospective studies. We didn’t use i.v immunoglobulin in this patient due to lack of resources. The role of steroids is debatable. The case is presented here for its rarity, and illustrates a fatal skin reaction due to high dose methotrexate, despite normal levels of serum methotrexate.

Conclusion

1. The case is presented here for its rarity, and illustrates a fatal skin reaction due to high dose methotrexate, despite normal levels of serum methotrexate.
2. Early recognition of methotrexate toxicity allowed prompt admission and supportive care, saving the child's life.
3. Methotrexate is a well-established drug of the oncological therapeutic arsenal governed by robust guidelines for introduction and monitoring which aim to minimize patient risk.
4. Pharmacogenomic evaluation of methotrexate may allow for future pre-treatment testing for risk of efficacy and toxicity.

References


Summary: Congenital anomalies of the mullerian system are common defects, reported in up to 3.2% of all women. In Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, the vagina and uterus are congenitally absent, both ovaries are of normal size and fallopian tubes are normal; rudimentary uterine horns may be present in this syndrome. Occurrence of myoma arising from mullerian remnant is an extremely rare. Here, we report a patient of MRKH syndrome with a large leiomyoma originating from the rudimentary uterus. A large pelvic mass was seen adherent to the rudimentary uterus. A 2x2 cm size cyst in the right ovary and right fallopian tube was normal. Left fallopian tube and ovary were normal and attached to the left side of the rudimentary uterus. The mass was removed in total with bilateral ovaries and omental sampling was done.

Keywords: Leiomyoma, MRKH, Ovarian tumor

Introduction: Congenital anomalies of the mullerian system are common defects, reported in up to 3.2% of all women. The prevalence of congenital uterine anomalies appears to be 6.7% in fertile population, and it is found in 7.3% of an infertile population. Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, the most severe anomaly of mullerian system, was first described by Mayer, Rokitansky, Kuster and Hauser. In MRKH syndrome, the vagina and uterus are congenitally absent, both ovaries are of normal size and fallopian tubes are normal; rudimentary uterine horns may be present in this syndrome. The etiologic factors of this syndrome are not fully understood, and environmental and genetic factors are thought to play a role.

Leiomyomas are a rather common occurrence in the normal uterus that can arise from remnant uterus. Occurrence of myoma arising from mullerian remnant is an extremely rare finding and only few cases reported in literatures so far.

Mullerian aplasia can be an isolated finding although associated anomalies often coexist. The incidence of associated urologic abnormalities ranges between 15–40%, and skeletal anomalies such as congenital fusion or absence of vertebra occur in approximately 12–50% of cases. Unilateral renal anomalies are associated with 50% of the patients. The various urinary tract anomalies reported are renal agenesis, pelvic kidney, fusion anomaly like horseshoe kidney and vesicoureteric reflux.

Concurrent association of pelvic mass with mullerian agenesis can be a diagnostic dilemma. Here, we report a patient of MRKH syndrome with a large leiomyoma originating from the rudimentary uterus.

Case report: A 38 year-old unmarried nulliparous presented with complaints of primary amenorrhea, mass and pain in the lower abdomen for 3 months. There was no history of cyclical vaginal bleeding, urinary or bowel complaints. She had no history of loss of appetite or weight. Patient had a past history of laparoscopic surgery at the age of 23 years but no reports were available. Patient was told verbally at that time that she is a true female but she doesn't have a uterus.

Physical examination revealed normal bilateral breasts, normal axillary and pubic hair patterns. Per abdomen examination revealed gross ascites, 6x4cm mass with restricted mobility in lower abdomen. There was no hepatosplenomegaly. External genitalia were normal. A blind vaginal pouch was present. Per rectal examination revealed bulky mass around 6x4cm size with restricted mobility adherent to POD. Clinical impression was bulky uterus or rudimentary horn.

Laboratory investigations revealed normal hormonal profile. CA-125 was 40.5 U/mL (normal value <35 U/mL). CT scan was suggestive of presence of lobulated cystic lesion in right adnexal region. Lesion showed internal septation within. Right ovary was not seen separately from lesion. Uterine mass appears bulky. There was gross ascites. Presence of few calculi was noted in left kidney. They gave an impression of a bulky mass in pelvis with ?Uterus. Bilateral mammasonography was normal.

The patient was then taken up for laparotomy and abdomen was opened with a midline vertical incision. A large pelvic mass was seen adherent to the rudimentary uterus. Rudimentary right horn of uterus was seen. There was a 2x2 cm size cyst in the right ovary and right fallopian tube was normal. Left fallopian tube and ovary were normal and attached to the left side of the rudimentary uterus. The mass was removed in total with bilateral ovaries and omental sampling was done.
Cut section of the mass revealed a large mass with cavity measuring 12 cm in diameter and filled with brown coloured fluid and necrotic material (Figure 1). Rest of the mass was grey white in colour and had whorled appearance. Histological features were suggestive of leiomyoma. Specimen also had two cysts measuring 0.6 and 2.0 cm in diameter filled with straw coloured fluid and diagnosed as simple right ovarian cyst. The patient was discharged after 8 days in good general condition.

**Discussion:**

MRKH syndrome is a rare disorder described as aplasia or hypoplasia of uterus and vagina due to early arrest in development of mullerian duct. The incidence reported is one in 4000–5000 female births and is typically diagnosed during puberty. It is the second most common cause of primary amenorrhea after gonadal dysgenesis. Women with this syndrome are characterized by presence of 46 XX karyotype, normal female secondary sex characters, normal ovarian functions absent or undeveloped uterus and upper part of the vagina. Failure of fusion and development of mullerian ducts around 7th to 8th post-conception age results in muscular thickening at the proximal end of each tube that are joined in the midline by a visible and palpable cord resembling hypoplastic bicornuate uterus without an endometrial lining.

The American fertility society’s (AFS) classification, based on uterine anomalies, is most commonly used to classify mullerian duct anomalies. Anomalies of vagina, tubes and urinary tracts are described as associated malformations. This classification system comprises seven classes: I) uterine hypoplasia and agenesis, II) unicornuate uterus, III) uterus didelphys, IV) bicornuate uterus, V) septate uterus, VI) arcuate uterus and VII), diethylstilbestrol (DES)-related anomalies. MRKH syndrome is a class I mullerian duct anomaly.

The extent of MRKH syndrome is variable, and it is associated with various additional malformations. This is reflected in the classification, which is subdivided depending on each additional malformation that is present into typical when tubes, ovaries, and renal system are generated and developed; atypical, when malformations in the ovary or renal system are present; and MURCS (mullerian aplasia, renal aplasia, and cervicothoracic somite dysplasia) association, when malformations are in the skeleton and/or heart; muscular weakness, renal malformations which puts our patient under classification of atypical type of MRKH syndrome. Rarely, an active endometrium can exist with uterine anlage, which becomes active in the presence of well estrogenised state.

Diagnosis of MRKH syndrome is often delayed until late puberty. The symptoms for presentation are amenorrhea, infertility and pelvic pain. These patients have the ovaries and fallopian tubes of normal functions and most of them have also two uterine remnants of different sizes. Incidence of leiomyoma of uterus is very high in the general female population. However, only few cases of leiomyoma have been reported in women with MRKH syndrome. As ovarian function is normal, estrogen-dependent pathological conditions can develop in the rudimentary uterus, including myomas, neoplasms and adenomyosis.

The exact pathogenesis of neoplastic transformation of uterine smooth muscle in a patient with normal uterus is not known. Cytogenetic abnormalities in the form of spontaneous chromosomal rearrangements are known to occur in uterine leiomyomas. These chromosomal arrangements may be responsible for the initiation and progressive growth of the leiomyomas.

As the proximal ends of mullerian ducts have smooth muscles, the presence of myoma in a case of mullerian agenesis is a theoretical possibility. However, occurrence of leiomyoma in a rudimentary uterine bulb has been rarely reported. The possible reason for this uncommon occurrence could be a decreased concentration or sensitivity of the estrogen receptors.

On ultrasound examination, leiomyomas are hypoechoic or heterogeneous masses. Cystic component with internal echogenic material may be seen in the leiomyomas due to cystic degeneration with necrosis or haemorrhage, like in our case. Calcifications may be seen as hyperechoic foci.

Differential diagnosis of leiomyoma of rudimentary uterus in MRKH syndrome includes ovarian fibroma, gastrointestinal stromal tumour (GIST) of intestine and extravesical leiomyoma of urinary bladder. Although myoma arising from a
rudimentary uterine anlage is a rare finding, it should be considered in the differential diagnosis of pelvic mass in patients with MRKH syndrome. About 30 to 50% of patients with Mullerian agenesis are associated with significant urologic abnormalities, including unilateral renal agenesis, unilateral or bilateral pelvic kidneys, horseshoe kidney, hydronephrosis, and hydronephrosis and ureteral duplication.\textsuperscript{3,4,8} This case has been reported for its rarity, along with associated diagnostic and management dilemma.

References
Diagnosis of Thymolipoma with Fine Needle Aspiration Cytology: A Case Report

Patel Trupti1, Girdhar Swati2, Shah Majal1, Shah Birwa3, Jetly Dhaval4
Associate Professor1, Resident1, Assistant Professor1, Ex Associate Professor4, Professor and Head1
Department of Pathology
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Summary:
Thymolipomas are rare anterior mediastinal tumours composed of mature adipose tissue and benign thymic tissue arising from thymus gland. Fine needle aspiration cytology (FNAC) is now considered to be the diagnostic method of choice for the study of mediastinal tumours including thymolipoma. Here, we report a case of 48 year lady presented with difficulty in breathing, fever and weakness since 15 days. CT scan of thorax showed large predominantly fat containing mass lesion with internal enhancing solid nodules and vascular component involving anterior mediastinum extending to both hemic thoraces. CT guided material taken from both cytology and histology. FNA smears revealed benign thymic component along with mature adipose tissue fragments suggestive of thymolipoma, which later on confirmed by histologically and immuno histochemically.

Keywords: Thymolipoma, mediastinal tumours, FNAC.

Introduction
Thymolipoma, a tumour distinct from simple lipoma of mediastinum, was first described by Lange in 1916.1 Thymolipoma accounts for 4% of all mediastinal tumours.2,3 The majority of these tumours are clinically quiescent, however, symptomatic patients may present with myasthenia gravis, upper respiratory tract infection, dyspnoea, tachypnea and chest pain.4,5 The diagnosis of mediastinal lesions can be challenging in surgical pathology material because of the numerous benign and malignant processes occurring at this site. Accurate and reliable diagnostic procedures are necessary in the management of mediastinal lesions to facilitate timely treatment. The usefulness of fine needle aspiration cytology (FNAC) for the diagnosis of mediastinal tumours has improved thanks to the advent of better imaging technique allowing accurate location of mediastinal masses. As a consequence FNAC is considered the method of choice for the study and diagnosis of tumours in all compartments of the mediastinum.6 Here, we report a case of thymolipoma primarily diagnosed on FNAC and later confirmed by histopathologically.

Case report:
A 48 year old woman had complained of difficulty in breathing since 15 days. Physical examination revealed a bilateral decrease air entry in lung fields more in right lung than left. Laboratory tests showed within normal findings. Chest radiographs showed possibility of right side moderate pleural effusion with possibility of underlying mass lesion. Computerised Tomography (CT) scan of thorax revealed large predominantly fat containing lobulated mass lesion with internal enhancing solid nodules and vascular component involving anterior mediastinum extending to both hemic thoraces. CT scan guided FNAC and biopsy was done. For cytology pre-fixed slides in methanol were received followed by routine Papanicolaou (Pap) stain. Biopsy material was sent to the histology department for routine Harris hematoxylin and eosin (HE) procedure.

Cytology Findings
Moderately cellular smears showing two distinct components: Fragments of mature adipose tissue and varying population of reactive lymphoid cells along with loose aggregates of bland looking epithelial cells. Correlating with CT finding possibility of thymolipoma was suggested (Figure 1). HE stain revealed two distinct but intermingled component: Thymic component showing varying population of reactive lymphoid aggregates along with Hassall’s corpuscles and mature adipose tissue. Necrosis, nuclear atypia, cellular pleomorphism or mitosis was not seen (Figure 2). IHC results showed positivity of CD2, CD5 and CD 20 in lymphoid cells suggestive of reactive thymic lymphocytes. Vimentin and S100 were positive in mature adipose tissue. EMA was positive in epithelial component of thymic tissue. Diagnosis of thymolipoma was given.

Discussion
The term thymolipoma was introduced in 1949 by Hall.7 The pathogenesis is unclear. It is rare benign, slow growing tumour, accounting for 2-9% of all thymic neoplasm and is made up of elements of varying embryonic origin, both mesodermal (fat) and endodermal (thymus epithelium).8 Generally it is well encapsulated, lobulated and doesn’t infiltrate adjacent structures. The most frequently reported symptoms being shortness of breath, chest pain, upper respiratory tract infections and chest heaviness.4,5 It is associated with myasthenia gravis in 10% of cases, as well as with aplastic anaemia, Graves’ disease, lymphangioma, chronic lymphatic leukaemia, Hodgkin’s disease, erythematous systemic lupus, hypogammaglobulinemia and erythroblastopenia.9 Our patient presented with difficulty in breathing, fever and weakness without any associated diseases. Mostly thymolipoma are seen in...
adolescents and young adults with a mean age of 23 years, with a frank male predominance; however our case was 48 year old female.

The histological differential diagnosis for thymolipoma includes lipoma, well-differentiated liposarcoma and thymic hyperplasia. The distinction between a lipoma and a predominantly fatty thymolipoma may be difficult, but extensive sampling and immunohistochemical staining for cytokeratin may highlight thymic epithelial elements in a thymolipoma. Liposarcomas typically have scattered nuclear atypia, lipoblasts, and no thymic epithelium. Thymic hyperplasia classically has unremarkable thymic architecture without presence of abundant adipose tissue. In our case both the components- thymic and mature adipose are present on FNAC as well as in biopsy, make diagnosis easier for such rare case.

**Conclusion**

If an anterior mediastinal mass is found, thymolipoma and other lipomatous tumours should be considered during differential diagnosis. To the best of our knowledge, this is a rare diagnosis of thymolipoma on FNAC.

![Figure 1](image1.jpg)

**Figure 1:** Low power view showing mature adipose tissue (A) and high power showing benign thymic component (B). (PAP stain)

![Figure 2](image2.jpg)

**Figure 2:** Section revealed mature adipose tissue (A) and benign thymic component (B) in low power and Hassel’s corpuscles (C) in high power. (HE stain)

**References**

**Orofacial Rehabilitation of Head and Neck Cancer Patient and Radiotherapy**
Pal Shweta
Dental Services

**Summary**
To evaluate effect of radiotherapy in oral rehabilitation process. Retrospective observational study of seven pre and seven post RT patients who underwent oral rehabilitation was done between June to August 2016. Observed as good, satisfactory or poor outcome. Good: Correction of deviation + achievement of masticatory activity Satisfactory: Partial correction of deviation + achievement of masticatory activity. Poor: Could not achieve both the functions. In Pre RT group Five (70%) had good outcome and three (30%) had satisfactory outcome. In Post RT group four (58%) had satisfactory outcome. Three (42%) had poor outcome. None had a good outcome. Pre RT Orofacial rehabilitation is better than post RT rehabilitation.

**IKAROS Protein and mRNA Expression in B Cell Acute Lymphoblastic Leukemia**
Mehta Shalvi
Immunohematology

**Summary**
IKAROS, a zinc finger transcription factor protein encoded by the IKZF1 gene is crucial for hematopoiesis in humans. Loss of function mutations in IKZF1 have been implicated in adult and pediatric B cell acute lymphoblastic leukemia (B-ALL). The study evaluated the incidence of IKAROS protein expression and isoforms in B-ALL patients. IKAROS protein expression was evaluated in total 67 de novo B-ALL patients using Flowcytometry and the IKAROS isoforms were analyzed using Reverse Transcriptase - Polymerase chain reaction (RT-PCR) method in 23 B-ALL patients. The incidence of the IKAROS protein and isoforms was analyzed and correlated with clinical and hematological parameters. IK-6 isoform was found to be the predominant isoform. Trend of high incidence of IKAROS protein over expression was noted in high blast count and abnormal WBC count, RBC and hemoglobin level while, presence of IK-6 isoform were associated with high WBC count and high blast count (>70%). Further, high incidence of both IKAROS protein over expression and IK-6 isoform were noted in CD34 negative as well as in aberrant T/ Myeloid expressing patients. Moreover, low incidence of IK-6 isoform was noted in patients who underwent induction remission. Based on the present findings, protein expression could be the result of wild type and/or mutant IKAROS and presence of IK-6 isoform was more associated with the conventional prognostic markers. Hence, in future, the study of IKAROS mRNA expression could help identify high risk patients. However, more number of patients needs to be studied to establish the clinical relevance of IKAROS isoforms.

**Surgical Management of Pelvic Sarcomas with Internal Hemipelvectomy: Oncologic and Functional Outcomes**
Shah Jaymin
Orthopedic Oncology

**Summary**
The objective of this study was to evaluate the oncological and functional outcome after internal hemipelvectomy surgery. From 2014 to 2016, 12 patients with pelvic bone tumors (2 with chondrosarcoma, 7 with Ewing's sarcoma, 3 with osteosarcoma) were evaluated for age, type of resection, reconstruction, radiotherapy or chemotherapy. The mean follow-up was 18 months (range 0.2-2 years). In 7 patients reconstruction was performed; in 5 there was no reconstruction. Two patients (16%) had infection developed at a mean follow up of 3 months. Surgical debridement and antibiotics in two patients led to complete recovery. None of the patients developed local recurrence. Two year disease-specific survival rate of all patients was 86.1%. The mean functional MSTS score was 20 for all patients. Internal hemipelvectomy following malignant tumors of pelvis provides good functional and oncologic outcomes.

**Neuroendocrine Tumours of Gastrointestinal Tract**
Modi Madhur
Pathology

**Summary**
Neuroendocrine terminology is used to define cells by their secretory products and cytoplasmic proteins. Their mode of transmission is endocrine or paracrine. Traditionally, well differentiated neuroendocrine tumours are carcinoid tumours. In this presentation the neuroendocrine tumours of stomach, small bowel, appendix and large bowel are described. A combined gross, microscopic, immunohistochemical and ultrastructural approach is required for the accurate diagnosis and classification of neuroendocrine tumours. Immunohistochemical markers like Synaptophysin, Chromogranin, Neuron Specific Enolase, Keratin and Carcinoembryonic Antigen are important for accurate diagnosis. Special
stains like mucicarmine, argentaffin and argyrophil stain are also helpful for diagnosis. Appendix is the most common site of neuroendocrine tumour. IHC plays a major role in the definitive diagnosis of neuroendocrine tumours.

Uterine Sarcoma, Experience at G.C.R.I.
Tiwar Rajnish
Gynecological Oncology
Summary
To study clinco-pathological characteristics, surgical challenges and prognosis in cases of uterine sarcomas. Retrospective study of cases of uterine sarcoma between 2001-2013, done at gynae-oncology department G.C.R.I. Total seventy cases of uterine sarcoma operated at institute, 57 cases enrolled in study. Out of 57 cases, leiomyosarcoma 24(42%), carcinosarcoma 23(40%), endometrial stromal sarcoma 7(12%) and adenosarcoma 3(6%). In all cases total abdominal hysterectomy and bilateral salpingoophorectomy was done. Pelvic, paraaortic lymphadenectomy was done in 28(14%) and omentectomy in 12(21%) cases as part of staging and debulking surgery. Out of 57 case, 38 (66%)belong to stage I, 7(12%) stage II, 9(15%) to stage III and 3(5%) to stage IV. Adjuvant therapy (chemotherapy, radiotherapy, hormonal therapy) was given in 33(57%) cases while 24(42%) cases kept on observation. Surgical complications occurred in 7(12%) cases, urinary bladder injury 4(7%) and bowel resection anastomosis in 3(5%) cases. Surgical difficulty occur in total 10(17%) includes internal iliac ligation, pre-op ureteric stenting, ureteric canal dissection. Total of 27/57(47.5%) cases develop recurrence of which 8 cases underwent surgery for recurrence and remaining cases 19 received chemotherapy. Overall survival at 3yr is (cases 37/57) 63% and at 5years (cases 23/57) 53%. Total of 18/57(31%) cases died of disease within 1 year of followup. Uterine sarcoma are aggressive tumors with poor prognosis and high recurrence rate of 45 to 50% inspite of complete surgery and adjuvant therapy.

Chromosomal Translocation in Acute Lymphoblastic Leukemia in North Indian Population
Bhimani Dhara
Cell Biology
Summary
Recurrent chromosomal abnormalities in the malignant cells of patients with acute leukemia are hallmark of the disease. Specific aberrations, which are frequently indicative of consistent underlying molecular lesions, can assist or even establish the diagnosis and determine optimal therapy. Karyograms of 51 North Indian patients (44 males and 7 females) of acute lymphoblastic leukemia (ALL) from the age group of 2 to 42 years were prepared and observed for the various chromosomal translocations and their frequency. Out of total thirty nine analyzed cases, translocation was detected in thirteen cases (33.33%), most frequent chromosomal translocation was t (9;22) being detected in 4 cases (10.25 %), t (4;11) in three cases (7.69%) and one case (2.56%) each was found with t (8;21), t (1;3), t (8;14), t (1;8), t (1;19), t (4;12), t (3;19). There was random distribution of various chromosomal translocations in different age group and sex. The unique finding of the present study was reporting of t (8;21), t (1;8), t (4;12) and t (3;19), each with one case which was not observed previously by any author in acute lymphoblastic leukemia in North Indians. The findings of the present study may be useful for pediatricians and physicians in predicting outcome, remission, survival and treatment response in acute lymphoblastic leukemia (ALL).

Everything is theoretically impossible, until it is done.
Robert A. Heinlein
## Presentations at the Clinical Meetings

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# Journal Club/Guest Lecture/Review Lecture Presentations

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Case Presentations for Morbidity, Mortality at Clinical Meetings
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About the Journal and Instructions to Author

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A manuscript will be reviewed for possible publication with the understanding that it is being submitted to Gujarat Cancer Society Research Journal at that point in time and has not been published anywhere, simultaneously submitted, or already accepted for publication elsewhere. The journal expects that authors would authorize one of them to correspond with the journal for all matters related to the manuscript. On submission, editors review all submitted manuscripts initially for suitability for formal review. Manuscripts with insufficient originality, serious scientific or technical flaws, or lack of a significant message are rejected before proceeding for formal peer-review. Manuscripts that are unlikely to be of interest to the Gujarat Cancer Society Research Journal readers are also liable to be rejected at this stage itself.

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The following documents are required for each submission:
1. Title Page (Font size: 12)
2. Title of manuscript (Font size: 16)
3. Summary and Keywords (Font size: 9)
4. Text (Introduction, Aims and Objectives, Materials and Methods, Results and Analysis, Discussion with Conclusions; Font size: 12).
5. Tables (separate page, Number Arabic numerals (e.g. 1,2,3) as it comes in results) (Font size: 12)
6. Figures and Illustration (separate page, JPEG format, Number Arabic numerals (e.g. 1, 2,3) as in results, if photographs of persons are used, the subjects or patients must not be identifiable).
7. Legends to Figures and Illustration: Present the legends for illustrations separate page using double-spacing, with Arabic numerals corresponding to the Illustrations. (Font size: 12)
8. References (separate page, Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text in numerals in superscript and parenthesis; Font size: 12).
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Units and Abbreviations

Avoid abbreviations in the title and abstract. All unusual abbreviations should be fully explained at their first occurrence in the text. All measurements should be expressed in SI units. Drug names Generic drug names should be used. Abbreviations of units should conform to those shown below:

- Decilitre dl Kilogram kg
- Milliliter ml
- Micrometer mm
- Minutes min
- Milligram mg
- Hours h
- Molar mol/L
- Millilitre ml
- Percent %

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The title page should include
1. Type of manuscript (article/case report)
2. The title of the article, which should be concise, but informative; (Title case, not ALL CAPITALS, not underlined)
3. The name by which each contributor is known (Last name, First name and initials of middle name), with institutional affiliation;
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- Uniformly American English
- Abbreviations spelt out in full for the first time
Summary and Keywords: Summary no more than 250 (150 for Case Report) words. Should have following headings: Introduction (state the purposes of the study or investigation), Materials and Methods (selection of study subjects/patients, observational and analytical methods), Results (give specific data and their statistical significance, where ever possible), and Conclusion (succinct emphasis of new and important aspects of the study or observations). Do not use symbols in the summary; rather, spell out what they stand for in full. Three to eight keywords must be included below the summary.

Text: This should consist of Introduction (including Aims and Objectives), Materials and Methods, Results, Discussion with Conclusions. Cite every Reference, Figures and Tables mentioned in the text in Arabic numerals (e.g. 1,2,3).

Introduction/Aims and Objective: State the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent information and references, and do not review the subject extensively. Do not include data or conclusions from the work being reported.

Materials and Methods: Describe precisely your selection of the observational or experimental subjects (patients, including controls). Identify the methods, apparatus (including manufacturer’s name and address in parenthesis), and procedures in sufficient detail to allow others to reproduce the method. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well-known. For new or substantially-modified methods, describe and give reasons for using them and evaluate their limitations.

Identify precisely all drugs and chemicals used, including their generic names, their manufacturer’s name, city and country in parenthesis, doses, and routes of administration.

Results: Present your results in a logical sequence in the text, Tables, and Illustrations. Do not repeat in the text all the data in the Tables or Illustrations. Emphasize or summaries only important observations. Specify the statistical methods used to analyze the data. Restrict Tables and Illustrations to those needed to explain the argument of the paper and to assess its support. Where possible, use Graphs as an alternative to Tables with many entries. Do not duplicate data in Graphs and Tables.

Discussion: Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including the implications for future research. Relate the observations to other relevant studies.

Tables: Print each Table double-spaced on a separate sheet. Number Tables consecutively in Arabic numerals (e.g. 1, 2, 3) in the order of their first citation in the text and supply a brief title, which should be shown at the top of each table.

Illustrations (Figures) and Legends for Illustrations: All Illustrations must be submitted in JPEG finished format that is ready for reproduction. Figures should be numbered consecutively in Arabic numerals (e.g. Figure 1, 2, 3) according to the order in which they have been first cited in the text. If photographs of persons are used, the subjects or patients must not be identifiable. Present the legends for illustrations using double-spacing, with Arabic numerals corresponding to the Illustrations.

Acknowledgements: State contributions that need to be acknowledged.

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A list of all the references cited in the text should be given at the end of the manuscript and should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in the text by Arabic numerals in superscript. Omit month and issue number. List all authors, but if the number is six or more, list first three followed by et al. The references should be cited according to the Vancouver agreement. Authors must check and ensure the accuracy of all references cited. Abbreviations of titles of medical periodicals should conform to the latest edition of Index Medicus. Some examples are shown below:

Standard Journal

Online Journal Article

Chapter in a Book

Online Book or Website

In Press

Referees
Generally, submitted manuscripts are sent to one experienced referee from our panel. The contributor’s may submit names of two qualified reviewers who have had experience in the subject of the submitted manuscript, but not associated with the same institution(s) as contributors nor have published manuscripts with the contributors in the past 10 years.
Dental Services at GCRI

Pal Shweta

Department of Dentistry provides general and special dental care to patients receiving cancer treatment for various types of cancers. A large number of patients are visiting for prophylactic dental check up prior to radiotherapy and chemotherapy. Post surgical rehabilitation of head and neck cancer patient is also done to achieve swallowing and masticatory functions. It also has done combination intra and extra oral prosthesis for functional and aesthetic rehabilitation of patients in order to reduce post treatment morbidity.

**Establishment of Department:** It started in 2008 as part time dental services in the department of radiotherapy which continued in 2009 when Dr Shweta Pal joined the Department under the guidance of Dr R. K. Vyas Head of Deptartment of Radiotherapy since then many dentist joined as part timer, Dr Chirag Modi, Dr Nimisha Patel, Dr Neha Patel, Dr Sani Patel, Dr Poonam Pandya.

Department has grown over a period of time we have fully equipped modern dental chair attached along with dental X-ray machine. On average 30 patients per day are visiting in OPD which includes new and follow up cases.

At present in morning Dr Shweta Pal and in the afternoon Dr Poonan Pandya are working in part time.

**Services**

Dental consultation in multidisciplinary approach for cancer care therapy. Dental procedures like simple to surgical teeth extraction are done. Selective tooth grinding, tooth fillings, scaling, root canal treatments,

A special rehabilitation in head and neck cancer patient post hemimandibulectomy and maxillectomy is also done.

Faculty: Dr Shweta Pal (General Dental Surgeon)
Dr Poonam Pandya (Endodontist)

**Training and academic activities**

Post graduate students from various private dental colleges are posted in our dept for exposure to dental oncology services. To name a few Ahmedabad dental college, Karunavati institute of dental sciences, Bopal dental college, Vishnagar dental college etc.

**Future directions**

we propose

1. Dental lab support for fabrication of mandibular guiding flanges, obturators and other prosthesis for onco patients.
2. Trained dental nurse or assistant to improve work efficiency.
3. implant supported prosthetic rehabilitation for cancer survivor especially young group of patients to reduce morbidity and enhance quality of life to them.
4. To have manpower for doing research paper work for reducing complications like osteonecrosis of jaw bone and prevent recurrence of oral carcinomas due to impinging tooth.

**Everything is theoretically impossible, until it is done.**

Robert A. Heinlein
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Lip Prosthesis

Obturator

Mandibular Guiding Flange

Impression and Cast

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