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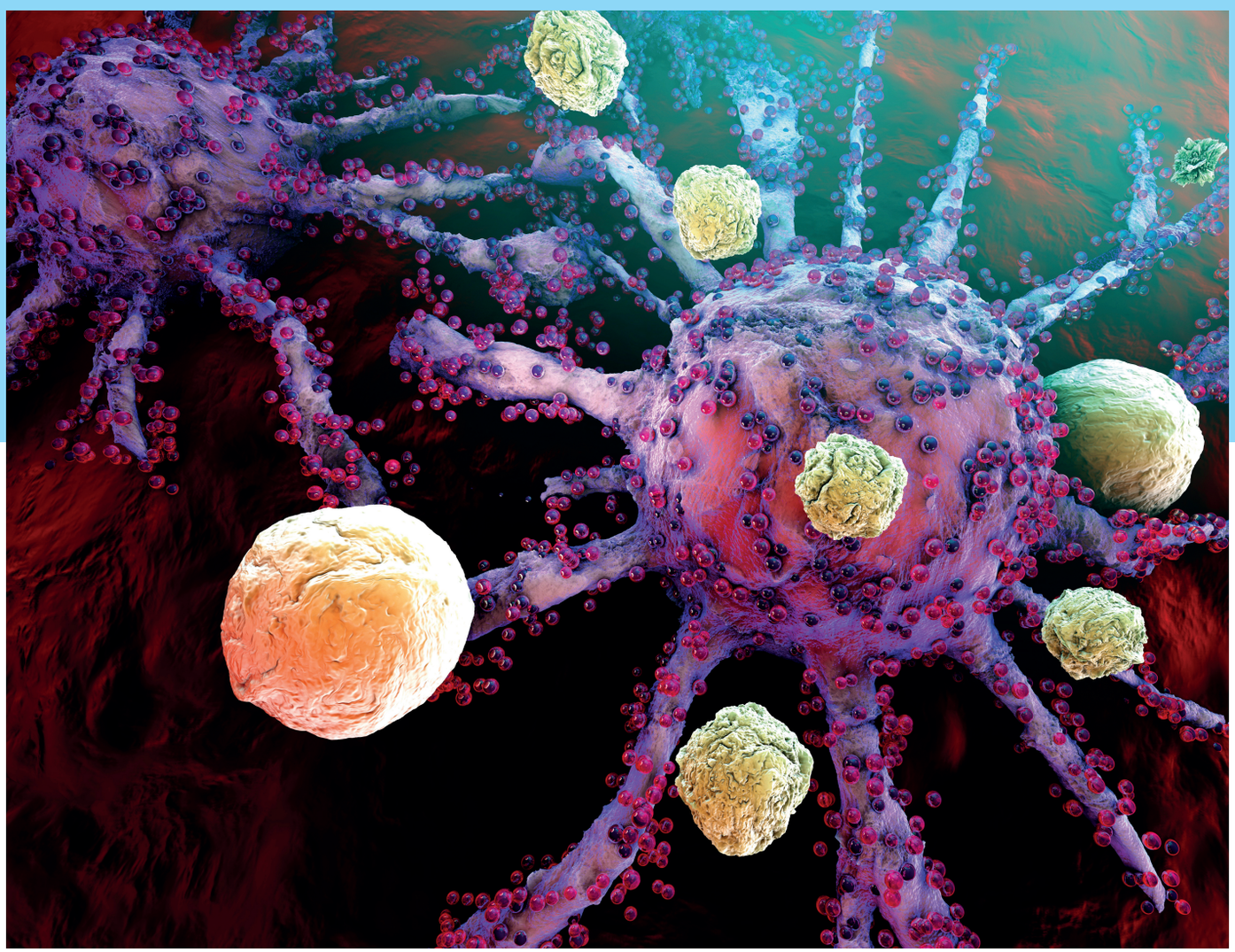

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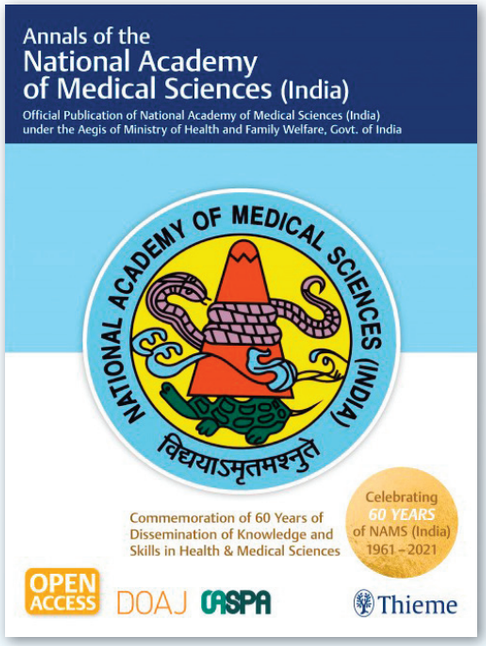

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Epidemiological Review: Esophagus Squamous Cell Carcinoma in India

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Abstract

Worldwide the incidence of esophagus squamous cell carcinoma (ESCC), remains one of the most common causes of cancer death. ESCC is one of the leading types of cancer in the North and Northeast regions of India among both genders. Risk factors of ESCC include tobacco, alcohol, areca nut, hot beverages, low fruit diet, poor oral hygiene, unpiped water, and human papillomavirus infection. This review tries to elaborate on various modifiable risk factors for ESCC, which have been studied worldwide and need to be studied in India. PubMed was used as a search platform using keywords, such as "esophagus cancer," "esophagus squamous cell carcinoma," "epidemiology," "India," "incidence," "mortality," "risk factors," "treatment," "survival," "prevention" and their corresponding Medical Subject Heading terms, were used in combination with Boolean operators "OR" and "AND." Studies from India are mostly hospital-based case-control studies from the North region. Further research is required in India to understand the etiology, to design large-scale screening and prevention strategies.

Keywords

- esophagus squamous cell carcinoma
- esophagus cancer
- review
- epidemiology
- risk factor
- India

Introduction

Esophagus squamous cell carcinoma (ESCC) contributes a significant 90% of the total esophagus cancer (EC) cases worldwide which is an aggressive condition with poor prognosis and low survival rates.[1] Moreover, within the high-incidence region of ESCC, like South America, Africa, Iran, and Asia, the etiologies vary.[2] Consumption of alternate sorts of tobacco, alcohol, hot beverages, low fruit or vegetable diet, processed food, unpiped water, maintaining poor oral hygiene, and human papillomavirus (HPV) infection are the few possible risk factors currently being explored for ESCC worldwide. ESCC has been a major health concern in Kashmir valley and Northeastern states of India where risk factors presently are understudied. This review corroborates the necessity for conducting large-scale epidemiological studies in India to elucidate the risk factors associated with ESCC. Additionally, this review expresses the necessity of presenting the EC burden data on the basis of histological subtypes, considering the paucity of knowledge in this format, and also viewing the vast differences in their etiologies.[2]

Materials and Methods

Advanced search option of the PubMed database was used with the keywords such as "esophagus cancer," "esophagus squamous cell carcinoma," "epidemiology," "India," "incidence," "mortality," "risk factors," "treatment," "survival," "prevention," and their corresponding Medical Subject Heading terms were used in combination, like "AND" and

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"OR," to find published studies on ESCC. This review study was conducted on studies published in English, from the year 2008 to 2020 on ESCC. We excluded animal model studies, studies other than on ESCC, commentaries, clinical or observational veterinary study, and clinical trial studies. Relevant data on descriptive epidemiology and risk factors were explored using databases such as the National Health Portal of India (NHP), Central Water Commission, India (CWC), National Family Health Survey India (NHFS), National Centre for Disease Informatics and Research–Indian Council of Medical Research (NCDIR-ICMR) India, National Cancer Registry Program (NCRP) of India, Census India 2011, National Health Mission India (NHM), International Agency for Research on Cancer (IARC) Monographs, World Health Organization (WHO) guidelines, Global Cancer Observatory 2020, and Cancer Incidence in five continents XI vol. IARC (CI5 XI).

Descriptive Epidemiology

Worldwide, 604,100 new cases and 544,076 cancer death were estimated for EC in the year 2020.[3] India ranks second in EC incidence trailing China which has the highest incidence of EC. In India, it is the fifth most common cancer type in males and the sixth most common cancer type in females. In India, the number of incident cases of esophageal cancer in 2020 was 63,180 out of which 40,183 were males and 22,997 females, and the prevalent cases were 68,607.[3] The male-to-female ratio in India is 2.4:1.[4] ESCC is the most common histological subtype among all cancer registries in India. The top five cancer registries having the highest incidence rate of ESCC are Mizoram, Kamrup Urban, Cachar, Sikkim, and Tripura registries.[5] As per the hospital-based cancer registry report, the esophagus was the leading site in KMIO—Bangalore, AMC—Dibrugarh, BBCI—Guwahati, and in PGIMER—Chandigarh among 35 to 64-year-old males.[6] However, the observed incident cases in the year 2020 have already exceeded the predicted number of incident cases for the year 2035, showing a significant rise in the incident rates.[7]

Survival Data

A study from Jammu, India, suggested that the frequency of survival in ESCC patients is lowered by intake of red chili, snuff, and smoking.[8] Studies from China and Brazil show factors such as gender, marital status, occupation, family history of any cancer, tumor topographical site, differentiation status, and pathological reports, are independent risk factors affecting the overall survival of EC.[9,10] Other factors such as, weight loss (kg), and body mass index (BMI) variation (kg/m^2) predict the stage at diagnosis in the ESCC.[10] The Surveillance, Epidemiology, and End Results (SEER) report of 18 regions from the year 2002 to 2008 for 5-year relative survival in EC continues to be low at around 16.9%.[11] The overall survival of EC is 5 to 30% as stated by the ICMR report. The disease is mostly detected at a stage where it is inoperable in most patients (70–80%), and with an expected survival of 7 to 12 months.

Risk Factors

Recent developments and finding in epidemiological studies have led to the identification of many risk factors associated with ESCC worldwide which need to be studied in India. ►**Fig. 1**.

Strongly Associated

Tobacco Use

Exposure to tobacco smoke and chewing tobacco products has been associated with ESCC. Case-control studies in India have seen a two- to seven-fold increase in the risk of ESSC for chewing tobacco, betel quid with tobacco having a dose–response relationship.[12] In India, the risk of developing tobacco-related cancer was found highest in the Northeastern region with maximum risk found for EC in women.[13] Hospital-based studies from India suggest an increase in the risk of ESCC by smoking tobacco, in the form of cigarettes, bidi, and hookah.[14–16] Habits such as consumption of nass, snuff, paan chewers, and betel quid chewers also increase the risk of ESCC.[14,15,17] Along with cigarettes, other forms of tobacco smoking such as hookah pipes, and cigars exhibit similar risks on ESCC. A study from India on secondhand smoking and ESCC risk reported odds ratio (OR) of 1.32 in exclusive secondhand smokers (never tobacco users), and OR of 3.41 in second-hand smokers who are active chewers, suggesting additive effects of tobacco-related carcinogens[16] (►**Table 1**). However, there are only a few studies in India evaluating the risk of tobacco chewing and its association with ESCC and adjusting for potential confounders.

Alcohol Use

Alcoholic beverages are known to be casually associated with ESCC as reported by IARC monograph.[18] A hospital-based case-control study from India found an increased risk of ESCC when associated with alcohol consumption, but without adjusting for all potential confounders, that is, tobacco chewing and smoking habits.[14] Another study from India, by Singh et al, reported statistically significant multivariate OR of 2.21, among ever alcohol drinkers for ESCC.[17] Although alcohol intake has a strong association with ESCC, few studies have observed a **J**-shaped relationship (rather than a linear relationship) between alcohol consumption and increased risk of ESCC.[19,20] Hence, designing health care policies is a challenge[21] (►**Table 2**).

Possibly Associated

Areca Nut

IARC has considered areca nut (AN) as a group-1 human carcinogen in 2003.[22] AN is consumed widely in Asian countries like India, Pakistan, Bangladesh, and Sri Lanka, with consumption observed higher in females.[23] A Taiwan study indicated that AN chewing history is significantly associated with the onset of cancer from a younger age and with poor response to chemoradiotherapy, in ESCC patient.[24] A meta-analysis study from Asia suggested that chewing AN was independently and significantly associated with an increased risk of ESCC.[25] Studies from India have shown a dose–response relationship and combined effect of tobacco consumption and AN (►**Table 3**).

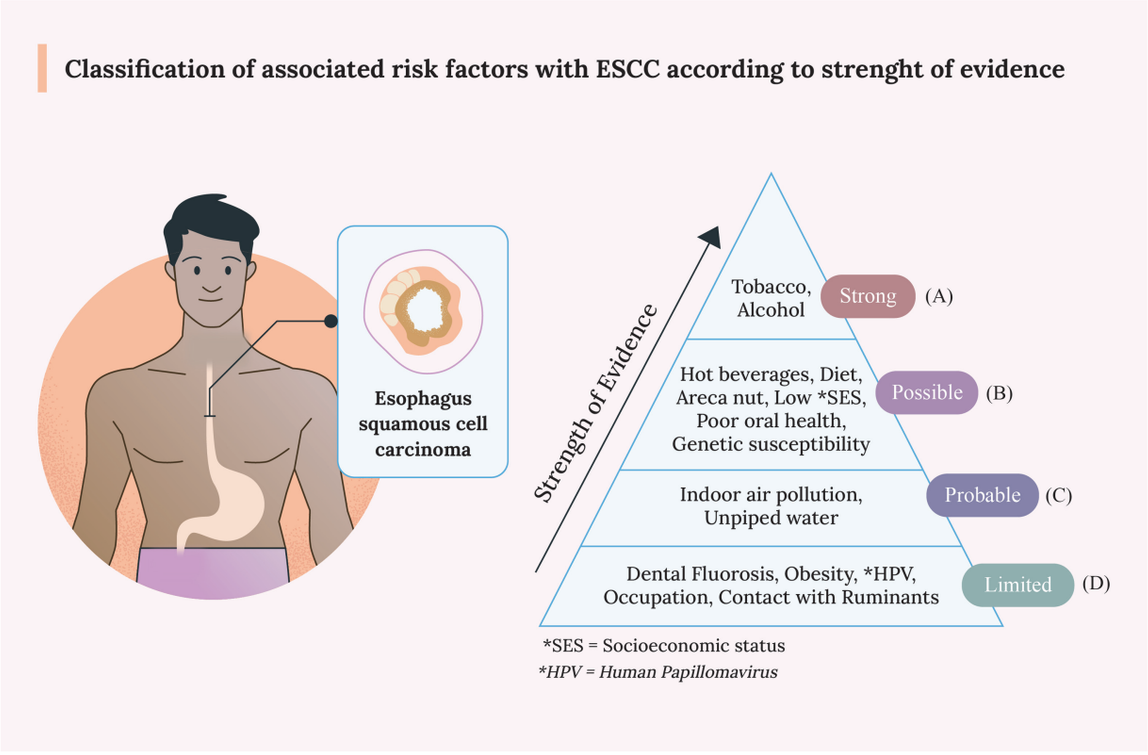

Fig. 1 Classification of associated risk factors with ESCC according to strength of evidence. (**A**) Strong: risk factors having strongest association as per literature are mentioned in this group followed by (**B**) Possibly associated risk factors, (**C**) Probably associated risk factors, and (**D**) risk factors having limited evidence. ESCC, esophagus squamous cell carcinoma

Poor Oral Health

A population-based case-control study from China, indicating habits of tooth brushing once or less per day, compared with tooth brushing twice or more per day, among nonsmokers and nondrinkers showed significant association with a 1.81-fold increased risk of ESCC.[24] The Golestan cohort study from Iran suggested that tooth loss is independently and positively associated with ESCC.[26] A recent case-control study from Africa showed increased ESCC risk when associated with decayed teeth and missing teeth[27] (►**Table 4**). A research study from India, Kashmir region showed an inverse association between cleaning teeth and ESCC risk, especially with toothbrushes compared with sticks or other tools of brushing, supporting previous studies from other high-risk countries.[28] A cross-sectional study published in 2019 from rural India to understand the prevalence of oral disease concluded that the prevalence of dental caries was 76.4%. The decayed, missing, and filled teeth (DMFT) score of subjects who did not use toothbrushes and toothpaste was significantly higher and the awareness about oral hygiene was observed to be low in the general population.[29]

Social Economic Status

Higher incidence of ESCC is observed in low or middle-income countries as compared with high-income countries.[30] A population-based case-control study from Golestan, Iran, indicates a strong inverse association between education, wealth, and being married with the risk of developing ESCC. A Swedish cohort study showed that divorce, widowhood, living alone, low educational attainment, and low income increased the risk for ESCC along with other subtypes of EC.[31] A study from China published in 2018 showed higher education (OR = 0.60), larger house area per person (OR = 0.71), and higher wealth score (OR = 0.43) were associated with a low risk of ESCC, and patients possessing several household appliances (>5 years) also had a lower ESCC risk.[32] Similar findings from a case-control study published in 2013, from Kashmir, India, observed that low socioeconomic status is associated with a high risk of ESCC.[33] Another study from North India suggests poor socio economic status results in lack of fresh fruit and vegetable intake and which is suspected to be one of the risk factors in development of esophageal cancer[34] (►**Supplementary Table S1**; available in the online version).

Although socioeconomic status is observed to be associated with esophageal cancer, it is not the direct cause in the development of esophageal cancer. The low socioeconomic status affects esophageal cancer through various causal pathways which include its association with poor nutrition, higher rates of tobacco consumption, and higher proportion of infection with HPV.

Diet

High consumption of fruits and vegetables showed an inverse association with the development of ESCC as reported in a

Table 1 Characteristics of tobacco studies (chewing, smoking, and inhalation) for ESCC in the population of India and worldwide

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–tobacco									
Tobacco chewing with other products									
Paan chewers with tobacco (more than 20 years)	OR = 1.5 77/204	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Nass chewing (ever chewer)	OR = 2.88 201/192	Dar et al[15]	2012	23033008	Kashmir	ESCC	702/1,663	Case control	Age, ethnicity, religion, place of residence, education level, cumulative use of cigarette, hookah, ever use of bidi, cannabis, gutka, alcohol, daily fruit, and fresh vegetable consumption
Tobacco inhalation									
Snuff	OR = 3.86 136/71	Sehgal et al[12]	2012	23107978	Jammu	ESCC	200/200	Case control	Not mentioned
Chewing products other than tobacco									
Betel nut chewer (ever chewer)	OR = 2.79 68/52	Singh et al[17]	2015	26045981	Assam	ESCC	99/75	Case-control	Not mentioned
Tobacco smoking									
Smoking tobacco	OR = 1.97 110/63	Sehgal et al[12]	2012	23107978	Jammu	ESCC	200/200	Case control	Not mentioned
Cigarette smoking	OR = 2.0 40/90	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Bidi smoking	OR = 1.8 122/252	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence, and occupation
Water pipe tobacco smoking									
Hookah (waterpipe tobacco smoking ever users)	OR = 1.85 420/699	Dar et al[15]	2012	23033008	Kashmir	ESCC	702/1,663	Case control	Age, ethnicity, religion, place of residence, education level, cumulative use of cigarette, hookah, ever use of bidi, cannabis, gutka, alcohol, daily fruit and fresh vegetable consumption
Indian study–Second hand smoking									
Secondhand smoker (never tobacco users)	OR = 1.32 31/60	Rafiq et al[16]	2016	26735535	Kashmir	ESCC	703/1,664	Case control	Age, ethnicity, religion, place of residence, income, gender, education, the wealth score, ever use of alcohol, salt tea consumption, frequency of close contact with animals, house type, cooking fuel, fruit and vegetable intake
Secondhand smoker (tobacco chewers)	OR = 3.41 15/11	Rafiq et al[16]	2016	26735535	Kashmir	ESCC	703/1,664	Case control	Age, ethnicity, religion, place of residence, income, gender, education, the wealth score, ever use of alcohol, salt tea consumption, frequency of close contact with animals, house type, cooking fuel, fruit and vegetable intake, tobacco smoking and smokeless tobacco use
International studies–tobacco									
Cigarette or pipe (ever)	RR = 1.33	Tran et al	2005	15455378	China	ESCC	1,958	Cohort	Age

Table 1 (*Continued*)

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Ever smoker	HR = 1.36	Fan et al	2008	18444169	Shanghai	EC	101	Cohort	Level of education, body mass index, number of drinks consumed per day, number of years of drinking, and summed intakes of preserved food items, fresh fruits, and fresh vegetables
Smoking tobacco index (daily tobacco intake × duration of smoking) overall survival	HR = 1.21	Liu et al	2020	32071596	China	ESCC	944	Cohort	Multivariate
Smokeless tobacco users	OR = 2.06–12.8	Gupta et al	2018	30264755	Eastern Mediterranean	EC	80 studies	Meta-analysis	
Ex-smokers	HR = 1.29	Cho et al	2017	28973012	Korean	EC	9,171	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and alcohol
Current smokers	HR = 1.87	Cho et al	2017	28973012	Korean	EC	9,171	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and alcohol

Abbreviations: BMI, body mass index; CI, confidence interval; EC, esophagus cancer; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio; RR, relative risk.

few studies.[35] Processed food is a source of N-nitroso amines compounds which play important role in the high risk of ESCC. N-Nitroso amines in processed meats are labeled as carcinogenic (group 1) in 2015 by IARC monographs and also red meat is classified as (group 2A) carcinogenic.[36,37] A cohort study from the Netherlands showed that the consumption of vegetables and fruits has an inverse association with ESCC.[38] A population-based case-control study in China mentioned a strong association between consumption of salted meat and ESCC.[39] A case-control study from the Golestan region in Iran indicated direct association between red meat consumption and ESCC.[40] Another cohort study from Golestan showed that a dietary deficiency of zinc and calcium is associated with ESCC.[41] A study from India, observed that lower intake of fresh vegetables and fruits is suspected to be a major risk factor for the development of ESCC[34] (►**Supplementary Table S2**; available in the online version). In India, the high-risk regions of ESCC consume majorly processed red meat, fermented vegetables, fermented black mustard seeds, and fermented fish to enhance the flavors and preserve the food during scarcity.[42]

Very Hot Beverages/Food

Drinking very hot beverages (≥65°C) is one of the probable risk factors for ESCC as reported by the IARC monograph and is classified as group-2A carcinogen.[43,44] A recent cohort study from Iran and a case-control study from Kenya strengthen the evidence for a strong association between very hot beverage consumption and risk of ESCC.[27,45] A population-based cohort study from China observed an increase in EC associated with a combination of hot tea, excessive alcohol, and tobacco.[46] A study from South America showed that hot mate drinking was associated with ESCC risk.[47] In India, a case-control study from Kashmir indicated that the habit of drinking salt tea was strongly associated with the risk of developing ESCC and not the consumption of hot tea. Although, it could be due to variations in reporting tea-drinking temperature[48] (►**Supplementary Table S3**; available in the online version).

Probably Associated

Indoor Air Pollution

Indoor air pollution or household air pollution occurs from the combustion of cooking fuel and has been studied as one of the risk factors for esophageal cancer. In the rural area of the developing countries where the incidence of ESCC is high, cooking fuels like coal, charcoal, wood, crop residue, animal dung, and other smoke-producing fuel are used for daily cooking. Compared to males, females are at a higher risk of indoor air pollution since most of the cooking is done by females in developing countries and where most of them are non-smokers or non-drinkers.[49] These fuels generate smoke containing Polycyclic Aromatic Hydrocarbons (PAH) which are classified as group 1, that is, carcinogenic to humans as per IARC.[50] A study from Iran, indicated that PAHs played a causal role in the etiology of esophageal cancer in high-risk population.[26] A study from Northern India suggested that

Table 2 Characteristics of alcohol studies for ESCC in the population of India and worldwide

Exposure	Risk estimates (95% CI) Case/control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–alcohol									
Alcohol	OR = 1.8 66/131	Ganesh et al[14]	2009	19846360	Mumbai	ESCC	442/1,628	Case control	Age, gender, residence and occupation
Alcohol	OR = 2.21 41/22	Singh et al[17]	2015	26045981	Assam	EC	110/75	Case control	Not mentioned
Zu (local liquor)	OR = 1.34 32/28	Lalpawimawha	2016	Not found	Mizoram	EC	138/276	Case control	Betel quid consumption, tobacco consumption, smoking, BMI at 20 years of age and family history of cancer; education level and income level, dietary habits and physical activity except for each independent variable
Zu (local liquor) + commercial	OR = 9.82 21/12	Lalpawimawha	2016	Not found	Mizoram	EC	138/276	Case control	
International studies–alcohol									
Mild-to-moderate drinkers	HR = 1.52	Cho et al	2017	28973012	Korean	EC	5,839	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and smoking status
Heavy drinkers	HR = 3.13	Cho et al	2017	28973012	Korean	EC	5,839	Cohort	Age, gender, exercise, income, BMI, diabetes mellitus, and smoking status
Light drinker	RR = 1.25	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	16 studies	Systematic review and meta-analysis	Systematic review and meta-analysis
Moderate drinker	RR = 2.32	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	27 studies	Systematic review and meta-analysis	Systematic review and meta-analysis
Heavy drinkers	RR = 5.38	Islami et al[20]	2011	21190191	Iran, Italy, France	ESSC	20 studies	Systematic review and meta-analysis	Systematic review and meta-analysis

Abbreviations: BMI, body mass index; CI, confidence interval; EC, esophagus cancer; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table 3 Characteristics of areca nut studies for ESCC in population worldwide

Exposure	Risk estimates (95% CI)	Study	Year	PMID	Location	Case type	Sample size	Study design
International study–areca nut								
Areca nut	OR = 3.05	Akhtar et al[25]	2013	23224324	Kuwait	ESCC	12 case-control study	Meta-analysis
Areca nut and tobacco smoking	OR = 6.79	Akhtar et al[25]	2013	23224324	Kuwait	ESCC	6 case-control study	Meta-analysis

Abbreviations: CI, confidence interval; ESCC, esophagus squamous cell carcinoma; OR, odds ratio.

using cooking fuels, like electricity (OR = 0.24), and LPG (OR = 0.10) were associated with lower ESCC risk in comparison to using less expensive fuels in the region, like animal dung, firewood, and biomass[33] (►**Supplementary Table S4**; available in the online version).

Unpiped water/Drinking Water Contamination

Relation between drinking water quality and cancer has been studied for a long time. Drinking water contaminants like arsenic (group 1), nitrates (group 2A), and disinfection by-products (groups 2B and 3), all are classified as carcinogenic by IARC monograph classification.[51] However, a study from Sri Lanka showed contradicting results where pipe-borne water was seen to have a six-fold risk for EC compared with the present study with other sources of water, but it could be due to other factors of water storage, and sanitization after collection of water.[52] Whereas, a study from Golestan observed a dose–response relationship between the duration of drinking unpiped water and ESCC[26,40] (►**Supplementary Table S5**; available in the online version). On the National Health Portal (NHP) of India, it is mentioned that the total urban and rural population consumes only 43.5% of their drinking water from the tap, the remaining population drinks water from unpiped sources, that is, well (11%), tube well (8.5%), hand pump (33.5%), spring (0.5%), river or canals (0.6%), pond or lake (0.8%), and other source (1.5%),[53] making it a necessary exposure to be studied.

Limited Data or No Data Associated

Obesity

Waist-to-hip ratio (WHR) and body mass index (BMI) are strong factors representing obesity in a population. Obesity is strongly associated with esophagus adenocarcinoma (EAC) as per many published studies worldwide. There are limited studies studying obesity as a risk factor in association with ESCC.[30] A recent study published from the United Kingdom, Biobank cohort, suggested that no significant associations were observed with anthropometric measurements or body fat composition in men,[54] and in women measurements, like weight, BMI, hip circumference, waist circumference, waist-to-height ratio, body fat, and trunk fat percentage were all inversely associated with ESCC[55] (►**Supplementary Table S6**; available in the online version). In India, this exposure in association with ESCC is still quite unexplored.

Dental Fluorosis

Natural fluoride belts are found in regions from Jordan, Egypt, Libya, Algeria, Sudan, Kenya, Turkey, Iran, Afghanistan, India, Northern Thailand, and China, and similar fluoride belts are observed in the United States and Japan.[56] Fluoride carcinogenicity in humans is understudied and is being classified in group 3 as per IARC monograph.[36] ESCC is plausibly associated with dental fluorosis as per recent findings from a case-control study in Kenya[27] (►**Supplementary Table S7**; available in the online version). Dental fluorosis is endemic as per the data published in the National Health Profile report 2019 from India and, presents a total number of 10,379 rural habitations from 16 states, showing exceeding levels of fluoride in their source of drinking water and highlights the need for safe drinking water in these habitations.[53] Studies in India show a high groundwater fluoride level correlation with a high prevalence of dental fluorosis in regions like the Northwest, South, and East, including the Gangetic Plains which warrants the needs to study it as a risk factor in the development of ESCC.[57–59]

Heavy Metals Consumption

Heavy metals, like cadmium, lead, chromium (IV), and arsenic, have been found in drinking water and farm soil, all of which have been, classified as carcinogenic(group-1) by IARC monograph.[51] A study from Taiwan suggested an increased level of nickel in farm soil is associated with the prevalence of EC.[60] A study from Iran observed high-lead intake from vegetables could be prevented in high-risk regions of ESCC which is beyond suggested levels by WHO[61] (►**Supplementary Table S8**; available in the online version). In developing countries, like India, most of the population is dependent on surface water and groundwater as a source of drinking water, hence most of the habitats are exposed to the presence of excess arsenic in the drinking water source.[62]

Human papillomavirus (HPV) Infection

A meta-analysis study conducted in the Chinese population reported pooled OR of 6.36 for HPV 16 infection and EC.[63] Another meta-analysis study on HPV types in ESCC observed OR of 3.55 for HPV 16 infection and OR of 1.25 for HPV 18 infection.[64] HPV 16 was found to be the most frequently observed genotype in ESCC (►**Supplementary Table S9**; online only).

Table 4 Characteristics of poor oral health studies for ESCC in population of India and worldwide

Exposure	Risk estimates (95% CI) Case | control	Study	Year	PMID	Location	Case type	Sample size (case/control)	Study design	Adjustment factors
Indian studies–poor oral health									
Cleaning of teeth with brush	OR = 0.11 Case | Control 50/528	Dar et al[28]	2013	23900216	India	ESCC	703/1,664	Case control	Age, ethnicity, residence, education, wealth score, fruit and vegetable intake, bidi smoking, gutka chewing, alcohol consumption and cumulative use of hookah, cigarette, and nass
Cleaning of teeth with finger	OR = 0.51 Case | Control 488/957	Dar et al[28]	2013	23900216	India	ESCC	703/1664	Case control	
International studies–poor oral health									
Frequency of brushing teeth <= 1	OR = 1.81 486/510	Chen et al	2017	27778330	China	ESCC	616/770	Case control	Age, gender, education, marital status, tobacco smoking, alcohol drinking, tea drinking, family history of ESCC, daily consumption of pickled vegetables, daily consumption of fresh fruits, and wealth score
≥6 tooth loss (after age 20)	OR = 1.48 266/330	Chen et al	2017	27778330	China	ESCC	616/770	Case control	
Excessive tooth loss (≥12 excess tooth loss)	HR = 1.66	Sheikh et al[26]	2019	30611753	Northeastern Iran	ESCC	50,045 individuals	Cohort	Age, gender, residence counties, ethnicity, quartiles of the socioeconomic status, opium consumption through smoking, opium consumption through ingestion, drinking hot tea at ≥60°C, daily intake of fruits, daily intake of vegetables, drinking un-piped water, indoor air pollution, daily contact with ruminants, alcohol drinking, cigarette smoking, nass chewing
Mswaki stick	OR = 1.7 133/75	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	Gender, ethnicity, alcohol and tobacco, alcohol intensity, beverage drinking, family history of EC, and continuous: age, education score, tooth brushing frequency + brush type + DMFT (not for lost/decayed teeth), leukoplakia, dental fluorosis
No. of missing teeth ≥ 6	OR = 1.3 87/55	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
No. of decayed teeth ≥ 3	OR = 4.4 131 | 37	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
DMFT count ≥ 8	OR = 3.0 133/54	Menya et al[27]	2019	30582155	Africa	ESCC	430/440	Case control	
Frequency of brushing teeth (never) tobacco users–fully adjusted	OR = 2.53 222/324	Abnet et al.	2009	18990747	Golestan, Iran	ESCC	283/560	Case control	Age, gender, place of residence, ethnicity, alcohol drinking, use of tobacco, opium, or both, education in three categories, number of appliances, and fruit and vegetable intake
Frequency of brushing teeth (never) alcoholic beverage drinkers–fully adjusted	OR = 2.15 222/324	Abnet et al.	2009	18990747	Golestan, Iran	ESCC	283/560	Case control	
Teeth loss	OR = 1.31	Chen et al	2015	26462879	China, Iran, Japan, India, the United States, Finland	ESCC	6 studies	Meta analysis	Not mentioned (Forest's plot)
teeth brushing	OR = 0.57	Chen et al	2015	26462879	China, Iran, Japan, India, the United States, Finland	ESCC	4 studies	Meta analysis	Not mentioned (Forest's plot)

Abbreviations: CI, confidence interval; DMFT, decayed, missing, and filled teeth; ESCC, esophagus squamous cell carcinoma; HR, hazard ratio; OR, odds ratio.

Indian Journal of Medical and Paediatric Oncology Vol. 43 No. 5/2022

Occupation

Occupational hazard as a risk factor in association with ESCC has received less attention. A population-based case-control study conducted in China showed OR of 1.69 in jobs involving high physical labor.[32] In India, a few studies conducted in Kashmir published that the risk of workers who are highly physically active or who are engaged in physically strenuous work are at higher risk of developing ESCC[33,65] (►**Supplementary Table S10**; available in the onlineversion).

Ruminants

Contact with the animal has been a risk factor which has not studied extensively, but we have a few case-control studies that mention the risk of ESCC from the contact with ruminants. A case-control study from India observed the association between daily close contact with animals and increased risk of ESCC as compared with no animal contact group. Animal contact for more than 50 years was associated with an increased risk, showing a dose–response association with ESCC.[66] Another case-control study from Iran showed an increased risk of ESCC when in contact with canines and ruminants in the ever contact group as compared with the group which was never in contact. Also, there was a dose–response relationship observed with the level of contact with the animals[67] (►**Supplementary Table S11**; available in the online version).

Prevention

Lifestyle modifiable changes could be adapted to prevent the risk of developing ESCC. Strong evidence suggests cessation of smoking tobacco, chewing tobacco, and drinking alcohol should be followed in high-risk populations. Improving socioeconomic status reduces the risk of EC.[32,33,68] Studies recommend a healthy diet with fresh vegetables and fruits that will help reduce the risk of developing ESCC. Pickled and salted food intake needs to be avoided, along with processed meat.[35,37–39,69] Behavioral changes are needed in a high-risk region where the intake of hot beverages is a common tradition.[43] Endoscopic screening and surveillance for conditions, such as dysplasia in the esophagus can lead to a reduction in the incidence of ESCC and reduce in the mortality rate.[70] Management of symptoms that can lead to conditions, like dysplasia, can be decreased with the help of pharmaceutical drugs, lifestyle changes, diet modifications, and diagnostic testing. Early detection and classification of high-risk populations can be done with help of a risk prediction model. Vaccination programs for a defined high-risk population can prevent cancer incidences. Maintaining regular oral hygiene prevents tooth loss and helps in preventing injury in the inner lining of the esophagus. Early age lifestyle modifications can help maintain health in the context of ESCC prevention.[71]

Discussion on Gaps in the Literature, Indian Perspective

In India, tobacco smoking in males is 19% and in females is 2%. On the another hand, smokeless tobacco prevalence in males is 29.6% and in females is 12.8%.[72] Association of different types of chewing tobacco and betel nut needs to be identified. Similarly, association with different types of tobacco smoke products, including bidi, needs to be studied in the Indian population adjusting for potential confounders. The duration of consumption and content of the local liquor consumed in high-risk regions of India in association with ESCC have not been studied yet. Traditional alcoholic beverages carrying cultural significance are commonly consumed during various special occasions in the high ESCC incidence region of India.[42] Similarly, raw ANs or fermented ones are commonly consumed alone or with betel leaf in high ESCC incidence region of India, thus they need to be studied in association with ESCC. Fermented, spicy, and processed food are consumed extensively in the high ESCC incidence region of India to meet their needs in extreme environmental conditions. Therefore, research on understanding the carcinogenic factors developed during food processing can help to design preventive policies for food preservations and cooking in high ESCC incidence regions.

In India, according to NHFS4 data, 55.7% of the rural population uses wood as their source of cooking fuel, and only 44% of the total urban and rural households had clean cooking fuel.[73] Indoor air pollution and socioeconomic status could be related since the population which has high social economic status (SES) can afford clean fuel for cooking and has low exposure to indoor air pollution. To understand the relation between indoor air pollution and the risk of ESCC development, we need further investigation. As per the NHFS4 survey data of India, rural households rely most on tube wells or boreholes (51%), followed by water piped into their dwelling, yard, or plot (18%).[73] In India, since more than half of the population lives in rural areas where tap water is unavailable most of the time, unpiped water consumption could be a potential risk for ESCC.

Conclusion

ESCC carcinoma affects millions of people worldwide every year having a poor prognosis and poor survival rate, especially in developing countries. A rapid increase in the incidence rate of ESCC needs the implementation of new strategies for diagnosis, treatment, and containment of the disease. The review studies modifiable risk factors, like obesity, unpiped water, dental fluorosis, heavy metals, diet, SES, and HPV, showing very few or no studies from India. The review indicates that there is a need to conduct descriptive, as well as large-scale analytical studies in India for generating evidence for risk factors associated with ESCC. Strict actions against the usage of modifiable risk factors leading to ESCC can be opted by the government policymakers to prevent such health conditions and improve overall public health.

Conflict of Interest

None declared.

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Quality of Life and Limb Functionality in Adolescents and Young Adults Surviving Bone Tumors in the Lower Extremity in a Developing Country: A Cross-Sectional Study

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Abstract

Introduction Due to higher survival rates among patients with bone tumors, there is a growing interest in determining these individuals' limb functionality and psychosocial prognosis.

Objectives This study aimed to analyze the differences in functionality and quality of life (QoL) related to health in patients diagnosed with a malignant bone tumor during childhood, according to the type of surgery performed.

Materials and Methods A cross-sectional study was performed for patients older than 14 years who treated for osteosarcoma or Ewing's sarcoma of the lower limb by who receiving surgery. To assess lower limb functionality and QoL among patients surviving malignant bone tumors, 19 patients surviving osteosarcoma or Ewing's sarcoma of the lower extremity were studied. An evaluation of functionality and QoL was done using the "Enneking and Medical Outcomes Study Short-Form 36 scales." We compared the functional results according to the surgical technique used. Categorical variables were compared according to the Mann–Whitney and Kruskal–Wallis tests, with an established 95% level of significance.

Results QoL among patients who had conservative surgery was not significantly better than amputee patients in the physical or mental aspects, nor in any of their components. Limb functionality, according to Enneking's staging, was significantly higher in non-amputee patients ($p = 0.035$).

Conclusion According to the data analysis done in this study, the QoL was found to be not significantly different, based on the type of surgery performed; however, there were differences in limb functionality.

Keywords
- survivorship
- quality of life
- osteosarcoma
- Ewing's sarcoma

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Introduction

In the last few decades, advances in the oncologic treatment of patients with malignant pediatric bone tumors have observed an improvement in cure rates, leading to higher numbers of cancer surviving patients.[1] In Peru, osteosarcoma and Ewing's sarcoma are the most common malignant bone tumors, reporting aggressive and metastatic behavior in around 40% of cases. The most common location for tumor development is the lower extremity of the human body.[2] Due to the high intensity of the oncologic treatment that includes chemotherapy, surgery, and radiotherapy, survivors could be stricken by a series of future sequelae affecting their quality of life (QoL), both physically and mentally.[3]

Definitive surgery of malignant bone tumors with the aim of complete removal of the tumoral lesion (amputation or member disarticulation) can be radical. However, the conservative surgery approach has been most commonly used by Peruvian institutions throughout the years.[2] Even though differences have been noted in limb functionality between nonamputee and amputee patients, studies on the QoL show contradictory results.[4,5] Ignorance of long-term sequelae, both medical and psychological, is a growing public health issue, since conducting such research studies on those topics would allow for formulation of preventive measures or early intervention approaches which are important among surviving patients who reach adulthood.[6]

This study compares lower extremity functionality and the QoL of young patients surviving malignant bone tumors who have undergone a specific type of surgery performed in a developing country. The study also examines statistically significant differences between the two gender populations, since vast literature and extensive research support the fact that the incidence of bone tumors (of lower extremity) occurs considerably more in male populations than in their female counterparts; the gender differences are shown to differ statistically in their postsurgical prognosis. This study included key postsurgery metrics of QoL and overall functionality. They were further explicitly evaluated in the nonamputee surviving patients with lower extremity malignant bone tumors and compared, as well as contrasted the gender-based differences.

Methods

Study Population

Peru is a South American country with a total population of 32.2 million inhabitants. At least 1,790 children and adolescents (0–19 years old) are affected with cancer each year.[7] Principal hospitals attending children with cancer in Peru are either a part of the Ministry of Health (MINSA), Social Security (EsSalud), or private sector. Rebagliati Hospital works as a public general hospital of EsSalud, attending nearly 120 children and adolescents with cancer every year.

Inclusion Criteria

Patients older than 14 years old at the time of the study and diagnosed with osteosarcoma or Ewing's sarcoma of the lower extremity as a child or adolescent (younger than 18 years old) were included for treatment from January 2002 to December 2014 in the Adolescent and Pediatric Oncology Unit at Rebagliati Hospital in Lima, Peru. Patients who had received surgical treatment and follow-up for at least 2 years after the end of treatment were included as well.

Exclusion Criteria

Patients were excluded if they were critically ill or unable to consent.

The sample size used in this study was determined based on a sufficient statistical power (80%) to detect at least 10% differences in outcome measures at a 5% significant level. According to the study protocol, the lowest age to answer questionnaires was decided to be 14 years of age.

Data Collection

Data on demographics, clinical characteristics, and treatment outcomes were collected by revision of medical records. Based on the type of surgery, patients were separated into amputees and those who received conservative surgery. This study further analyzed the gender differences with similar diagnoses and surgical approaches (in nonamputee survivors). Patients were contacted by phone or interviewed in person to answer the questionnaire on Medical Outcomes Short (MOS) Form-36 Health Survey (SF-36; **Supplementary Material S1**; available in the online version); a tool widely used internationally to rate the QoL. Additionally, the Enneking score (Musculoskeletal Tumor Society [MSTS]; **Supplementary Material S2**; available in the online version) was used to estimate the functionality of the previously affected extremity. Based on the questionnaire responses, the analysis was done to understand differences in life quality and extremity functionality since disparities in those areas had been reported in the past based on the gender of the patient. Primary outcomes measured were limb functionality and QoL, whereas secondary outcomes measured were social functioning and overall health perception.

Statistical Analysis

Categorical variables were compared according to Mann–Whitney (bivariable) and Kruskal–Wallis (multivariable) tests to the scores obtained in the questionnaire on MOS SF-36 and the Enneking score, with an established 95% level of significance.

Ethics

The study was performed following the principles set out in the Helsinki Declaration and was approved by the Rebagliati Institutional Ethics Committee in July 2018. Informed patient consent was obtained prior to enrolment to all participants (**Supplementary Material S3**; available in the online version). In the case of patients younger than 18 years, parental consent was also needed.

Results

From 2002 to 2014, 27 cases of patients surviving bone sarcomas of the lower extremity were registered. Out of those, five could not be located, and three patients died in

another institution due to the progression of the disease. Nineteen patients (11 males and 8 females) with an average current age of 20 years were studied. Seven patients were from Lima while 12 were from several regions of Peru (Arequipa, Callao, Cajamarca, Trujillo, and Tacna). Seventeen patients received a diagnosis of osteosarcoma and two were diagnosed with Ewing's sarcoma. The most common surgical approach used was conservative surgery (15 cases, 78.9%), amputation being the least frequent among survivors (4 cases, 21.1%). At the time of diagnosis, the average age of patients was 15 years, that is, most were adolescents. Most survivors of bone sarcomas of the lower extremity presented localized disease (16 cases, 84.2%). The group of patients who underwent conservative or salvage surgeries presented a higher incidence of postsurgical complications (neurovascular injuries and deep wound infections) compared with the group of amputee patients (33.3 vs. 0%; ►**Table 1**).

QoL among patients who had conservative surgery was not significantly better than amputee patients in either the physical or mental aspects, nor in any of their components (►**Fig. 1**). Among nonamputees, social functioning ($p = 0.014$) and overall health perception ($p = 0.026$) were better among men

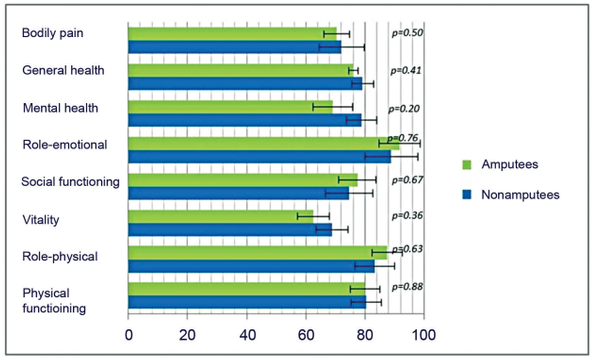

Fig. 1 Quality of life among patients who had conservative surgery.

(►**Table 2**). Limb functionality, according to Enneking's staging, was significantly higher in nonamputee patients ($p = 0{,}035$).

Discussion

Our study focuses on evaluating the QoL and lower extremity functionality among patients surviving malignant bone

Table 1 Clinical features of patients surviving malignant bone tumors of the lower extremity according to type of surgery

	Patients who had conservative surgery of lower limb ($n = 15$) Median (range)/n (%)/mean ± SD (range)	Patients who had amputation surgery ($n = 4$) Median (range)/n (%)/mean ± SD (range)	p-Value
Age at diagnosis (y)	15 (11–17)	15 (13–15)	
Current age (y)	20 (14–25)	21.5 (16–27)	
Gender			
Male	7 (46.7)	1(25)	
Female	8 (53.3)	3 (75)	
Diagnosis			
Osteosarcoma	13 (86.7)	4 (100)	
Ewing's sarcoma	2 (13.3)	0 (0)	
Stage			
Localized	14 (93.3)	2 (50)	
Metastatic	1 (6.7)	2 (50)	
Tumor location			
Distal femur	8 (53.3)	3 (75)	
Proximal femur	2 (13.3)	1 (25)	
Proximal tibia	4 (26.7)	0 (0)	
Fibula	1 (6.7)	0 (0)	
Postsurgical complications			
Yes	5 (33.3)	0 (0)	
No	10 (66,7)	4 (100)	
Quality of life			
Physical functioning SF-36	79.1 ± 7.4 (64.8–93.2)	78.04 ± 5.1 (71.6–83.7)	0.76
Mental health SF-36	76.2 ± 9.6 (60–97.3)	71.6 ± 7.1 (62.2–68.6)	0.45
Enneking's test			
Total score (%)	78 ± 14.6 (53.3–100)	59.1 ± 18.3 (50–86.6)	0.035

Abbreviations: SD, standard deviation; SF-36, Short Form-36 Health Survey.

Table 2 Comparison by gender of different scales of quality of life and functionality in nonamputee patients surviving malignant bone tumors of the lower extremity

Category	Male ($n = 7$) Mean ± SD (range)	Female ($n = 8$) Mean ± SD (range)	*p*-Value
Enneking's test			
Score (%)	76.2 ± 12.7 (53.3–86.7)	79.6 ± 16.9 (53.3–100)	0.75
Quality of life			
Physical functioning SF-36	79.5 ± 7.7 (64.9–90.5)	78.7 ± 7.7 (68.9–93.2)	0.82
Mental health SF-36	79.8 ± 9.9 (65.3–97.3)	73.2 ± 8.8 (60–88)	0.18
Components			
Bodily pain	70.1 ± 1 2.5 (45.5–81.8)	73.9 ± 18.5 (45.5–90.9)	0.31
General health	83.4 ± 6.3 (72–92)	75.5 ± 6.6 (68–88)	0.026
Mental health	81.4 ± 11 (66.7–100)	76.7 ± 10.4 (66.7–96.7)	0.38
Role emotional	90.5 ± 13.1 (66.7–100)	87.5 ± 23.1 (50–100)	0.78
Social functioning	82.9 ± 17 (50–100)	67.5 ± 12.8 (50–80)	0.014
Vitality	72 ± 13.8 (58.3–100)	66.1 ± 7.9 (54.2–75)	0.45
Role: physical	80.4 ± 15.9 (62.5–100)	85.9 ± 12.4 (62.5–100)	0.47
Physical functioning	79.5 ± 9.7 (66.7–90)	81.3 ± 11.8 (66.7–96.7)	0.86

Abbreviations: SD, standard deviation; SF-36, Short Form-36 Health Survey.

tumors in the transition period between adolescence and adulthood facing challenges linked to the oncologic treatment they received. We found no significant difference in the QoL, neither in the physical or mental aspects, nor in any of their components among patients who had conservative surgery versus amputation. In past decades, amputation was the treatment of choice for localized disease control of malignant bone tumors. Now, both national and international organizations support the idea that conservative surgery is the standard treatment and a priority in the multidisciplinary team against osteosarcoma and Ewing's sarcoma.[2,8,9] This subject is acquiring relevance in public health due to the potential need to employ additional resources or support services in physiotherapy and psychosocial therapy.[7,10]

Most studies involving patients surviving pediatric bone tumors have been conducted in high-income countries and do not specifically examine patients whose lower limbs have been compromised.[11,12] In our study, the QoL among amputee patients compared with that of the group who underwent conservation surgery did not change significantly, a finding similar to that of most studies,[8,9,13–17] but different from others.[18–20] Nevertheless, the functionality of the extremity was significantly higher in the group of patients who had conservative surgery, as reported in other studies.[21,22]

Although patients surviving bone sarcomas could suffer a series of subsequent events (recurrences, new surgeries on the affected limb, metastasis, or retarded effects of medication), their adaptation level to the social environment relating to educational, or employment level is not much different from that of the general population.[4,5] It is important to note that postsurgical complications are generally more common in patients who had conservative surgery, as shown in our study.[16,19]

Related to gender, this study showcases that social functioning and overall health perception were better among men in the group of patients who had conservative surgery. This is consistent with several literature reviews produced which predominantly stated, although lower extremity bone tumors are more common in males, their QoL and functional scores are statistically more than that of females (based on variations of the Mann–Whitney test).[23,24] In contrast, a study showed that men had diminished performance in the work environment and were less likely to be married.[7]

Limitations and Strengths

Within the limitations of our study, there is a potential selection bias. This is because some patients were excluded from this study, since they could not be located or contacted, probably leaving aside survivors with more significant performance difficulties or greater negative impact on their QoL. Another drawback involves the retrospective nature of the study with the limited number of cases per group since bone sarcomas are infrequent pathologies with high mortality rates, especially in lower- and middle-income countries. Among the strengths of this study, it is essential to note that evidence has been produced of a relatively homogeneous group of patients who have mostly undergone conservative surgeries, a treatment approach demonstrating an upward trend in terms of its utility, further providing evidence in a country of limited resources. Future research should focus on a better understanding of these patients' functional status and QoL.

Conclusion

In conclusion, this study indicates that the QoL of patients who have suffered bone neoplasia of the lower extremity during their pediatric years in a developing country is not significantly different due to the nature of the surgery performed, even though there were differences in limb functionality. The latter increased among patients who underwent conservative surgery. A subsequent analysis with a larger number of patients is needed to verify such results.

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None.

Conflict of Interest
None declared.

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A Prospective Single-Arm Study of Melphalan, Prednisolone and Lenalidomide (MPL) as First Line Treatment in Elderly Patients with Multiple Myeloma – An Institutional Study

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Abstract

Introduction Multiple myeloma in the elderly population is rising in India. Such frail transplant-ineligible patients are less frequently included in clinical trials. Moreover, novel agents are not accessible to everyone. Melphalan-based chemotherapy regimens are frequently used in elderly myeloma patients. Our study revisited the role of melphalan, prednisone, and lenalidomide (MPL) as front-line therapy in this subgroup of patients.

Objective The aim of this study was to determine the response, tolerance, and outcome of MPL in elderly patients with newly diagnosed multiple myeloma.

Materials and Methods This prospective study was conducted at the Department of Medical Oncology at a tertiary cancer center during January 2012 to September 2013. Newly diagnosed patients with multiple myeloma >60 years who were transplant ineligible formed the study subjects. Eligible patients received oral melphalan 0.18 mg/kg from D1 to 4, prednisone 2 mg/kg from D1 to 4, and lenalidomide 10 mg from D1 to 21 q28 days. Patients who achieved complete response/very good partial response (CR/VGPR) after 6 cycles of MPL received maintenance with lenalidomide 10 mg from D1 to 21 q28 days (MPL-L) until progression or 1 year whichever was earlier. Quality of life was assessed using the Eq. 5D questionnaire.

Results Out of 46 patients, 25 were males and 21 were females. Median age was 67 years (range: 60—83 years). Majority had immunoglobulin G myeloma, followed by immunoglobulin A subtype. The median quality of life score at baseline was 50 (range: 30–70). Forty patients completed six cycles of MPL. The main toxicity was grade 1 to 2 hematological. There were no treatment-related deaths. Twenty-two (55%) achieved CR, 5 (13%) achieved VGPR, 4 (10%) achieved partial response, 6 (15%) achieved stable

Keywords
- MPL
- elderly myeloma
- lenalidomide maintenance

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disease, and 3 (7%) had progressive disease. Twenty-seven patients received lenalidomide maintenance. At a median follow-up of 55 months, the 2- and 5-year progression-free survival was 60 and 18%, respectively. The overall survival at 2 and 5 years were 80 and 53%, respectively. The median number of subsequent lines of treatment was 2 (range: 1–4). The quality of life was improved and preserved in all study subjects. At 8 years, three patients had second malignant neoplasms and seven are alive.

Conclusion MPL-L is a well-tolerated and effective regimen in elderly myeloma with good overall response rates.

Introduction

Multiple myeloma (MM) is a plasma cell disorder that accounts for 10 to 15% of hematological malignancies. The incidence of MM in India is lower when compared with the West (1/1,00,000 vs 4.1/1,00,000), but, as per recent statistics, the numbers are expanding.[1] As the life expectancy of the general population is on the rise, the proportion of elderly patients with various malignancies is expected to rise as well. MM deserves special mention in this seam, as the majority affected are elderly, frail, and transplant ineligible. The median survival of elderly patients with MM has improved in recent years with the advent of newer agents, starting from bortezomib in late 2000s.[1] In 1990s, combination of melphalan, prednisone, and thalidomide was considered as a standard of care in elderly MM, who were transplant ineligible.[1] Present study looked at the role of lenalidomide along with melphalan and prednisone, herein after referred as MPL-L (melphalan-prednisone-lenalidomide induction followed by lenalidomide maintenance) in elderly patients as front-line therapy in MM.

Materials and Methods

This prospective single-arm study was conducted at the Department of Medical Oncology at our tertiary cancer Institute, in India, during 2012 to 2013. Patients with newly diagnosed MM above 60 years of age, transplant ineligible, were included in the study. Patients with an Eastern Co-operative Oncology Group performance status of ≤ 2 with adequate organ function as indicated by the laboratory tests (hemoglobin [Hb] > 8 g/dL, platelet count $>75000/mm^3$, absolute neutrophil count $> 1000/mm^3$, serum creatinine <2.5mg/dL, serum bilirubin < 1.5mg/dL, aspartate aminotransferase/alanine aminotransferase [ALT/AST] <2.5 times upper limit of normal) were included for the study. Patients with uncontrolled intercurrent infections, renal failure, congestive cardiac failure, and previous history of thromboembolic episodes were excluded from the study. The study was approved by Institutional Ethics Committee and patients were recruited after obtaining informed consent. The recruitment was consecutive and all eligible patients during the study period (January 2012 to September 2013) were considered for the study. Baseline demographic profile, blood parameters (Hb, total white blood cell (WBC) count, differential count, platelet count, serum creatinine, blood urea, serum bilirubin, ALT/AST, total protein, serum albumin, serum globulin, serum sodium, serum potassium, serum calcium, immunoglobulin assay, free light chain assay, serum electrophoresis), bone marrow study details, and skeletal survey were considered for the study. Imaging with computed tomography/magnetic resonance was done as indicated. Baseline cytogenetics for the study group was not done as it was not available to us during the study period. Eligible patients received oral melphalan 0.18 mg/kg from D1 to 4, prednisone 2 mg/kg from D1 to 4, and lenalidomide 10 mg from D1 to 21 q 28 days (MPL). After 6 cycles of MPL, patients who achieved complete response (CR)/very good partial response (VGPR) received maintenance with lenalidomide 10 mg from D1 to 21 q 28 days until any sign of relapse or progression or 1 year whichever was earlier (MPL-L). Patients with partial response/stable disease (PR/SD) were given six more cycles of induction MPL. All patients received aspirin and cotrimoxazole prophylaxis throughout the treatment. For staging, International Staging system (ISS) was used.[2] Response to treatment was assessed by International Myeloma Working Group criteria.[3] Toxicity was graded using CTCAE v3. Quality of life (QoL) was assessed using the Eq. 5D questionnaire.[4] The toxicity assessment was done at each visit. The QoL was assessed at baseline, after 3 and 6 months of MPL and after 12 months of maintenance lenalidomide. The primary endpoint was response assessment, that is, attainment of CR/VGPR/PR)/SD/progressive disease (PD), and the secondary endpoints were progression-free survival (PFS), overall survival (OS), toxicity assessment, and QoL. During maintenance, clinical examination and laboratory investigations (Hb, total WBC count, platelet count, serum creatinine, blood urea, serum calcium, immunoglobulin assay, free light chain assay, and serum electrophoresis) were done q3monthly. Further follow-up was done q6monthly with clinical examination and investigations, as above, or earlier if the patient was symptomatic. PFS was calculated from the date of diagnosis to the date of first progression or death. OS was calculated from the date of diagnosis to the date of last follow-up or death.

Statistical Analysis

The categorical variables are expressed in frequency and proportion. The continuous variables are summarized using mean and standard deviation. The OS and PFS are estimated using Kaplan–Meier method and association of survival

Table 1 Toxicity profile of study subjects

	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hematological toxicity				
Anemia	17 (37)	17 (37)	4 (9)	1 (2)
Thrombocytopenia	17 (37)	6 (13)	6 (13)	1 (2)
Neutropenia	14 (30)	12 (26)	3 (6)	1 (2)
2 (4.3%) patients developed febrile neutropenia				
Nonhematological toxicity				
Fatigue	15 (33)	10 (22)	0	0
Pneumonitis	4 (9)	0	0	0
Deep vein thrombosis	0	1 (2)	0	0
Rash	4	0	0	0

with comparator parameters is tested using logrank test. The risk is estimated using Cox Regression. A *p*-value of <0.05 is considered to be significant. SPSS v.20 was used for the analysis.

Ethics

The study was approved by the Human Ethics Committee (HEC 37/2011, dated January 12, 2012). The trial is registered under the Clinical Trials Registry - India (CTRI) (CTRI/2013/04/003565). Written informed consent was obtained from all study subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Baseline Characteristics

A total of 65 patients were screened for the study. Out of 55 patients who were eligible for the study, 46 patients received the study drug. Nine patients did not report back for treatment. Twenty-five patients were males and 21 were females. The median age was 67 years (range: 60–83 years). Seventeen (37%) patients were in 60 to 65 years age group, 14 (30%) were in 66 to 70 years, and 15 (33%) patients were in >70 years age group. Twenty patients had documented comorbidities at the time of study entry. Thirty-three patients had IgG myeloma, 7 had immunoglobulin A (IgA) myeloma, 5 had light chain myeloma, and 1 had nonsecretory myeloma. According to the ISS staging system, 19 had stage I, 13 had stage II, and 14 had stage III MM. All had CRAB (hypercalcemia, renal impairment, anemia and bone lesions) criteria at presentation. Seven patients had hypercalcemia, 10 patients had renal impairment, 15 patients had anemia, and 40 patients had bone lesions. Urine Bence-Jones proteins were demonstrable in six patients. The median QoL score at baseline was 50 (range: 30–70).

Treatment Received and Outcome

All 46 patients received at least one cycle of chemotherapy and 40 patients completed six cycles of MPL. The main toxicity was grade 1 to 2 hematological in nature. Nonhematological toxicities included fatigue (grade 1–2), pneumonitis (grade 1), and deep vein thrombosis (grade 2). Four (8.7%) patients required granulocyte colony stimulating factors (GCSF) and two (4.3%) patients had febrile neutropenia that were managed conservatively. Two patients were withdrawn from the study, the reasons being allergy to lenalidomide and severe hematological toxicity to chemotherapy. There were no treatment-related deaths. The summary of adverse events is shown in ►**Table 1**.

The response assessment was done after six cycles of MPL. Twenty-two (55%) patients achieved CR, five (13%) achieved VGPR, four (10%) achieved PR, six (15%) achieved SD, and three (7%) had PD. The median time to response was 3 months (range: 3–6 months) and the median time to maximum response was 6 months (range: 6–9 months). Out of 27 patients who received lenalidomide maintenance, 23 completed 1 year of treatment, 3 patients relapsed, and one was lost to follow-up. Out of 10 patients with PR/SD, 5 received six additional cycles of MPL, among which, 3 achieved CR and 2 progressed. The remaining 5 received MP further.

The median follow-up was 55 months. The 2- and 5-year PFS were 60 and 18%, respectively (►**Fig. 1**). The OS at 2 and 5 years were 80 and 53%, respectively (►**Fig. 2**). The 5-year PFS for IgG subtype was 13.5 versus 9.7% for all other subgroups combined (p-value $= 0.597$) (►**Fig. 3A**). The 5-year OS for IgG subtype was 64.2 versus 27.7% for all other subgroups combined (p-value $= 0.032$) (►**Fig. 3B**). The 5-year PFS for ISS stage 1, 2, and 3 were 23, 10 and 0% (p-value $= 0.116$), respectively and the 5-year OS for ISS stage 1, 2, and 3 were 60, 59 and 40% (p-value $= 0.193$), respectively. Age was not a significant factor in our study.

Twenty-four patients received next line of treatment, with bortezomib-based chemotherapy in the majority, at a median duration of 31 months (range: 8–102 months). The

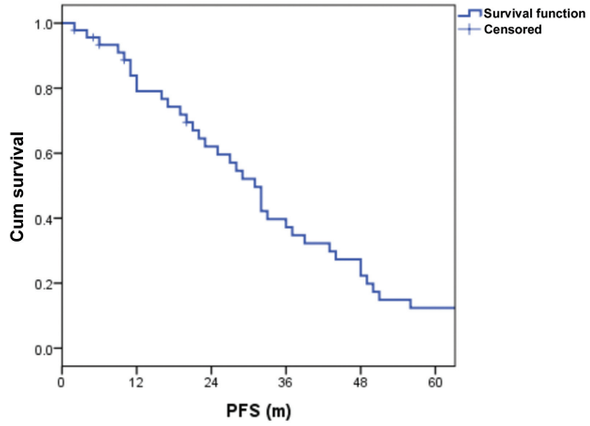

Fig. 1 Progression-free survival (PFS).

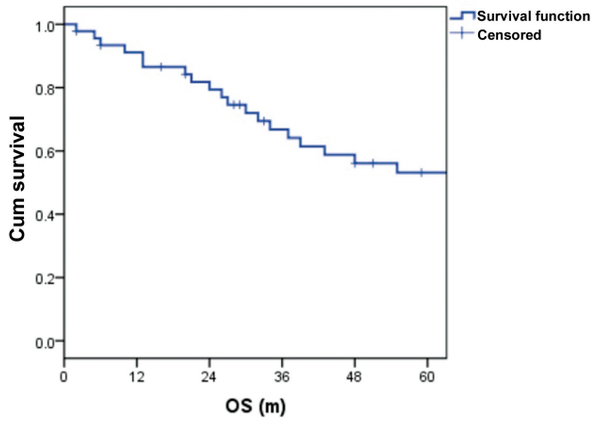

Fig. 2 Overall survival (OS).

median number of subsequent lines of treatment was 2 (range: 1–4). The median PFS in those who completed 1 year maintenance was 41 months (range: 20–111 months) and median OS was 69 months (range: 20–111 months). At 8-year follow-up, seven patients are alive (►**Fig. 4**). Three developed second malignancies, in the form of squamous cell carcinoma esophagus at 2 years, clear cell renal cell carcinoma at 3 years, and carcinoma larynx at 5 years.

QoL Assessment

The QoL was improved and preserved in all the study subjects. At the point of study entry, the median QoL was 50 (range: 30–70). The median QoL after 3 cycles of MPL, 6 cycles of MPL, and after 12 cycles of maintenance lenalidomide were 60 (50–90), 90 (50–100), and 100, respectively.

Discussion

The treatment armamentarium of elderly patients with MM is abounding. Choosing the upfront treatment of an elderly transplant ineligible MM patient depends on the performance status, organ reserve, comorbidities, and polypharmacy. MP, the once considered standard of care in elderly MM has undergone various combinations and has evolved to the present treatment schedules. The added benefit of thalidomide to MP (MPT) was demonstrated in the benchmark trial, Intergroupe Francophone du Myelome (IFM) 99–06, and henceforth was continued as the new standard of care in the treatment of elderly MM in late 1990s and early 2000s.[5] MPT was better than MP in terms of PFS, OS, and time to progression. The benefit of lenalidomide in combination with MP was studied by Palumbo et al in 2007 and it was found to be an effective regimen with good response rates.[6] A subsequent phase I/II trial of MPL in transplant ineligible MM patients, with a median age of 74 years, demonstrated an objective response rate of 69% and manageable toxicity profile.[7] In the phase III trial EA106, Stewart et al compared MPT and MPL in newly diagnosed transplant ineligible MM. In this study, both the study arms had similar PFS and OS with a favorable hematological (73 vs. 58%; $p = 0.007$) and non-hematological (59 vs. 40%; $p = 0.001$) toxicity profile for MPL.[8] Palumbo et al in 2012 investigated the role of MPL induction followed by maintenance lenalidomide (MPL-L) among 459 transplant ineligible MM patients. MPL-L was

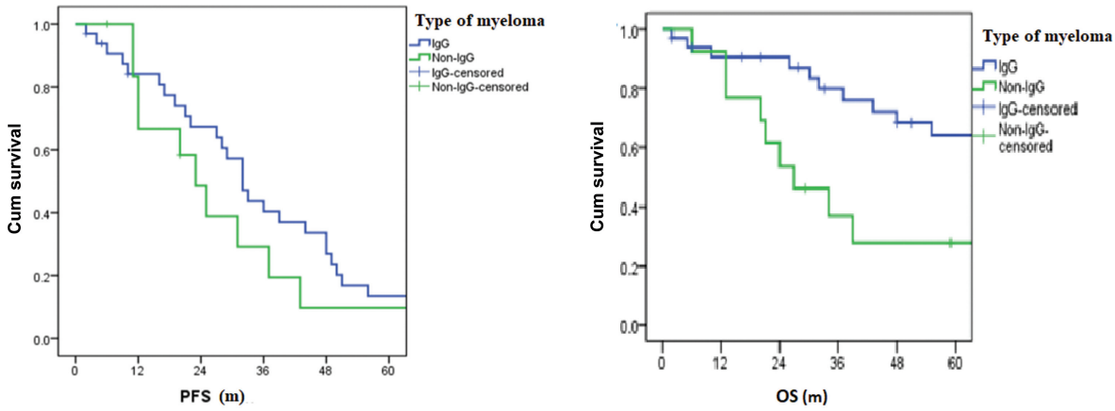

Fig. 3 (A) Progression-free survival (PFS) versus type of myeloma. (B) Overall survival versus type of myeloma (OS). IgG, immunoglobulin G.

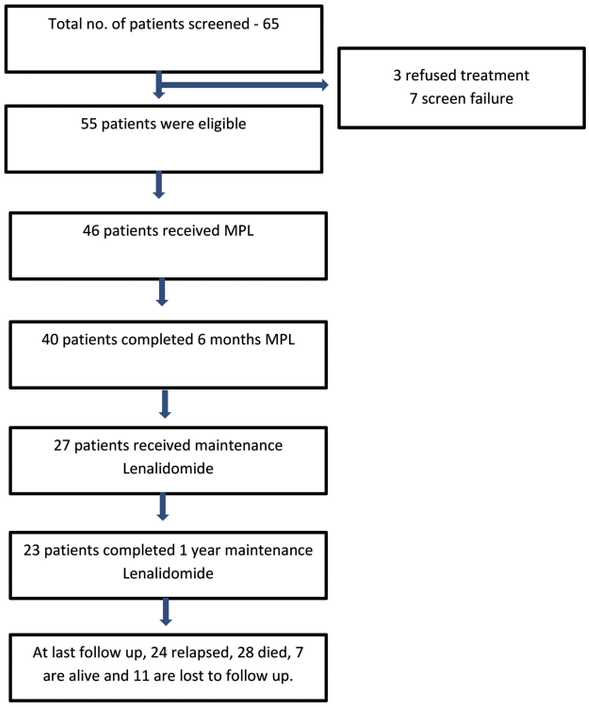

Fig. 4 Consolidated Standards of Reporting Trials (CONSORT) diagram. MPL, melphalan, prednisone, and lenalidomide.

found to significantly improve the PFS, and the greatest benefit was seen in 65 to 75 years age group.[9]

Our study investigated the role of MPL followed by maintenance lenalidomide as front-line in transplant ineligible MM patients. In our study, IgG subtype and ISS stage 1 were the commonest. The regimen was well tolerable and all the described toxicities were managed conservatively. There were 16 grade 3 to 4 hematological events. Two (4.3%) patients had febrile neutropenia and four (8.7%) required GCSF support. There was no treatment-related mortality. However, in the MM-015 study, grade 3 to 4 hematological toxicities are reported as the most common.[9]

In our study, the percentage of patients with at least a PR was 78% after six MPL. As per MM-015 study also, a CR/PR rate of 77% was seen in the MPL-L regimen. The median PFS in MM-015 study was better for MPL-L than MP, 31 and 13 months, respectively, with continued benefit at maintenance of lenalidomide as well.[9]

As the majority of clinical trials enroll fit and young patients, the data on elderly patients is very scarce. Focus on the tolerability and QoL maintenance is imperative in managing elderly MM patients. As per MM-015 study, 16% of patients had to discontinue the drug due to adverse events; however, it is lower than that with MPT (33–45%) and V(bortezomib) MP (12–34%). In our study, only one patient was withdrawn due to poor treatment tolerance. In EA106 trial, which compared melphalan, prednisone, thalidomide with thalidomide maintenance (MPT-T) and melphalan-prednisone-lenalidomide with lenalidomide maintenance (MPR-R), survival was similar in both, while QoL assessment favored MPR-R arm at the end of induction.[10] In our study group, the QoL was maintained and was progressively better throughout the treatment protocol unless the disease was progressive. The 2- and 5-year PFS were 60 and 18%, respectively, and the OS at 2 and 5 years were 80 and 53%, respectively. The survival was better for IgG subtype in our study. ISS was not statistically significant for PFS in our study, probably due to the small sample size and as the majority were in ISS stage 1. The median number of subsequent lines of treatment was 2 (range: 1–4). At 8-year follow-up, seven patients are alive and three developed second malignancies.

Our study has the limitation of a small sample size. We could not perform baseline cytogenetics in our study as it was unavailable during the study period. Elderly, frail patients with MM who are not fit for intensive chemotherapy can have meaningful remission rates with MPL-L regimen. This is a well-tolerated and effective oral regimen and studies comparing this with bortezomib-based regimens in elderly MM need to be explored in the future.

Conclusion

To conclude, MPL-L is an effective and well-tolerated regimen in elderly myeloma with good overall response rates.

Disclaimer

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Conflict of Interest
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A Longitudinal Study to Reexamine the Mental Health Impact on Radiation Oncology Health Care Workers with the Launch of COVID-19 Vaccination Strategies in India

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Abstract

Introduction The novel coronavirus disease 2019 (COVID-19) catastrophe caused significant mental threats to health care workers (HCW), especially during the first wave of the pandemic. India successfully implemented vaccination strategies in January 2021 that is likely to ameliorate the mental health impact of HCWs. The current survey aims to identify the change in impact following vaccination and address the issues affecting mental health.

Objective The primary objective is to reevaluate the stress levels of radiation oncology HCWs with vaccine implementation and compare it with the mental health status at the onset of the pandemic. The secondary objective is to identify the current causative factors influencing mental health.

Materials and Methods Health care workers who participated in the initial mental health impact survey at the outset of the COVID-19 pandemic from May to July 2020 were included in this study. Two hundred eligible HCWs were reassessed of the total 363 initial assessments. The 7-item Generalised Anxiety Disorder (GAD-7), 9-item Patient Health Questionnaire (PHQ-9), and 22-item Impact of Events Scale-revised (IES-R) was again served for assessing anxiety, depression, and posttraumatic stress disorder. The Mc Nemar test was

Keywords
- mental health
- radiation oncology
- COVID-19 vaccination
- anxiety
- depression
- stress

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used to evaluate the change and significance of the mental health impact. Univariate and multivariate analyses were done to identify the causative factors affecting mental health.
Results The cohort's median age was 30 years (interquartile range [IQR]: 27–33). The incidence of moderate-to-severe level anxiety, depression, and stress significantly declined to 6.5% ($p = 0.031$), 9% ($p = 0.01$), and 19% ($p < 0.001$) compared with 39.5, 40.5, and 30.5% during the pandemic onset. On further analysis, HCWs with affected family members had higher levels of stress ($p = 0.002$). The rest of the parameters did not have significant impact on mental health outcomes.
Conclusion With public education, awareness, and vaccination strategies, the second follow-up survey conducted after vaccine implementation demonstrated a significant number of HCWs in the radiation oncology community, exhibiting a decline in the incidence of anxiety, depression, and stress levels compared with the initial wave of the pandemic.

Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic, a catastrophic health crisis witnessed in the 21st century, had adversely affected mental health across the globe.[1] The relentless increase in the number of cases and the unpredictable nature of this pandemic had further exacerbated the public's psychological distress.[2] In India, more than 4.3 crore cases have been identified so far, with above 5.2 lakh COVID-19-related deaths.[3,4] The psychological impact of COVID-19 on humanity makes it imperative to address issues concerning mental health with a degree of urgency.[5]

Although there is an acute shortage of health workforce, we have nearly 5.76 million health care workers (HCWs).[6] Mental stress had taken a toll on our HCWs during this critical period, affecting their professional and personal life. A few of the apparent reasons attributed were lengthy working hours, multiple shifts, risk of contracting the infection, transmitting it to family members back home, nonavailability of personal protective equipment (PPE), isolation, quarantine, and segregation from families.[7] In terms of availability of beds, our country has approximately 713,986 hospital beds across 25,778 hospitals in the government sector which is as low as 13.76 beds per 10,000 people.

During the first pandemic wave, more significant anxiety and panic was reported consequent to the rising number of fatalities and unavailability of a vaccine. Various studies were conducted on the deteriorating mental health condition of HCWs. HCWs from oncology and, especially, branches like radiation oncology, have more frequent contact and exposure to the patients due to the fractionated and prolonged course of treatment. A multinational study conducted in India from May 2020 to July 2020 with 758 participants of the radiation oncology fraternity, comprising various Asian countries revealed significant anxiety, depression, and stress levels s in HCWs.[8]

With the rising number of cases and deaths, the public, including HCWs, was apprehensive about contracting the infection and the possibility of a next wave. The beginning of 2021 witnessed the approval of vaccines to fight the pandemic that had caused untold misery and deaths across the globe.[9] However, around 20 to 30% of the population were also apprehensive about the vaccine's side effects.[10] India inaugurated its vaccination drive program on January 16, 2021.[11] Two vaccines were approved, the Covaxin which is an inactivated viral vaccine and Covishield which uses the viral vector platform. The country expedited its vaccination drive on a war footing, and 1 billion cumulative vaccine doses were administered by October 21, 2021.[12] This remarkable achievement was possible due to continued efforts from government agencies, vaccine manufacturers, and HCWs.

The ongoing vaccination drive, the resultant decrease in the severity of infections, and a marked fall in death rates are likely to have boosted the morale of most of our HCWs. On the other hand, the public was also apprehensive about the shortage of vaccines, their effectiveness, side effects, and the possibility of a second pandemic wave. We could see that a proportion of them was still unable to cope with the stress despite continued awareness and vaccine implementation. Hence, our study aimed to evaluate the change in the mental health status of radiation oncology HCWs following the mass vaccination drive in India and compare it with that at the beginning of the pandemic and identify the various causative factors negatively impacting their mental health.

Materials and Methods

This longitudinal study was conducted as a continuation of the survey done during the onset of the pandemic to reexplore the mental health status of HCWs with the advent of vaccine implementation strategies. The initial assessment from various Asian countries was published earlier this year.[8] The data collection variables included demographic profile, history of COVID-19 contact, testing, and infection with vaccination status. Responses of the mental health assessment tools were analyzed. The case record form with all data variables is given in the **Supplementary Material S1** (available in the online version).

Participants

The mental health status of radiation oncology HCWs from four tertiary cancer care centers in India was assessed from January 2021 to May 2021. This period was chosen because the first wave of the pandemic was tailing down, and vaccination strategies for HCWs were just implemented and slowly picking up across the country. Participants were requested to fill out the survey via a google form. Three reminders were sent for completing the survey, and each question was marked mandatory to avoid missing data. The closure date for the response to the survey was fixed as May 10, 2021.

Inclusion and Exclusion Criteria

Our study included radiation oncology HCWs from India who filled the survey at the pandemic onset, aged 18 years and above. There was no cut-off for the upper age limit. The participants included radiation oncology clinicians, physicists, technologists, nurses, and allied workers. Participants who did not participate in the initial survey were excluded.

Data Collection

Of the 363 Indian participants who participated in the initial survey, 200 responses were received, forming the study sample for the current analysis. ►**Supplementary Fig. S1** (available in the online version) represents the number of participants evaluated during the first and second surveys. The demographic profile, including a history of vaccination status, was documented. The 7-item Generalised Anxiety Disorder (GAD-7), 9-item Patient Health Questionnaire (PHQ-9), and 22-item Impact of Events Scale-revised (IES-R) was again utilized for assessing anxiety, depression, and posttraumatic stress disorder. Univariate and multivariate analysis was done to identify the causative factors affecting mental health. No subgroup analysis was performed. For GAD-7, scores 0 to 4 represent minimal, 5 to 9 mild, 10 to 14 moderate, and 15 to 21 severe anxiety. For PHQ-9, scores 0 to 4 represent none, 5 to 9 mild, 10 to 14 moderate, 15 to 19 moderately severe, and 20 to 27 severe depression. For IES-R scores from 0 to 88, a total score of 24 or more for posttraumatic stress disorder is a clinical concern.[13,14]

Statistical Analysis

Statistical Package for Social Sciences software, Version 25, was utilized for data analysis. The McNemar test was used to evaluate the change and significance of the mental health impact. Important causative factors for anxiety, depression, and stress were analyzed. Significant factors were entered into a multivariate Cox's proportional hazards model and expressed as hazard ratio (HR) with a 95% confidence interval (CI). A p-value of ≤ 0.05 was considered statistically significant.

Ethics

Tata Memorial Centre Institutional Ethics Committee approval was taken (project no: 3482, dated: May 13, 2020), and Clinical Trial Registry of India registration (CTRI no.: 2020/05/025212) was done before the initiation of the study. Informed consent was obtained from all participants. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013.

Results

A total of 200 participants were assessed again for anxiety, depression, and stress. It was observed that 108 (54%) were married, 103 (51.5%) aged above 50 years, and 105 (52.5%) had less than three rooms in the household. Comorbidities were present in 26 (13%) participants. Among all the participants, 93 (46.5%) were physicians and 197 (98.5%) of HCWs had above secondary education. ►**Table 1** shows the demographic profile of the participants.

History of testing for COVID-19 and contracting the infection at any point of time during the pandemic was recorded for all study subjects. Overall, 113 (56.5%) of the participants got tested for COVID-19 among which 29 (14.5%) got infected. Also, 27 (93.1%) participants recovered from the infection by 2 to 4 weeks; however, two (7%) HCWs took nearly 4 to 6 weeks to recover. There was a total of 46 (23%) participants whose family members tested positive among whom 6 (13%) had both the participant and the family getting infected which was an important finding not usually asked in the questionnaire while evaluating mental health. About 152 (76%) of the participants had the facility for vaccination within the hospital itself. However, getting it done was voluntary, and 145 (72.5%) participants received at least one dose of the vaccine at the survey time. ►**Table 2** depicts the history of COVID-19 testing, infection, contact, and vaccination status for all participants.

The incidence of anxiety, depression, and stress levels were estimated in all the participants (►**Fig. 1**). It was noted that moderate-to-severe level was seen in 13 participants (6.5%), moderate-to-severe depression in 18 participants (9%), and moderate-to-severe stress in 38 (19%). It was noticed that the adverse impact on mental health had a decreasing trend during the span of vaccine implementation compared with the survey done at the beginning of the pandemic. ►**Fig. 2** shows the change in the levels of anxiety, depression, and stress that changed over the course of the pandemic. The levels of moderate-to-severe anxiety decreased from 39.5 to 6.5% ($p = 0.03$), depression from 40.5 to 9% ($p = 0.001$), and stress levels from 30.5 to 19% ($p < 0.001$). Following precautions for personal protection, health education about the transmission of infection, public awareness, and vaccine implementation is likely to have contributed to change in mental health status over time.

Univariate analysis was done to assess the factors which determine anxiety, depression, and stress levels. It was seen that none of the factors was significant for anxiety and depression among all. However, for stress levels, COVID-19 infection among family members significantly contributed to increased stress levels ($p = 0.002$). ►**Table 3** shows the univariate analysis for stress. The tables of univariate analysis for anxiety and depression are shown in the

Table 1 Demographic profile of all participants

Participants		***n* = 200**	
Median age [IQR] in years		30	[27–33]
		n	%
Gender	Female	87	43.5
	Male	113	56.5
Marital status	Divorced or separated	1	0.5
	Married	108	54.0
	Single	91	45.5
Number of rooms in the household	<3	105	52.5
	≥3	95	47.5
Children less than 15 years	0	135	67.5
	1	44	22.0
	≥2	21	10.5
Age more than 50 years	No	97	48.5
	Yes	103	51.5
Occupation	Administrator	3	1.5
	Allied health care worker	20	10.0
	Nurse	4	2.0
	Physician	93	46.5
	Physicist/therapist	80	40.0
Cadre	Junior staff (<10 years' experience)	124	62.0
	Senior staff (>10 years' experience)	26	13.0
	Student	50	25.0
Comorbidities	No	174	87.0
	Yes	26	13.0
History of smoking or tobacco use	No	191	95.5
	Yes	7	3.5
	Do not want to disclose	2	1.0
Educational qualification	Above secondary	197	98.5
	Below secondary	3	1.5

Abbreviations: COVID-19, novel coronavirus disease 2019; IQR, interquartile range.

►**Supplementary Tables 1** and **2** (available in the online version).

Discussion

The COVID-19 pandemic has undoubtedly impacted the mental health of a significant proportion of the population. A survey conducted in the United States revealed that 4 in 10 adults reported anxiety or depressive disorder, compared with 1 out of 10 in the prepandemic era.[15] Conspicuous factors impacting mental health include fear of getting infected, isolation, quarantine for long periods, lack of social life and financial burden. As the pandemic unfolded, individuals at a high risk of psychological stress were the frontline workers, including doctors, nurses, community health workers, sanitation workers, police personnel, and others. They relentlessly provided care and assistance to the affected needy as the pandemic raged across the country.[16] Long working hours, multiple shifts, fear of transmitting the contagion to family members, and inadequacy of emergency medical equipment, including PPEs, manifestly exacerbated the stress level during the initial wave of the pandemic, even as the unprecedented lockdowns derailed the health care system across the world.[17]

Cancer care was affected during the pandemic across the globe and in India.[18,19] Despite grave challenges, the center delivered uninterrupted cancer care services.[20] At the onset of the pandemic, a multinational survey was conducted across Asian countries to assess the anxiety, depression, and stress levels among HCWs in the radiation oncology community from May to July 2020. The study revealed

Table 2 History of COVID-19 testing, infection, contact, and vaccination status

		n (200)	%
Close contact	No	40	20.0
	Yes	160	80.0
Place of Contact	Society	13	8.1
	Workplace	138	86.3
	Other	9	5.6
Testing for COVID-19	No	87	43.5
	Yes	113	56.5
COVID-19 positive	No	171	85.5
	Yes	29	14.5
Weeks for recovery	2 to 4	27	93.1
	4 to 6	2	6.9
Family members contracted COVID-19	No	154	77.0
	Yes	46	23.0
HCW and family +ve	Yes	6/46	13
Vaccination facility	No	48	24.0
	Yes	152	76.0
Volunteering to get vaccinated	No	55	27.5
	Yes	145	72.5

Abbreviations: COVID-19, novel coronavirus disease 2019; HCW, health care worker.

significant levels of anxiety (34.8%), depression (31.2%), and stress (18.2%) among HCWs.[8]

The current analysis of 200 participants across various tertiary cancer care centers in India shows that 80% had close contact with a COVID-19-positive patient, with 86% at the workplace. A surge in COVID-19-positive patients within the hospital was seen as cancer patients were a vulnerable group to contracting infection consequent in decreased overall immunity. The hospital policy did not insist on testing asymptomatic patients who visited the institution daily for radiation treatment.[21] However, patients posted for brachytherapy procedures were routinely tested. This aggravated the existing case burden for COIVD-19. Around 14.5% of the HCWs tested positive, and nearly 7% tested free from the virus after 4 to 6 weeks. The more prolonged periods of isolation had impacted mental health.

As the year came to a close, vaccines were developed in various countries. In December 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19 in individuals 16 years of age and older.[22] India's COVID-19 vaccination drive commenced in the middle of January with the approval of Covishield and Covaxin vaccines for restricted emergency use.[23] HCWs of our country were among the first to receive the vaccine doses.[24] Also, 76% of the participants had access to vaccination centers within the hospital itself.

As the vaccination program commenced, there was skepticism among a minority of the public on whether to get vaccinated or not. This is a natural corollary to the media reports on the efficacy and side effects of various parts of the world. In March 2021, the Danish Health Authority reported severe cases of blood clots with the Vaxzevria COVID-19

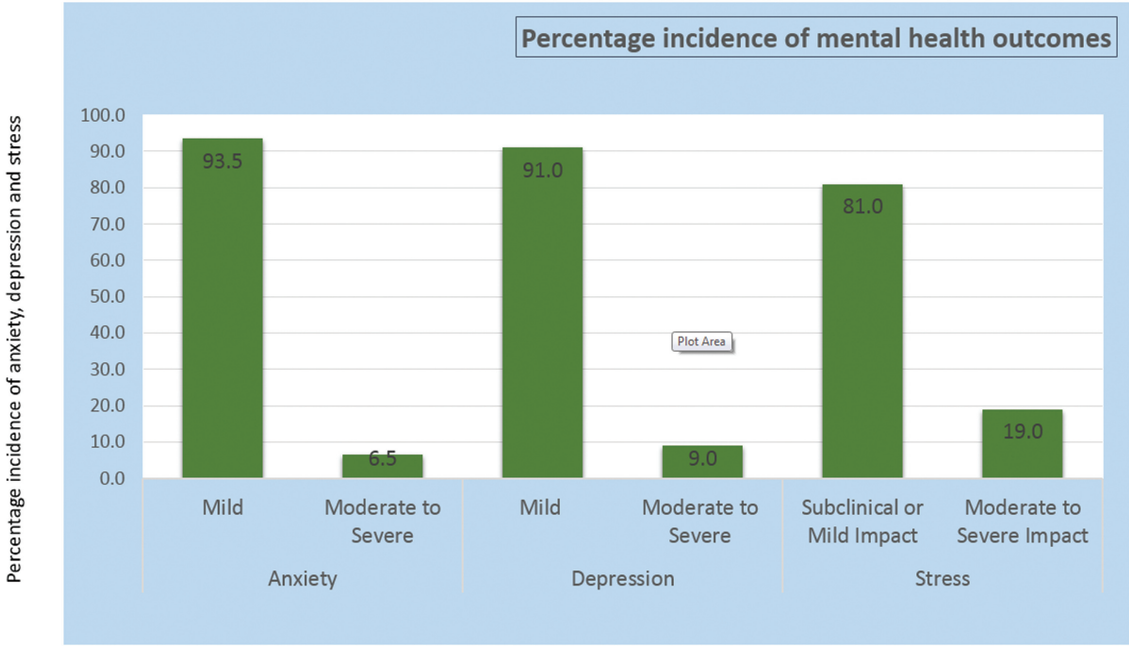

Fig. 1 Percentage incidence of mental health outcomes during second survey.

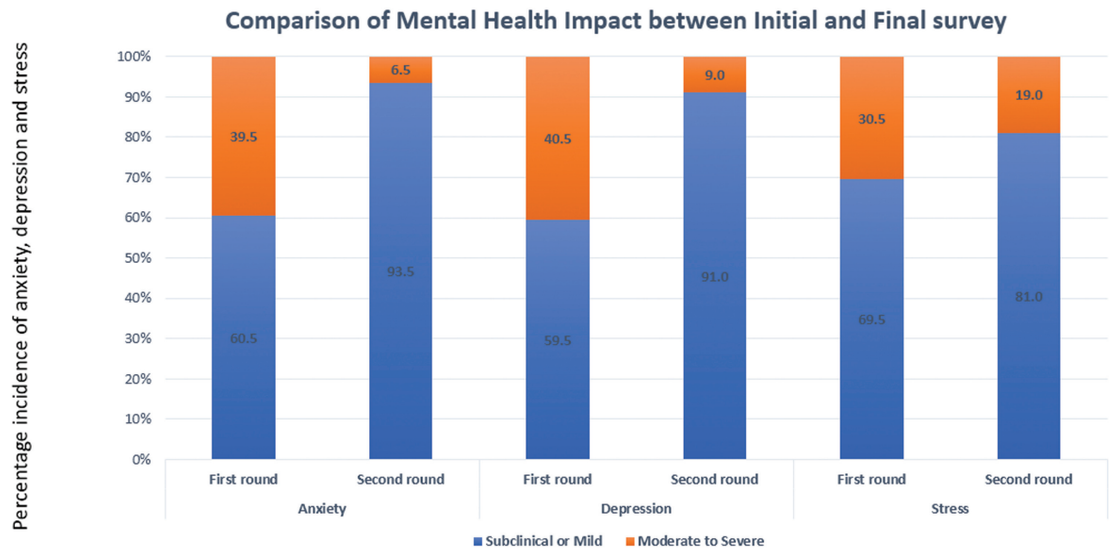

Fig. 2 Comparison of mental health impact between initial and final survey.

Table 3 Univariate analysis for stress levels

Variables to assess the change in impact		Mild Impact ($n = 162$) *n* (%)	Mild-to-severe Impact ($n = 38$) *n* (%)	*p*-Value
Median age [IQR] in years		29.5 [27–33]	30 [28–34.25]	0.118
Gender	Female	72 (82.8)	15 (17.2)	0.578
	Male	90 (79.6)	23 (20.4)	
Marital status	Divorced or separated	1 (100.0)	0 (0.0)	0.881
	Married	87 (80.6)	21 (19.4)	
	Single	74 (81.3)	17 (18.7)	
No. of rooms in household	<3	87 (82.9)	18 (17.1)	0.482
	≥3	75 (78.9)	20 (21.1)	
Children in the house <15 years	0	110 (81.5)	25 (18.5)	0.837
	1	36 (81.8)	8 (18.2)	
	2	16 (76.2)	5 (23.8)	
Adults >50 years	0	84 (86.6)	13 (13.4)	0.05
	≥1	78 (75.7)	25 (24.3)	
Occupation	Administrator	3 (100.0)	0 (0.0)	0.437
	Allied health care worker	19 (95.0)	1 (5.0)	
	Nurse	3 (75.0)	1 (25.0)	
	Physician	73 (78.5)	20 (21.5)	
	Physicist/therapist	64 (80.0)	16 (20.0)	
Cadre	Junior staff	98 (79.0)	26 (21.0%)	0.335
	Senior staff	20 (76.9)	6 (23.1)	
	Student	44 (88.0)	6 (12.0)	
Comorbidities	No	140 (80.5)	34 (19.5)	0.791
	Yes	22 (84.6)	4 (15.4)	
Smoking	No	154 (80.6)	37 (19.4)	0.746

Table 3 (*Continued*)

Variables to assess the change in impact		Mild Impact ($n = 162$) *n* (%)	Mild-to-severe Impact ($n = 38$) *n* (%)	*p*-Value
	Yes	6 (85.7)	1 (14.3)	
	Do not want to disclose	2 (100.0)	0 (0.0)	
Educational qualification	Above secondary	161 (81.7)	36 (18.3)	0.093
	Below secondary	1 (33.3)	2 (66.7)	
Close contact	No	33 (82.5)	7 (17.5)	0.787
	Yes	129 (80.6)	31 (19.4)	
COVID-19 testing	No	71 (81.6)	16 (18.4)	0.847
	Yes	91 (80.5)	22 (19.5)	
COVID-19 positivity	No	139 (81.3)	32 (18.7)	0.802
	Yes	23 (79.3)	6 (20.7)	
COVID-19 in family members	No	132 (85.7)	22 (14.3)	0.002
	Yes	30 (65.2)	16 (34.8)	
Vaccination facility	No	35 (72.9)	13 (27.1)	0.102
	Yes	127 (83.6)	25 (16.4)	
Volunteering for Vaccine	No	43 (78.2)	12 (21.8)	0.532
	Yes	119 (82.1)	26 (17.9)	
Longer period of isolation				

Abbreviations: COVID-19, novel coronavirus disease 2019; IQR, interquartile range.

vaccine. There were also isolated cases of a neurological disorder, such as Guillain–Barré syndrome, in scarce vaccinated people.[25,26] There were also doubts regarding the vaccine's effectiveness against the mutating variants of the virus. This could be the reason that why 27. 5% of the participants abstained from vaccination at the time of the survey.[27]

In April 2021, India witnessed a second pandemic wave with more than 6.9 million new cases and 48,000 deaths.[28] India administered more than 84 million vaccine doses, an average of 2·8 million per day in April 2021. Our second survey project reassessed the mental impact among the same subset of radiation oncology HCWs from India who participated in the initial questionnaire. They revealed decreasing anxiety, depression, and stress levels compared with the initial survey. This was primarily due to greater preparedness of the government, health care system and growing confidence of the people in combating the pandemic. Vaccines had brought optimism, and fatalities had decreased concomitantly, reducing the severity of the infection. Continued awareness about safety precautions and compliance also contributed to the positive mental health impact continuum.

Several studies reported a positive impact on mental health following vaccine implementation in various parts of the world. In an extensive survey of 453,167 volunteers from the United States, vaccinated participants had a 13% lower risk of developing anxiety and 17% lower risk of depression than nonvaccinated patients. In another survey from the United States, vaccination was associated with declines in distress and perceived dangers of infection, hospitalization, and death. In another large study of 8,003 adults who were vaccinated between December 2020 and March 2021, decreased mental distress levels were reported after receiving the first dose.[29–31]

In our study, in univariate analysis, none of the demographic factors impacted anxiety or depression. However, COVID-19 among the family members was significant ($p = 0.002$) in affecting stress levels. HCWs were perennially in fear of infecting their families.[32,33] Social stigma was an important concern during the pandemic. Several incidents of stigmatization were reported against frontline workers. Families of HCWs were subjected to social quarantine as they were also considered a contagion source.[34] Many health professionals lived away from families during the pandemic. If a family member gets COVID-19, it is likely to be more stressful; one of the main concerns for the HCWs is that the infection may have been transmitted from their workplace. Spread among other members, especially elderly parents, joint families, and societies, shutting down essential services for the affected household could further aggravate the distress.

In an attempt to improve the mental health of the HCWs, mass counseling sessions were organized within the center by psychologists leading to positive results. Subjects with acute psychological distress were also given individual counseling. Our center also addressed mental health concerns during this period with professional support. The services offered included counseling and psychotherapy for various problems like

anxiety, loneliness, relationship issues, difficulty sleeping, depression, trauma, self-harm, and others. It was also made sure that all counseling sessions were strictly confidential. These sessions are held weekly through online platforms for easy accessibility for all participants.

Creating awareness and persistent measures to educate the people paid rich dividends in significantly reducing the levels of moderate-to-severe anxiety, depression, and stress among HCWs in the radiation oncology community. In general, it can be interpreted that the mental impact after vaccination strategies were implemented, vis a vis, the second wave was better compared with the first. In one of the recent studies, it was seen after 12 weeks of the double dose of vaccine. These measures, along with the decreasing trend of COVID-19 fatalities and fall in severe infections, have generated hope that our fraternity's mental health and well-being will improve in due course of time.

Limitations and Strengths

Our study had several limitations. Out of the 363 participants who were surveyed at the first pandemic wave, only 200 could complete the present one. This was mainly because of the long gap between the two surveys wherein many participants had changed the workplace. At the time of the survey, vaccination strategies were just getting implemented, and the public had doubts regarding the safety and efficacy. This could also have possibly impacted the response rate. The stress among the participants was higher during the initial months of the pandemic, especially with an increase in case fatalities and nationwide lockdowns; however, with increased public awareness, compliance to precautionary measures, and ease of restrictions, results may have been confounded.

This study highlights the importance of studying the mental health of HCWs during the pandemic, as the psychological footprint of a disaster is supposedly more prominent than the medical footprint. Effective corrective actions should be implemented to provide a safe work environment that will facilitate work–life balance, effective communication, and information, health promotion, job security, and lend risk-adapted psychosocial support.

Conclusion

Continued health education, compliance to safety precautions and effective vaccination strategies have produced beneficial results. The second survey conducted at the launch of vaccine implementation strategies showed that a significant number of HCWs in the Radiation Oncology community had declining trends of anxiety, depression, and stress levels compared with the pandemic's initial wave.

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Conflict of Interest
None declared.

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Prospective Observational Study of Evaluating Cisplatin-Induced Ototoxicity in Patients

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Abstract

Introduction Platinum-based chemotherapeutic agents cisplatin and carboplatin are two of the most widely used drugs in cancer today. They display wide range of adverse reactions; among them, ototoxicity is an important cumulative toxicity that more commonly observed with cisplatin. At a later stage, it can affect speech of individual and lead to communication problem with decreased cognitive function and depression in cancer survivors. Periodic monitoring of hearing loss with pure-tone audiometry (PTA) provides early evidence of ototoxicity which may decrease debilitating effect of the same in a patient.

Objective The primary objective of this study was to assess cisplatin-induced ototoxicity. We also investigated its severity, reversibility, and other modifying risk factors.

Materials and Methods We conducted a prospective observational descriptive type of epidemiological study. The study was conducted over 80 randomly selected cancer patients (for estimation of sample size, the following formula was used $n = [Z\alpha^2\ PQ]\ /\ d^2$), who were starting with their first cycle of cisplatin from August 2018 to July 2020. This study was conducted at tertiary cancer care center in western Gujarat which caters patients from all over India. We performed PTA in all randomized patients at baseline and periodically. We classified hearing loss according to the World Health Organization (WHO) criteria.

Results A total of 30% ($n = 24$) patients developed cisplatin-induced ototoxicity according to WHO criteria at end of 3 months after starting the first cycle of cisplatin. It was sensory neuronal, affecting both the ears equally, and was seen predominantly at high frequency. We observed hearing loss at 3 months to be significantly more common in the 301 to 400 mg/m^2 cumulative dose group (47%), as compared with the other two groups (0–200 mg/m^2 and 201–300 mg/m^2; $p < 0.05$). It showed dose dependency with cisplatin. In the multivariate step-wise regression model, baseline hearing loss (odds ratio [OR] = 17.71, 95% confidence interval [CI]: 6.57–118.91, $p < 0.05$) and cumulative cisplatin dose of more than 300 mg/m^2 were significantly associated with hearing loss at 3 months (OR = 6.62, 95% CI: 2.33–18.74, $p < 0.05$).

Keywords

- cisplatin ototoxicity
- ototoxicity monitoring
- dose dependent toxicity
- ototoxicity
- pure-tone audiometry
- hearing loss

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Conclusion Cisplatin-induced ototoxicity manifests as a bilateral high frequency sensorineural hearing loss. Cumulative dose of cisplatin is an important predictor of development of ototoxicity. Baseline and periodic audiometric monitoring could detect ototoxicity early which leads to possible limitation on the severity of ototoxicity.

Introduction

According to the GLOBOCAN 2020 data, the total number of new cases of cancer was 19,292,789, and total mortality was 99,58,133.[1] Among them, the most common cancers diagnosed in females after breast cancer were head and neck, cervical, lung, and gastrointestinal cancers. These cancer types were observed to be common in males as well. The platinum-based chemotherapeutic agents, cisplatin and carboplatin, are two of the most widely used chemotherapeutic agents in these types of cancer.

Cisplatin has various dose limiting and cumulative toxicities. Ototoxicity is an important cumulative toxicity of cisplatin. This exclusively affects the cochlea. For cisplatin, hearing loss is bilateral, sensory neuronal, irreversible, and generally occurs at higher frequencies (>4 kHz) and is proportional to the cumulative dose of the drug.[2] Hearing loss is common at the higher frequencies when the cisplatin dose is greater than 60 mg/m^2.[3] Often, it is accompanied by transient or permanent tinnitus which is commonly reversible on the completion of treatment.[4]

In literature, the rate of hearing loss is variably reported between 4 and 90%, depending on the drug dose, age of the patient, preexisting hearing loss, concurrent cranial radiation, some genetic factors, or concurrent use of other ototoxic medications.[5] A correlation between genetic variants and hearing loss has been found for cisplatin-detoxifying enzymes (glutathione-S-transferase),[6] nucleotide excision repair proteins, and megalin (low-density lipoprotein).[7]

Recently, sodium thiosulfate has been approved by the Food and Drug Administration (FDA) to prevent cisplatin-induced ototoxicity in children aged between 1 and 18 years.[8] Unfortunately, it is not yet approved for adult patients. The nature of ototoxicity is such that it often goes undetected until speech intelligibility is affected[9] and usually detected only when a communication problem becomes evident. These patients can be prescribed a hearing aid,[10] cochlear implant,[11] or other assistive device (text messaging or audio streamers), and other special accommodations which will optimize the quality of life for cancer survivors.

Early detection of ototoxicity is an essential component of cancer care in patients receiving cisplatin. Pure-tone audiometry (PTA) remains the first-line diagnostic tool for the screening, diagnosis, and follow-up of hearing status in these patients. So, by doing baseline and periodic audiometry, we can prevent administration of such ototoxic drug in patients of preexisting hearing loss and could detect cisplatin-induced sensory neuronal hearing loss (SNHL) early.

Therefore, this study aims to serve as a resource for health professionals to enhance their understanding of ototoxicity and its regular monitoring in patients receiving cisplatin to prevent ototoxicity. The primary aim of our study is to evaluate cisplatin-induced ototoxicity in cancer patients. Our objectives were to study the dose and effect relationship of cisplatin ototoxicity, severity and reversibility of cisplatin ototoxicity, and other associated risk factors enhancing cisplatin-associated ototoxicity.

Materials and Methods

This prospective study was performed among randomly selected 80 patients with diagnosed cancer and commencing treatment with cisplatin from August 2018 to July 2020 at a tertiary cancer health care center in western Gujarat. For estimation of sample size, the following formula was used:

$$n = [Z\alpha^2\ PQ] \ / \ d^2$$

Where:

- $Z\alpha$ = value of standard normal variate corresponding to α level of significance = 1.96 (corresponding to 95% confidence interval).
- P = likely value of parameter = 20%.
- $Q = 1 - P = (100 - 20)\% = 80\%$.
- d = margin of errors (measure of precision) = 0.10 (10%).

Inclusion Criteria

Inclusion criteria are listed below:

- Adults >18 years of age.
- Positive diagnosis of cancer.
- Commencing the first cycle of chemotherapy with cisplatin.
- Patients on concurrent radiation with cisplatin were also included.

Exclusion Criteria

Exclusion criteria are as follows:

- Patients presenting with profound hearing loss (more than 91 db) at baseline assessment, as it would be difficult to evaluate them according to the American Speech Language–Hearing Association criteria.[12]
- Patients who have previously received cisplatin chemotherapy.

- History of medical condition, such as tuberculosis and malaria (medications used in these conditions are ototoxic) or diabetes, heart failure, and renal failure medications, of which can affect the hearing threshold.

A total of 80 patients were randomly selected fulfilling the above inclusion criteria. Data collection was done in form of history, examination, complete blood count (CBC), biochemistry, biopsy of accessible site, imaging of relevant site, tumor markers, history regarding hearing loss, tinnitus, and pure-tone average at high frequency. PTA was performed at baseline frequency, at first, third, and sixth months (from beginning the first cycle of cisplatin) in both the ears. Patients were asked about symptoms like hearing loss, tinnitus, and vertigo with each PTA test. We have tested the hearing threshold in decibel (dB) from 250 to1,200 Hz for both the ears during PTA at multiple time period as discussed above. But for comparison of the hearing threshold in dB, we have used only 8-kHz frequency, as cisplatin-induced hearing loss occurs only at high frequency. The difference between hearing threshold (in dBHL) from the baseline audiogram and the posttreatment audiogram of all the patients were counted.

Significant hearing loss was considered in the following scenarios: approximately 20 Db decline in hearing observed at any single test frequency, oral 0-dB decline at two adjacent frequencies, or loss of response at maximum audiometer outputs for three consecutive frequencies where there was previously measurable hearing. This was based on the American Speech Language and Hearing Association criteria.[13] We graded severity of cisplatin-induced ototoxicity according to the World Health Organization (WHO) criteria.[14]

In primary outcome, we found that cisplatin ototoxicity is proportional to cumulative doses of drug. For secondary outcomes, we studied effect of age, sex, concomitant cranial radiation, chemotherapy given with cisplatin, baseline hearing loss, and cumulative dose. Among them, baseline hearing loss and cumulative doses of cisplatin, both being associated with ototoxicity, were found to be statistically significant.

Statistical Analysis

The data were entered in MS Excel spread sheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Quantitative variables were compared using paired *t*-test. Qualitative variables were analyzed using Chi-square test.

Ethics

The study was approved by the Institutional Ethics Committee clinical studies, Apollo Hospitals International Ltd., Ahmedabad, Gujarat, India. (approval no: ECR/30/INST/GJ/2013/RR; approved on July 16, 2018). The study was conducted according to the principles outlined in the International Conference on Harmonization Good Clinical Practice guidelines and in compliance with the protocol, the Data Protection Act and all other ethical and regulatory requirements, as appropriate for the study. All study participants were explained about study, and written informed consent was obtained from them. The Helsinki Declaration was followed which said that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

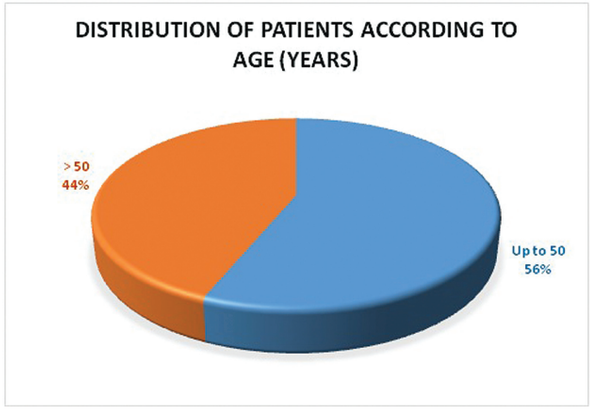

Fig. 1 Distribution of patients according to age.

Results

This study included 80 patients of cancer, commencing their treatment with first dose of cisplatin repeating either 1 or 3 weekly, given as concurrent with radiotherapy, as an adjuvant or as a neoadjuvant form with other chemotherapy agents or as a single agent.

We found that mean age of the patients in our study was 48.9 ± 10.11 years (range: 22–67 years; ►**Fig. 1**). Here, 70% ($n = 56$) of the patients were males and rest were women (30%, $n = 24$). The most common diagnosis for which cisplatin was prescribed was squamous cell carcinoma of head and neck (42.5%, $n = 34$). Treatment history of the patients revealed that 42.5% ($n = 34$) of the patients received cranial radiation therapy along with cisplatin. Gemcitabine, docetaxel with 5-fluorouracil, etoposide, bleomycin with etoposide, and pemetrexed were used with cisplatin, respectively, in 23.8 ($n = 19$), 10 ($n = 8$), 10 ($n = 8$), 7.5 ($n = 6$), and 6.3% ($n = 5$) of the patients.

Of our study population, 32.5% ($n = 26$) received 0 to 200 mg/m^2 cumulative dose of cisplatin, with median dose being 180 mg/m^2. A total of 43.8% ($n = 35$) patients received 201 to 300 mg/m^2 cumulative dose, with median dose of cisplatin being 290 mg/m^2. About 23.8% ($n = 19$) of patients received 301 to 400 mg/m^2 of cisplatin with a median dose being 320 mg/m^2 (►**Fig. 2**).

At baseline, the mean PTA in right ear was 22.59 ± 4.03 dB which increased significantly to 32.89 ± 16.22 dB at 3 months ($p < 0.001$), and in left ear it was 22.59 ± 3.85 dB which increased significantly to 33.01 ± 16.04 dB at 3months ($p < 0.001$) (►**Table 1**).

Among the study population, 7.4% of the patients had mild hearing loss before starting cisplatin chemotherapy. Decibel

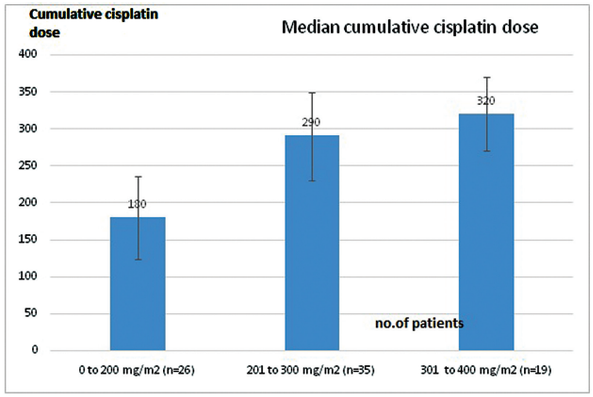

Fig. 2 Median dose of cisplatin given to the patients in the three groups.

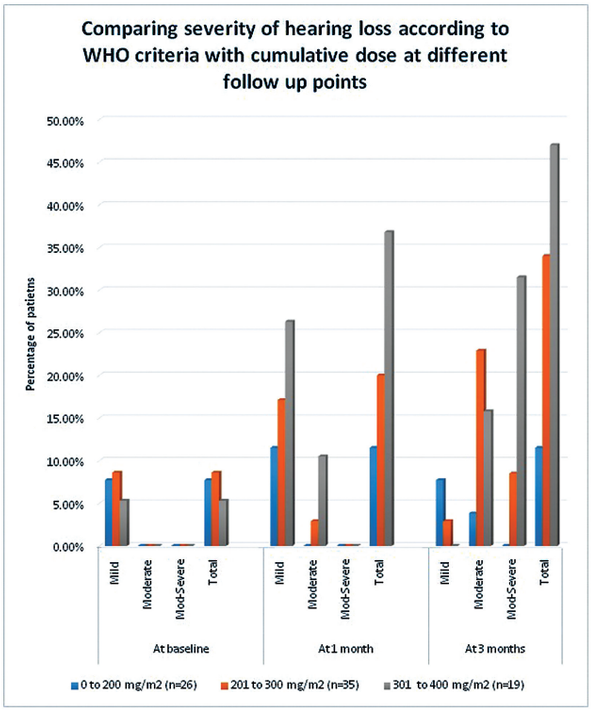

Fig. 3 Comparison of patients in different dose groups with the severity and type of hearing loss according to WHO grading. WHO, World Health Organization.

of mild hearing loss was recorded to be 26 to 40 dB. At 1-month follow-up, we observed that 17 (21.3%) patients had hearing loss; the severity of hearing loss was not significantly associated with the dose of cisplatin, given to the patients ($p = 0.13$). At 3 months, we found that ototoxicity was associated with cumulative dose of cisplatin, as 24 patients (30%) had hearing loss, and it was significantly more common in the 301 to 400 mg/m^2 cumulative dose group (47%) as compared with the other two groups ($p < 0.05$; ►**Fig. 3**). Irreversible sensorineural hearing loss (SNHL) was confirmed with repeat PTA at sixth month.

We found that subjective hearing loss was significantly more common in the 301 to 400 mg/m^2 cumulative dose group (36.8%) as compared with patients in the other two-dose groups ($p < 0.01$). Tinnitus was not found to be significantly associated with the cumulative dose of cisplatin given to patients ($p = 0.14$), and it was reported by 8.8% (7 out of 80) of the patients.

We assessed the effects of age, gender, history of cranial radiation, chemotherapy given with cisplatin, baseline hearing loss, and cumulative cisplatin dose on ototoxicity. In multivariate step-wise regression analysis, baseline hearing loss (odds ratio [OR] = 17.71, 95% confidence interval [CI]: = 6.57–118.91, $p < 0.05$) and cumulative dose of cisplatin more than 300 mg/m^2 (OR = 6.62, 95% CI: 2.33–18.74, $p < 0.05$) were found to be significantly associated with hearing loss at 3 months (►**Table 2**).

Discussion

Cisplatin-induced ototoxicity manifests as bilateral high-frequency sensorineural hearing loss in a dose-dependent manner[15] with continued exposure to cisplatin gradually, it affects low frequency associated with speech.[16] This will further lead to impairment in functional status, cognitive status, and depressive symptoms in cancer survivors.[17] Cisplatin ototoxicity is produced by several distinct mechanisms,[18] mainly it is due to preferential damage to the basal turn of the cochlea,[19] where it involves the formation of reactive oxygen species (ROS) and reduction of antioxidative enzymes within the cochlea causing intrinsic apoptosis of outer hair cells[20,21] which are involved in neural transmission of sound.

The reported incidence of cisplatin ototoxicity is variable, ranging from 26% to over 90% due to many treatment and patient-related factors which include both genetic and non-genetic risk factors. Data from clinical trials can be difficult to compare due to differences in the dose of the drug administered, both within a cycle and the total amount administered over multiple cycles, the time interval between courses, method of administration, treatment duration, and differences in patient populations.

Table 1 Comparison of baseline and 3-month PTA for right and left ear side

	PTA (dB)	Mean	Standard deviation	*p*-Value
Right ear	Baseline	22.59	4.03	< 0.01
	At 3 months	32.89	16.22	
Left ear	Baseline	22.59	3.85	< 0.001
	At 3 months	33.01	16.04	

Abbreviations: dB, decibel; PTA, pure-tone audiometry.

Table 2 Factors associated with sensorineural hearing loss in our patients at 3 months

Parameter	Univariate analysis			Multivariate analysis**		
	OR*	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age (in y)						
Up to 50	Reference	–	–	–	–	–
> 50	1.82	0.67–4.91	0.23	1.82	0.54 to 6.09	0.33
Female gender	1.12	0.39–3.25	0.94	–	–	–
Crania radiation Received	0.53	0.19–1.51	0.23	0.91	0.17–4.83	0.91
Concomitant chemotherapy given	4.8	1.45–16	< 0.01	2.06	0.26–16.37	0.49
Baseline HL	16.76	1.83–153.48	< 0.01	17.71	6.57–118.91	< 0.05
Cumulative cisplatin dose (mg/m^2)						
0–200	Reference	–	–	Reference	–	–
201–300	3.51	0.86–14.23	0.07	4.13	0.67–15.23	0.12
301–400	5.57	1.23–25.21	< 0.05	6.62	2.33–18.74	< 0.05

Abbreviations: CI, confidence interval; HL, hearing loss; OR, odds ratio.

Of our study population, 32.5% received 0 to 200 mg/m^2 cumulative dose of cisplatin, 43.8% received 201 to 300 mg/m^2 cumulative dose, and 23.8% received 301 to 400 mg/m^2 of cisplatin. The study by Dwivedi et al evaluated cisplatin ototoxicity dosage of cisplatin ranged from 50 mg to 115 mg/m^2 with cumulative dose ranging from 250 to 850 mg.[22]

In our study, at baseline, mean PTA in right ear was 22.59 ± 4.03 dB at 8 kHz which increased significantly to 32.89 ± 16.22 dB at 3 months ($p < 0.001$) at same frequency. Similarly, at baseline, mean PTA in left ear was 22.59 ± 3.85 dB at 8 kHz which increased significantly to 33.01 ± 16.04 dB at 3 months at same frequency ($p < 0.001$). Similarly, Arora et al reported that in 57 patients, mean baseline hearing threshold at all tested frequencies was 54.4 dB which increased to 73.1 dB after 3 months.[23]

In our study at 3 months, 30% of patients had bilateral sensorineural high-frequency hearing loss (at 8 kHz) according to WHO criteria, incidence and characteristics of hearing loss of our study correlate with studies done by Dwivedi et al,[22] Dutta et al,[24] and Green et al.[25]

We observed that 7.4% had hearing loss at baseline, increased to 21.3% at 1 month and 30% at 3 months follow-up. At 3 months, it was significantly associated with dosage of cisplatin ($p < 0.05$).We also found that moderate-to-severe hearing loss was significantly more common in patients in 301 to 400 mg/m^2 cumulative dose group (31.5%) as compared with patients in the other two dose groups ($p < 0.01$). This observation establishes the dose effect relationship of cisplatin-induced ototoxicity similar to study done by Bokemeyer et al[26] and Frisina et al.[27] Irreversible nature of hearing loss was confirmed by repeat PTA at 6 months which correlates with studies done by Dwiwedi et al[22] and Arora et al.[23]

We found that tinnitus was reported (evaluated by taking history) by 8.8% of patients and was not significantly associated with the cumulative dose of cisplatin ($p = 0.14$). Incidence of same has been reported from 2 to 36% in literature.[28,29] Study by Skalleberg et al showed that tinnitus was not associated with cumulative dosage of cisplatin which is comparable to our study.[30]

In literature, cumulative dose of cisplatin has been considered as an important factor enhancing cisplatin ototoxicity,[26] similarly we found that cumulative cisplatin dose of more than 300 mg/m^2 (OR = 6.62, $p < 0.05$) and baseline hearing loss (OR = 17.71, $p < 0.05$) were found to be significantly associated with hearing loss at 3 months on multivariate analysis. Apart from dose, age[31] and sex[32] are also associated with cisplatin ototoxicity but we did not find such association.

Audiological monitoring should aim to identify the hearing loss early and reduce its impact on the individual's life by means of proper medical and hearing intervention.[33] Yu et al[34] compared the effectiveness of monitoring cisplatin-induced ototoxicity in adult patients using extended high-frequency PTA (EHF-PTA) or distortion-product otoacoustic emission (DP-OAE). The incidence rate of cisplatin-induced ototoxicity was 40% with EHF-PTA or DP-OAE which correlates with detection rate of SNHL by PTA of our study.

There have been many studies with multiple otoprotective agents, none of these agents yet approved in preventing cisplatin ototoxicity in adults.[16] Our study showed that periodic PTA could detect SNHL early. As today, the only way to prevent cisplatin ototoxicity lies on early detection followed by dose modification or substitution with other platinum compound like carboplatin. But care should be taken to prevent compromise in oncologic efficacy.

Limitations

Our study has few limitations, as we have not compared hearing loss at different high frequencies. Comparison was done only at 8 kHz at 0, first, and third months. Also after the third month, most of the patients had finished their treatment, so we were not able to change or modify the cisplatin doses. We have also not performed cost–benefit analysis.

Conclusion

We observed that at 3 months, 30% of the patients had bilateral high-frequency sensorineural hearing loss according to the WHO criteria. Patients with baseline hearing loss and cumulative dose of more than 300 mg/m^2 had significantly higher odds of developing cisplatin-induced hearing loss. Results of our study showed that audiometric monitoring provides early evidence of decreased hearing ability. We can modify the doses or can substitute cisplatin with other platinum compounds like carboplatin. However, it still does not completely prevent ototoxicity. We recommend audiometric testing (with main focus on high frequency), periodically for all patients at baseline, first, third, and sixth months after starting cisplatin doses.

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Conflict of Interest
None declared.

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High-Dose Methotrexate-Induced Dermatological Eruption: A Rare Manifestation of Chemotoxicity

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High-dose methotrexate (HD-MTX) that is given in the form of continuous infusion over 24 hours forms an essential part of extra compartmental therapy pediatric-inspired protocols for treatment of acute lymphoblastic leukemia (ALL). Dermatological eruptions due to HD-MTX are rarely reported as compared with low-dose MTX (LD-MTX) therapy given for immunodermatological disorders. Defects in skin and mucosa pave way for bacterial invasion and sepsis in a neutropenic patient adding up to complications and contributing to morbidity due to ALL.

We report a 24-year-old female diagnosed as Philadelphia positive B cell ALL treated with Berlin-Frank-Munchester-95 protocol, who developed severe methotrexate-induced dermatological eruption post first HD-MTX infusion. She had an uneventful induction course with documented minimal residual disease negativity post induction. After documenting baseline normal complete blood count and biochemistry values, hydration along with alkalinization was started as per institute's protocol. Interacting medications such as dasatinib, septran, 6-mercaptopurine, and folate were stopped. HD-MTX was administered at a dose of 5 gm/m^2 as a 24-hour infusion. Her maximum serum level of MTX at 36 hours was 1.38 micromol/L and leucovorin rescue was guided according to Bleyer's nomogram. She was conservatively managed for grade 2 emesis and headache on day 4 of administration. She was discharged on day 6 with balanced pH and soda bicarbonate mouth gargles for mild oral soreness. On day 9, she started developing abdominal pain, bloody stools, with high-grade fever, requiring immediate readmission. She looked sick, febrile, icteric with multiple pruritic plaques on an erythematous base distributed all over the body, palmoplantar erythrodysesthesia, and grade 4 oral mucositis (►**Table 1**). Her laboratory investigations were suggestive of severe myelosuppression along with grade 2 AKI and grade 3 transaminitis according to Common Terminology Criteria for Adverse Events Version 5.0. She was given bowel rest with total parenteral nutrition, broad spectrum antibiotics, granulocyte colony stimulating factor, transfusion support with red blood cells, and platelets including granulocyte infusion to tide over the gram-negative bacterial sepsis. The skin care included application of topical urease cream with mild corticosteroids for palmoplantar lesions, emollients for generalized skin lesions, and balanced pH gargles for oral mucositis. The skin lesions became hyperkeratotic over time and healed with desquamation as shown in ►**Fig. 1**. Her general condition improved after an inpatient stay of 14 days with good nursing care.

Pulse LD-MTX therapy given weekly without leucovorin rescue for psoriasis and rheumatoid arthritis commonly causes dermatological eruptions at a lower threshold than HD-MTX (0.2 vs 1 mM/L).[1] Perifolliculitis, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis occur due to immunologic mechanisms from drug presentation by keratinocytes to cytotoxic

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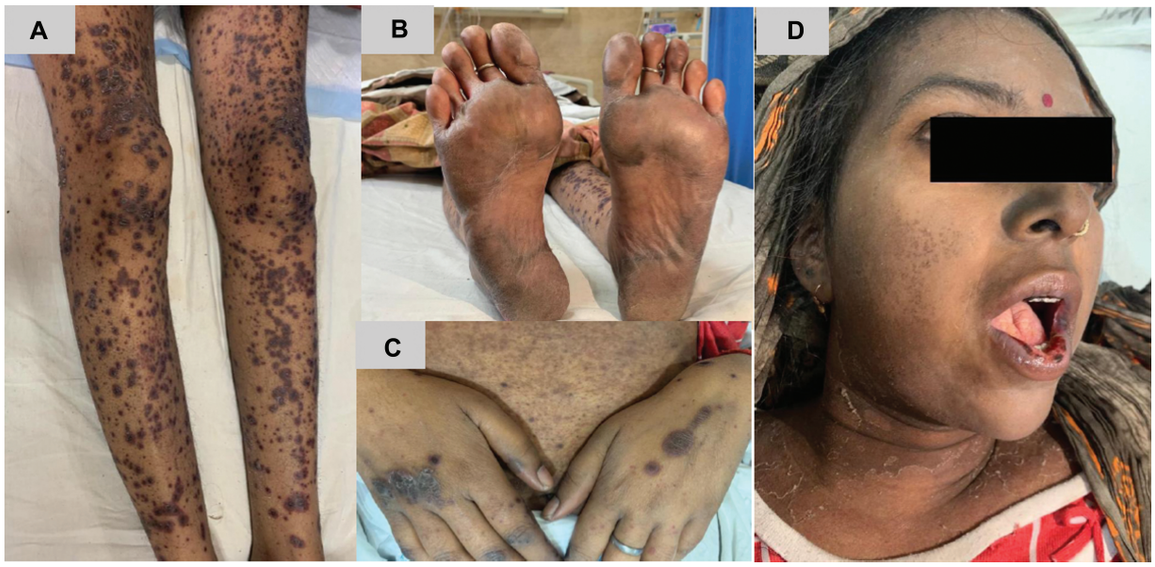

Fig. 1 (**A**) Pruritic plaques on an erythematous base, (**B**) plantar erythrodysesthesia, (**C**) hyperkeratotic plaques over dorsum of hand, (**D**) oral mucositis and facial skin in healing stage with peeling of epidermis.

Table 1 Possible Differential Diagnosis considered during admission

Differentials encountered	For	Against
Stevens-Johnson syndrome with sepsis-induced multiorgan dysfunction	Skin and mucosal lesions, timing of drug administration	No typical skin blistering seen except on palms Palmoplantar involvement, typical chemotherapy induced
Severe varicella infection	Fever, oral ulcers, skin lesions	Renal and liver impairment

T lymphocytes.[2,3] Palmoplantar erythema with bullous lesions result due to concentration of this drug in eccrine glands.[4] Histopathological changes like acanthosis, epidermal necrolysis, interface dermatitis, and dyskeratosis result due to direct toxicity on rapidly multiplying keratinocytes.[5] Dasatinib forms backbone of pH + ALL and is known to delay the proper clearance of methotrexate.[6] Other known risk factors include advanced age, hypoalbuminemia, preexisting renal dysfunction, and low folate stores in the patient's body. Variations in expression of genes *SLCO1B1*, *BCRP*, and *ABCB1* along with single nucleotide polymorphisms of various enzymes involved in metabolism of methotrexate like 5,10-methylene-tetrahydrofolate reductase and thymidylate synthetase can predict individual toxicities.[7] Our patient had significant toxicity despite adequate clearance and stopping interacting medications like dasatinib, thus involving genomics into discussion. Ensuring a robust supportive care with the use of dermoprotective agents will surely enhance faster recovery of such patients.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

Conflict of Interest

None declared.

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Ayurveda Maintenance Therapy in Recurrent Ovarian Cancer

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Abstract

Despite optimal surgery and first-line platinum-based doublet chemotherapy, approximately 70 to 80% of patients with epithelial ovarian cancers relapse. Two cases of recurrent ovarian cancer (ROC) were treated with non–platinum-based Ayurveda maintenance therapy (AMT) consisting of drugs having a herbal and herbomineral origin. This regimen was followed over a period of 3 years and progression-free survival (PFS) was noted along with platinum-free interval (PFI). Two patients were diagnosed with *BRCA*1 mutated recurrent high-grade serous ovarian carcinoma and treated with the per-oral AMT regimen labeled as ZINCA-30 in our hospital after completion of standard of care treatment and followed up until progression. The ZINCA-30 regimen comprising *Jasada* (traditional Zinc preparation), *Indukanth kwatham* and *Curcuma amada* powder in combination was prescribed based on *Rasayana chikitsa* postulated in Ayurveda. The patients were followed up every 3 months. The progression-free survival observed in these patients was 28 months and 45 months, respectively. These two pilot cases suggested an increased platinum-free interval (PFI), improved progression-free survival (PFS) in recurrent ovarian cancer (ROC), with the AMT labeled as ZINCA-30 after chemotherapy.

Keywords

- recurrent ovarian cancer
- progression-free survival
- platinum-free interval
- ayurveda maintenance treatment
- ZINCA-30

Introduction

Despite optimal surgery and first-line platinum-based doublet chemotherapy, approximately 70 to 80% of patients with epithelial ovarian cancers show a relapse.[1] The most important features that influence the treatment choice in recurrent ovarian cancer (ROC) with respect to systemic therapy are tumor histology, *BRCA* mutation status, platinum-free interval (PFI), and previous treatment with an anti-VEGF monoclonal antibody. The presence of germline or somatic *BRCA* mutations allows platinum-responsive patients to optimize the chemotherapy efficacy and prolong progression-free survival (PFS) using a PARP inhibitor given as maintenance therapy until progression.[1]

Response to platinum re-treatment in recurrent epithelial ovarian cancer is related to PFI. The most preferred and accepted chemotherapy in the treatment of platinum-sensitive (PFI $>$ 6 months) recurrence is platinum-based combination regimens. It is considered that extending the PFI with non-platinum agents may enhance the response and the outcome of subsequent re-challenge with platinum.[2]

Therefore, the exploration for therapies with minimal toxicities to increase the PFS was initiated. Time to relapse

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is an important prognostic factor in ovarian cancer as subsequent chemoresponse is based on this time interval.[3]

In the doctrines of Ayurveda, the clinical stages and treatments for benign and malignant tumors have been discussed in detail.[4]

Rasayana chikitsa is one of the therapeutic segments of Ayurveda, which helps to improve immunity, consists of compounds having immune-stimulant, immune-modulator effects and hence they restore health.[5] A regimen with drugs having anti-cancer properties and predominant *Rasayana* herbs and minerals has been described here for the management of ROC.

Methodology

We report the detailed course as elaborated in ►**Table 1** and the follow-up of Ayurveda maintenance treatment (AMT) labeled as ZINCA-30 in two cases of recurrent high-grade serous ovarian cancer in our institution. Two *BRCA* mutated patients (refer to ►**Table 1** for details) of ROC were offered AMT ZINCA-30. These patients after completing the standard chemotherapy were not willing for any conventional maintenance therapy and had opted for ZINCA-30.

The per-oral ZINCA-30 regimen prescribed for both the patients has standardized *Jasad Bhasma (JB)*, *Indukanth Kwatam* (*IK*) tablets and powdered *Amra-Haridra* (*AH*) (*Curcuma amada*); daily dosage to be continued until the next recurrence. *IK* tablets (the detailed composition is mentioned in ►**Supplementary Table S1**) (3,600 mg/day) were prescribed 30 minutes before food, while the *JB* (10 mg /kg/day) and *AH* (1,200 mg/day) combination was advised to be taken after consuming food.

The treatment was started after the last chemotherapy cycle in both patients. These patients were followed up 3 monthly with clinical as well as laboratory evaluation including biochemistry, CA 125, and sonological evaluation of the abdomen and pelvis.

Patient 1 (PSK) was on regular follow-up until November 2020 when she presented with mild pain in the abdomen. Her clinical examination was unremarkable and CA-125 level was normal. A PET CT evaluation on 02/11/2020 showed nodal recurrence along the right iliac vein and a mesenteric node. Thus, she had a PFS of 28 months after three earlier recurrences as mentioned in ►**Table 1**.

She was treated with six cycles of paclitaxel and carboplatin from 06/11/2020 to 01/03/2021 and is now in complete regression (CR) as reported in PET CT dated 03/04/2021.

Patient 2 (BSK) has had a PFS of 45 months and has shown no signs of relapse at the time of submitting the manuscript.

The CA-125 level was within normal range throughout the period of observation until the last follow-up in both the patients (►**Supplementary Table S2**). The mean ± standard deviation (SD) value of CA-125 in U/mL was 5.15 ± 1.12 in patient 1-PSK and 7.72 ± 1.61 in patient 2-BSK, over the total duration of follow-up.

All hematological and biochemical parameters including liver function tests and renal function tests were observed to be within the normal limit (►**Supplementary Table S3**). There are no clinically noticed, pathology (laboratory) documented, or patient-reported adverse events or side effects with ZINCA-30 in both cases.

Discussion

Epithelial ovarian cancer (EOC) is the most fatal among recurring gynecological malignancies and around 75% of females with EOC are diagnosed at FIGO stage III or IV.[6]

The median PFI of 11.9 months (interquartile range [IQR]: 3.6–21.9) among 28 recurred patients with the median number of treatment lines 4 (IQR: 3–6) and median of 2 (IQR: 2–3) platinum lines was observed in a retrospective study between 2004 and 2014 with at least 3 years follow-up among 40 *BRCA* mutation carriers (26 *BRCA1* and 14 *BRCA2*) with a mean age of 54 years, all underwent cytoreduction surgery and received platinum chemotherapy.[7]

GOG-0218 (PFS 14.1 vs. 10.3, $p < 0.001$) and ICON7 (PFS 19.8 vs. 17.4, $p < 0.001$) trials suggested that the use of bevacizumab maintenance after standard chemotherapy prolongs median PFS in ROC patients.[8]

In the AGO-OVAR-16 trial, pazopanib maintenance therapy for 24 months after the completion of first-line platinum-based therapy improved PFS by 5.6 months compared with placebo.[9] SOLO2 investigated olaparib maintenance after ≥ 2 lines of chemotherapy for ovarian cancer patients with germline *BRCA* mutations. The study concluded that olaparib significantly improved PFS as compared with placebo (19.1 months vs. 5.5 months, $p < 0.0001$).[10]

The maintenance treatment options are being explored in the ROC setting including targeted therapy with vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and tyrosine kinase inhibitors (TKI) such as pazopanib and nintedanib.[11]

Fatigue, hematological, and GI toxicities are the most commonly observed adverse events with PARPi therapy.[12] GI tract symptoms such as nausea, vomiting, anemia, neutropenia, fatigue, and abdominal pain are reported as primary adverse effects. Rare but serious adverse events of developing acute myeloid leukemia (AML) have been reported with phase III study of olaparib.[13]

In the phase 3 AGO-OVAR 16 study, grade 3 or 4 AEs of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib arm than with placebo, and the treatment-related discontinuation rate was also higher with pazopanib (33.3% vs. 5.6%).[14]

It has been observed in two phase III clinical trials in newly diagnosed advanced-stage ovarian cancer GOG 218 and GOG 262, around 18% of EOC were associated with *BRCA1* and *BRCA2* mutations and differed in tumor biology and treatment response.[15]

The platinum-free interval is the most important predictive factor for a response to subsequent lines of chemotherapy. It is also the most important prognostic factor for PFS and overall survival (OS) in patients with ROC. A non-platinum regimen is generally preferred as the most appropriate

Table 1 Details of cancer treatment

	Event Chronology	Patient 1-PSK	Patient 2-BSK
	Age in years	50	48
	Co-morbidity	Hypothyroidism 10 years	No
	Family history	Not significant	Mother: ovarian cancer Brother: non-Hodgkin lymphoma
	Cancer antigen 125 (CA 125) at diagnosis	158 U/mL	2881 U/mL
	Primary cytoreduction surgery	Total abdominal hysterectomy + bilateral salpingo-oophorectomy + omentectomy on 23/06/2010	Total abdominal hysterectomy + bilateral salpingo-oophorectomy + omentectomy on 11/7/2015
	Diagnosis–histopathology report	Bilateral high-grade serous cyst-adenocarcinoma FIGO stage III-B	Bilateral grade III serous papillary adenocarcinoma FIGO stage III-B
	BRCA mutation	Positive in intron 16 of the *BRCA1* gene C.5074 + 1G > A	Positive in exon 2 of the *BRCA1* gene p.Glu23ValfsTer17
Previously received cancer therapies	Chemotherapy 1st line	6 cycles nanoparticle formulation of paclitaxel + carboplatin, last on 21/12/ 2010	6 cycles of paclitaxel + carboplatin last on 29/11/2015
	Recurrence 1	12/03/2013 (PFS: 26 months)	25/07/2017 (PFS: 20 months)
	Chemotherapy 2nd line	6 cycles of gemcitabine + carboplatin, last on 23/09/2013	6 cycles of pegylated liposomal doxorubicin + carboplatin, last on 21/02/2018
	Recurrence 2	30/06/2016 (PFS: 33 months)	—
	Chemotherapy 3rd line	6 cycles of doxorubicin + carboplatin, last on 19/10/ 2016	—
	Recurrence 3	11/01/2018 (PFS: 15 months)	—
	2nd cytoreduction surgery followed by chemotherapy 4th line	6 cycles of liposomal doxorubicin + carboplatin until 02/07/ 2018	—
Ayurveda maintenance treatment ZINCA-30	Progression-free survival (PFS)	Started from 02/07/2018 to 01/11/ 2020	Started from 21/05/2018 till the date of latest follow up on 19/11/ 2021
Present status		Recurrence 02/11/2020 (PFS: 28 months)	No recurrence until 19/11/2021 (PFS 45 months and continued)

approach when the disease recurs early after the chemotherapy, and platinum-based chemotherapy is usually recommended if the platinum-free interval exceeds 12 months.[16]

The goals of therapy in ROC should be palliation of cancer-related symptoms, maintenance of the quality of life, and extension of life. Hence, there is a significant impetus for research for focusing on newer maintenance treatments for ROC.[17]

Therefore, the option of ATM was explored with the effective role of *Rasayana* properties of the herbs and minerals in the ZINCA-30 regimen.

Rasayana drugs in Ayurveda are herbal/herbomineral preparations or individual herbs used to rejuvenate or attain the complete potential of an individual to prevent diseases and degenerative changes that lead to the disease. The probable mechanism may be immune-stimulation, quenching free radicals, enhancing cellular detoxification mechanisms, repairing damaged non-proliferating cells, inducing cell proliferation, and self-renewal of damaged proliferating tissues, and replenishing those by replacing damaged or mutated cells with fresh cells.[18]

A combination labeled as ZINCA-30 regimen comprising *Jasad Bhasma* (classical Ayurveda Zinc preparation), *Indukanth Kwatham* tablets and powdered *Curcuma amada* (*Amra-Haridra)*, was prescribed considering safety and efficacy in cancer treatment as discussed here. The *Jasad bhasma* (JB) is a bioabsorbable *Rasayana* preparation from *Rasashashtra*[19]; the pharmaceutic treatise of Ayurveda. The safety and bioactivity studies of the JB are well studied and documented.[20] It has the presence of macro-, micro-, and nano-particles[21] in the final safe[22] products

manufactured as per the guidelines of Ayurvedic Formulary of India.[23] JB is a zinc-based preparation, which was also studied in resistant ovarian cancer using SKOV3 and ES2 ovarian cancer cell lines and showed potential as a second-line treatment.[24] *Amra Haridra* (AH), as mentioned in Ayurvedic Pharmacopeia of India,[25] commonly called as mango ginger and botanically known as *Curcuma amada Roxb*. is a medicinal species of turmeric known for its anticancer potential, including ovarian cancer. It works by targeting the nuclear factor-αB (NF-αB) pathway in human ovarian cancer cell lines SKOV3ip1 and HeyA8.[26,27] *Indukant Kwatham* (IK)[28–30] has therapeutic implications for the cases of intra-abdominal cysts, ovarian cysts, benign and malignant ovarian tumors termed as *Raktaja-Gulma*.[31] *Indukant Kwatham* has immunomodulatory effects after chemotherapy and is used in the form of aqueous or lipid extract.[32,33] These patients were punctual for treatment and follow-up over the 3 years and continued to appear for their scheduled follow-ups. In these cases, the ZINCA-30 regimen was non-platinum based and the PFS observed was 28 months and 45 months. There were no reported or noted AEs during the entire period of treatment in these patients.

For the patients treated here, in whom the recurrence was observed after 28 months, the complete response (CR) was observed on PET CT at the end of platinum-based chemotherapy (PBC), which may be because of a significant increase in the platinum sensitivity. The complete response to the re-challenged platinum-based treatment after AMT ZINCA-30 may be a possible scope of further study.

Therefore, the AMT ZINCA-30, being a non–platinum-based regimen may have a potential role in maintenance treatment after SOC as well as to increase the PFI, which eventually may lead to better OS, without any AEs or events.

Conclusion

1. Ayurveda maintenance therapy, ZINCA-30 can be a potential lead as an alternative non–platinum-based treatment option for increasing PFS in ROC.
2. The observations in these preliminary cases indicated increased PFI with AMT, ZINCA-30 after standard chemotherapy in ROC.

Limitations and Further Scope

This communication is merely a preliminary outcome of continued clinical observations, and a well-planned formal study is needed to test this hypothesis further.

Assessing the quality of life with the Global QOL Score and affordability can be studied in addition to this.

Conflict of Interest
None declared.

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Pulmonary Aspergillosis Silently Presenting as Pneumothorax in Children with Leukemia: A Report of Three Cases

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Abstract

Aspergillosis causes invasive pulmonary disease in patients with hematological malignancies. Children with invasive pulmonary aspergillosis (IPA) usually have nonspecific radiographic findings unlike cavitary lesions commonly seen in adults. Pneumothorax due to rupture of peripheral fungal lesion may be a severe complication in patients with neutropenia. Here, we describe three children during induction chemotherapy for B-lymphoblastic leukemia with pneumothorax as a presenting feature of pulmonary aspergillosis.

Keywords
- leukemia
- pediatric oncology
- pneumothorax
- pulmonary aspergillosis

Introduction

Invasive pulmonary aspergillosis (IPA) is a potentially fatal opportunistic infection in patients with hematological malignancies and stem cell transplant recipients.[1,2] Acute necrotizing bronchopneumonia, hemorrhagic pulmonary infarction, and lung abscess have been described in a large retrospective review of culture documented aspergillus infection in pediatric cancer patients but none of them manifested with pneumothorax.[3] We describe our observations of three children with B-lymphoblastic leukemia (B-ALL) who developed spontaneous pneumothorax that represented the first sign of IPA.

Case Description

Case 1

A 7-year-old male presented with fever, pallor, hepatomegaly, and splenomegaly. He was diagnosed with B-ALL and started on remission induction chemotherapy as per the Indian Childhood Collaborative Leukemia Group (ICiCLe) protocol under the intermediate-risk arm.[4] On day 22 of induction, child complained of difficulty in breathing and chest pain on left side. On physical assessment, the trachea was shifted to the right and hyperresonant percussion note on left hemithorax. Chest radiography showed lucent area in left lung field with absent bronchovesicular marking suggesting a pneumothorax with tracheal shift to right (►**Fig. 1**). An emergent chest tube thoracostomy was performed. Contrast-enhanced computed tomography (CECT) showed bilateral patchy areas of consolidation involving left lower lobe, left upper lobe, and right lower lobe.

Serum galactomannan (GM) level was analyzed by immune-enzymatic sandwich microplate assay and was found to be optical density index of 0.85. Any value of >0.5 optical density index is considered positive by the assay. Blood culture was negative. The patchy consolidation resolved after 6 weeks of amphotericin B deoxycholate therapy at dose of

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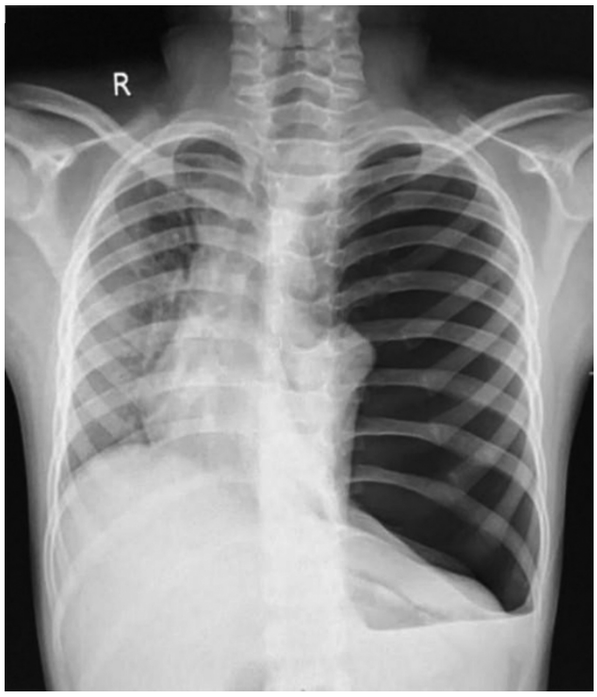

Fig. 1 Pneumothorax with tracheal shift to right

1 mg/kg/day once daily. In retrospect, it was noticed that there was rapid recovery of neutrophil counts from 500 to 1,500 cells/µL within 48 hours when child developed pneumothorax. At the end of induction, bone marrow was in remission and minimal residual disease was <0.01%.

Case 2

A 9-year-old female presented with fever and easy fatigability since 4 weeks. Physical examination revealed pallor; cervical, axillary, and epitrochlear lymphadenopathy; hepatomegaly ; and splenomegaly. The child was diagnosed with B-ALL having hyperdiploidy and chromosome 6q deletion. Remission induction chemotherapy was started as per the ICiCLe protocol under the intermediate-risk arm. Second week of induction was complicated by reversible posterior leukoencephalopathy syndrome (RPLS). On day 30 of induction, child developed pleuritic chest pain on the right side. Chest radiograph suggested right pneumothorax which was confirmed on CECT thorax. There were multiple ill-defined heterogeneously enhancing nodules of varying size in bilateral lung fields in random distribution. Few cavitary lung lesions were observed in the anterior basal segment of right lower lobe. The child was started on amphotericin B deoxycholate with suspicion of invasive fungal infection. There was a recent neutrophil count recovery from 600 to 1,100 cells/µL when child had developed pneumothorax. Two days later, a small subcutaneous swelling was noted on anterior abdominal wall in the left iliac region. It was firm and tender on examination. The specimen obtained by needle aspiration was sent for microbiological evaluation which revealed septate fungal elements. Serum GM was positive with an index value of 2.11. There was modest improvement on CECT thorax after 3 weeks of therapy, with persistence of lung nodules in bilateral lung fields. Pneumothorax resolved spontaneously. Serum GM was negative (optical density index of 0.30) after 6 weeks of amphotericin B. Despite a challenging course of remission induction complicated by RPLS and invasive aspergillosis (IA) with pneumothorax, the child was able to achieve a post induction minimal residual disease of <0.01%.

Case 3

A 9-year-old male with fever since 2 weeks had pallor, cervical lymphadenopathy, and oraganomegaly. On evaluation, child was diagnosed with B-ALL with hyperdiploidy and started on induction chemotherapy as per the ICiCLe protocol. On day 28, the child developed right-sided chest pain on deep inspiration. There were decreased chest excursions and diminished breath sounds on right hemithorax. Chest radiography showed collapse of right lung with lucent area in peripheral lung field with absent bronchovesicular marking suggesting a pneumothorax. Needle decompression of pleural space was performed followed by chest tube thoracostomy. CECT thorax showed patchy areas of consolidation in right lower lobe. Serum GM assay was positive. Child responded well after 3 weeks of amphotericin B dosage and achieved remission at the end of induction.

Discussion

The incidence of invasive fungal infections (IFIs) has increased over the last few years along with the increased number of immunocompromised patients.[5] Timely diagnosis and prompt initiation of antifungal treatment are crucial for care.[6] Spontaneous pneumothorax in children receiving remission induction chemotherapy for leukemia is seldom encountered. Pneumothorax occurs in approximately 13% of adults who have pulmonary fungal infection while receiving chemotherapy for hematological malignancies. But the incidence of pneumothorax due to IPA in pediatric age is not known, since it is exceedingly rare.

IPA is categorized as “proven,” “probable,” and “possible” based on clinical, microbiological, and radiological criteria as per the revised European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) consensus definition.[7] In this report, we describe pneumothorax as the first manifestation in one “proven (case 2)” and two “probable (cases 1 and 3)” cases of IPA. Bacterial blood cultures were negative, and fungal blood cultures were sent for testing but showed no growth in all the three cases.

Bronchoalveolar lavage could not be performed in patients due to prevailing clinical conditions and resource constraints. All the patients were on fluconazole for primary antifungal prophylaxis since beginning of the induction therapy. Voriconazole was continued as secondary prophylaxis after discontinuation of amphotericin B. Steroids were continued at second or third dose, and further induction was resumed once patients were clinically stable along with antifungal therapy.

Opportunistic infections during the early phase of leukemia treatment are a two-fold blow. They not only hamper the timely delivery of cytotoxic agents but are also difficult to treat and often lethal. The German ALL–Berlin–Frankfurt–Muenster (BFM) study group reported that fungal infections were responsible for one-fifth of fatal infections in pediatric ALL patients.[8]

Aspergillus was implicated in two-thirds of those with invasive fungal infection.[8] Corticosteroids and prolonged neutropenia are known risk factors for this.[9] Pulmonary aspergillosis presents with fever, pleuritic chest pain, and hemoptysis. Corticosteroids may mask the common presenting symptoms of IPA, mainly fever and cough. In a large survey of patients with IPA, typical manifestations were significantly less common in patients receiving steroids.[10] The occurrence of spontaneous pneumothorax may be the first manifestation of subpleural fungal infection in patients with leukemia. Poor nutrition, presence of subpleural lesion, bouts of excessive coughing, and prolonged corticosteroid therapy are various precipitating factors. Pleural lesions were seen in cases 2 and 3.

In review of radiological findings in children with IPA consolidation, perihilar infiltrates, multiple small nodules, peripheral nodular masses, and pleural effusions have been described but no findings have been suggestive of pneumothorax.[11] In a multicenter retrospective analysis of pediatric invasive pulmonary aspergillosis, the most common diagnostic radiologic finding was of nodules.[12] Children with proven IPA commonly have nonspecific changes on CECT compared with halo sign, air crescent formation, or cavitation seen in adults.[8] Rare possible complications of pulmonary aspergillosis include bronchopericardial fistula, pericarditis, tension pneumopericardium, and pericardial tamponade.[13]

A temporal correlation between neutrophil count recovery and occurrence of pneumothorax in patients with invasive fungal pneumonia has been demonstrated.[14] The neutrophils are attracted to site of infection by chemotactic factors. Along with its microbicidal activity, neutrophils release reactive oxygen intermediates and proteolytic enzymes like collagenase and elastase. These cytolytic molecules cause collateral damage by destruction of surrounding pulmonary parenchyma. This might explain the paradoxical clinical deterioration with neutrophil recovery observed in two of the cases (1 and 2) we described.

Early suspicion of aspergillosis helped us to start appropriate antifungal agent early, with favorable outcome during a crucial period of remission induction. The advent of biomarker tests such as the GM enzyme immunoassay (GM-EIA) provides a potential adjunct for noninvasive diagnosis of IA.[15] A limitation to our approach was that histopathologic or cytopathologic evidence of mold could not be proven in cases 1 and 3. Bronchoalveolar lavage and fungal DNA polymerase chain reaction (PCR) could not be performed due to resource constraints.

Conclusion

Our observation helps us to be vigilant for sudden deterioration and pneumothorax in children with ALL on induction therapy. A possibility of IPA should be considered when encountered with pneumothorax in children with leukemia on intensive chemotherapy. Based on clinical and radiological observations, recent recovery of neutrophil counts and presence of subpleural or peripheral lesion may increase the likelihood of pneumothorax.

Note

The manuscript has been read and approved by all the authors, and the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflict of Interest

None declared.

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Multiple Complications Secondary to L-asparaginase In a Child with Philadelphia-Chromosome-Positive Acute Lymphoblastic Leukemia: Case Report with Review of Literature

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Abstract

Even though L-asparaginase remains an essential drug for the treatment of childhood acute lymphoblastic leukemia (ALL), its use is associated with several unique toxicities. In this care report, we discuss a young boy with ALL who developed multiple complications simultaneously, including pancreatitis, gastrointestinal perforation, and left ventricular thrombus secondary to L-asparaginase during induction chemotherapy. Patient received immediate surgical intervention for the perforation and was commenced on anticoagulation therapy for the thrombus but eventually expired. This report highlights the importance of being aware of toxicities secondary to the use of L-asparaginase. Multiple complications secondary to L-asparaginase have been rarely reported previously and can be fatal.

Keywords

- Philadelphia-chromosome-positive acute lymphoblastic leukemia
- acute pancreatitis
- ventricular thrombus
- gastric perforation
- L-asparaginase

Introduction

L-asparaginase has become an integral part in the management of childhood acute lymphoblastic leukemia (ALL) and failure to receive its intended course has been associated with poor outcome.[1,2] However, L-asparaginase is also associated with a number of unique toxicities, some of which can have life threatening consequences.[3] Here we present a patient with Philadelphia-Chromosome-positive Acute Lymphoblastic Leukemia (Ph^+ ALL) who experienced two rare complications during induction therapy: gastric perforation and a left ventricular thrombus which led to his demise.

Case Report

An 8-year-old male presented with on and off fever, bruising over shin and chest and easy fatigability for 2 weeks. A complete blood count showed a total leukocyte count (TLC) of 153×10^9 /L with a differential count of 60% lymphocytes, 3% neutrophils, 0.1% eosinophils, and 27% blasts in the peripheral blood. A bone marrow examination was done, flow cytometric

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analysis along with FISH study which was positive for t(9;22), confirmed the diagnosis of B-lineage Ph^+ ALL. A real-time quantitative polymerase chain reaction (RT-PCR) was suggestive of p190 BCR/ABL fusion transcript. Cerebrospinal fluid analysis was uninvolved for disease. He was treated as per the modified COG AALL1131 protocol. Induction chemotherapy consisted of prednisolone (60 mg/m^2/day; 1–28 days), vincristine (1.5 mg/m^2/d; days 1, 8, 15, and 22), native *Escherichia coli* L-asparaginase (10,000 U/m^2/d; days 1,4, 7, 10, 13, 16, 19, and 22) daunorubicin (30 mg/m^2/d; days 1 and 15), intrathecal methotrexate (12 mg; days 1, 8, and 30) along with daily imatinib (340 mg/m^2/once daily) from day 10. Chemotherapy was administered through peripheral intravenous lines on an outpatient basis. Treatment was uneventful up to day 29 of induction when he presented with abdominal pain and fever. On examination, heart rate was 86/min, blood pressure was 100/70 mm Hg and respiration was 22/min. Abdomen was mildly distended, diffusely tender, and bowel sounds were present. He was started on intravenous fluids, intravenous antibiotics (cefoperazone-sulbactam and amikacin), and analgesics for abdominal pain. The complete blood count showed a hemoglobin of 5 g/dL, platelet of 49×10^9/L, and TLC of 0.42×10^9/L with an absolute neutrophil count of 0.1×10^9/L. Blood tests showed an elevated lipase (1,164 U/L), elevated D-dimer (3,700 ng/mL), with a normal serum sodium (137 mEq/L) and potassium (4.2 mEql/L) and no organism was isolated from blood culture. In view of the above symptoms in a neutropenic child, computerized tomography (CT) scan of the abdomen with contrast was performed on the day of admission which revealed a bulky pancreas with fat stranding consistent with acute pancreatitis, as well as perforation of the greater curvature of the stomach resulting in pneumoperitoneum (►**Fig. 1a** and **b**). An incidental finding on CT scan was a well-defined hypodense mass in the left ventricle (LV) of the heart which an ultrasound study showed lacked vascularity; two-dimensional echocardiography confirmed a mass of 3.01×1.49 cm arising from the interventricular septum with a normal ejection fraction of 60% (►**Fig. 1a** and **c**). Imaging findings and elevated D-dimer both strongly suggested a diagnosis of intraventricular thrombus. The child was shifted to the intensive care unit (ICU) where he was continued on analgesics and intravenous antibiotics and kept nil by mouth. He underwent an emergency laparotomy for his abdominal emergency. Intraoperatively, there was a single perforation on the posterior wall of the stomach, and two impending perforations on the proximal jejunal wall, all of which were closed in two layers, using 4-0 polydioxanone suture (►**Fig. 1d** and **e**). The surgical procedure was uneventful. Postoperatively, the child continued to be neutropenic (absolute neutrophil count: of 0.1×10^9/L) with a platelet count of 40×10^9/L. He was continued on intravenous antibiotics and was started on the low-molecular weight heparin (LMWH) enoxaparin at 1 mg/kg/dose twice a day for the large cardiac thrombus. Given his postoperative state and neutropenia, it was decided to defer any major cardiac surgery. The day after surgery the child was extubated from the ventilator and started on clear liquids, his pancreatic enzymes had returned to normal. On the subsequent day (postoperative day 2) he developed a sudden cardiac arrest and could not be revived. Permission for autopsy was not obtained.

Discussion

Philadelphia chromosome (Ph^+) ALL comprises only 3%–5% of childhood ALL, the outcomes of which have been dismal until the addition of tyrosine kinase inhibitor, imatinib.[4,5] While imatinib has been linked to pneumatosis intestinalis in a child with acute leukemia, most clinical trials for childhood Ph^+ ALL have not reported this as a significant toxicity.[4–6] Of interest was L-asparaginase, linked to pancreatitis in 6.7%–18% of children being treated for ALL.[7] The clinical course of drug-induced pancreatitis can vary from mild to severe and in our patient serum lipase returned to normal within 72 hours and CT abdomen showed no evidence of pseudocyst or necrosis, excluding severe pancreatitis as a cause of gastrointestinal perforation.[8] Gastrointestinal tract perforation is reportedly seen in less than 1% of patients on induction therapy for ALL.[9] L-asparaginase-related jejunal perforation has been described in a patient with ALL, with the etiology related to the prothrombotic state induced by reducing levels of natural anticoagulants such as protein C, protein S, Antithrombin III, and plasminogen.[10,11] Also, imatinib has very rarely been reported to cause bowel perforation, but given the rarity and length of exposure it is unlikely to be the causative factor in our patient.[12–14]

Thrombotic complications are seen in 2%–7% of patients with ALL receiving asparaginase. The driving mechanism for thrombosis is related to the depletion of L-asparaginase-dependent hemostatic protein synthesis. Thrombotic events most often occur during induction and corticosteroids may contribute by increasing synthesis of procoagulants as well as by inducing vascular changes.[15] Majority of patients develop venous thrombosis, but arterial thrombosis has also been reported.[16] Thrombosis secondary to L-asparaginase is usually managed with LMWH. L-asparaginase may need temporary discontinuation in the presence of clinically significant thrombotic events, however, re-exposure is considered to be safe and feasible and is usually done under the cover of anticoagulation therapy.[3] Intracardiac thrombus amongst patients receiving L-asparaginase usually involves the right atrium in 2%–14% of children with ALL and is usually related to the presence of catheter tip in right atrium while the LV has not been described as a site for a thrombus.[17,18] LV thrombosis has been described in patients with hypereosinophilic syndrome, as well as in a child with acquired protein C deficiency.[19,20] Amongst adults, LV thrombus commonly occurs following myocardial infarction but has also occasionally been described amongst patients with cancer.[21–23] LV thrombus poses a risk of embolism resulting in ischemic stroke and peripheral embolism, because of which immediate anticoagulation therapy is recommended. In adults the preferred anticoagulation is usually oral warfarin along with low dose aspirin for 3 to 6 months.[23] Surgery is recommended if the general condition of the patient is preserved. Since

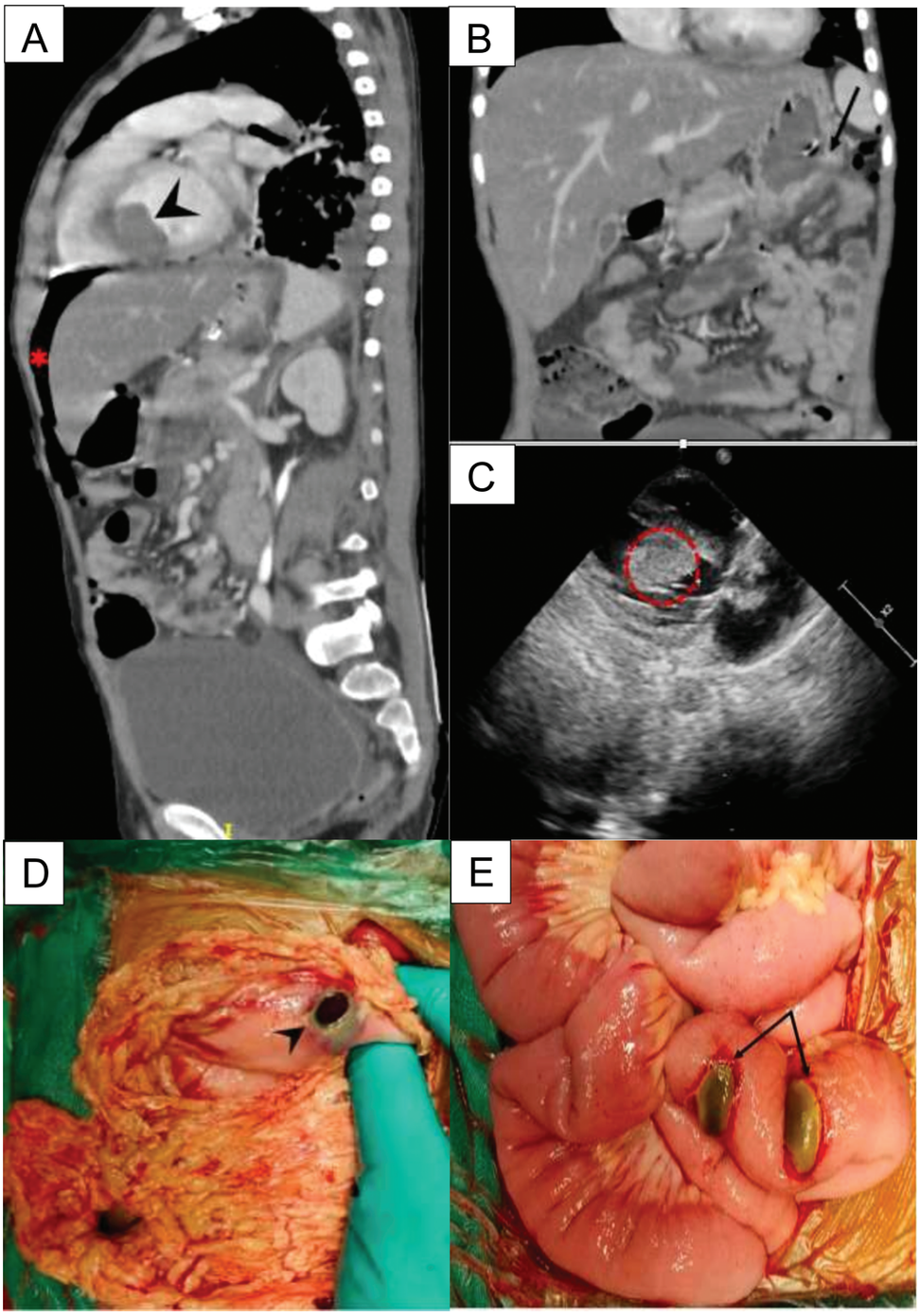

Fig. 1 (**A**) CT abdomen showing left ventricular thrombus (*arrow head*) and pneumoperitoneum (*) (**B**) with gastric perforation (*arrow*). (**C**) 2D-echocardiography confirming the presence of left ventricular thrombus (*outlined circle*). (**D**) Intraoperative findings showing perforation of greater curvature of stomach (*arrow head*) (**E**) impending perforation of jejunum (*double arrow*).

our patient was a child who had undergone a major gastric surgery, he was commenced on subcutaneous LMWH and since he was severely neutropenic it was decided to defer any cardiac surgery until the time of count recovery.

Our patient did not have any past history of thrombotic episodes or family history of thrombophilia, but the co-occurrence of these unusual complications made us strongly suspect a underlying prothrombotic condition exacerbated by L-asparaginase therapy.[10] The prevalence of genetic prothrombotic abnormalities amongst children with ALL varies around the world, and we do not pre-emptively screen for thrombophilia given that such testing is expensive, and not easily available. The Dutch Children's Oncology Group has debated the benefit of more aggressive screening and LMWH

prophylaxis during induction for those found to have thrombophilia.[24] The role of genetic predisposition for pancreatitis is less clear but recent genome-wide association studies have found different candidate single-nucleotide polymorphisms associated with pancreatitis in patients with ALL.[25] We could not rule out a pre-existing cardiac thrombus as a baseline 2D-echo was unavailable. Also, thrombotic events and gastric perforation during ALL therapy are often considered to be multifactorial rather than secondary to a single drug. But, the occurrence of several unique toxicities which are often shown to be associated with L-asparaginase, all occurring simultaneously in a patient would be the highlight of this case report.

Conclusion

Though L-asparaginase is an essential drug for the management of childhood ALL, it does possess a unique toxicity profile. Unfortunately, our patient simultaneously experienced several toxicities, including pancreatitis, LV thrombus, and gastrointestinal perforation leading to his demise. Lack of familiarity of the toxicity profile of this drug can make L-asparaginase a difficult drug to use. Being vigilant for these unusual toxicities especially during induction chemotherapy is essential for optimal patient care.

Source of Support
None.

Declaration of Patient Consent
The authors certify that they have obtained all appropriate patient consent forms.

Conflict of interest
None declared.

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Challenges of Skeletal Reconstruction in Growing Children—Hobson's Choice

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Reconstruction of skeletal defects after resection for bone tumors in children is challenging due to (a) small size bones, (b) limited bone stock, (c) challenges with microvascular anastomosis, and (d) risk of limb length discrepancy. Reconstructions should be durable to ensure long-term stability and allow for axial growth. Reconstruction with metal prosthesis, biological reconstruction, and allo/auto-prosthesis composites come with challenges unique to them. This is further compounded in our country with constraints of resources and advanced stage of presentation.

Tumors around the joint need prosthetic reconstruction. Pediatric patients need some form of expansion that is built into the prosthesis which can be periodically expanded to account for longitudinal growth. Third-generation metal prostheses where the expansion is noninvasive (Juvenile Tumour System, Stanmore Implants Worldwide, Stanmore, United Kingdom) have revolutionized the management of these patients. This has overcome the problems of (a) multiple surgeries and (b) infection, in second-generation implants that were minimally invasive and needed repeated surgeries to expand the prosthesis which was based on an elongating screw or telescoping mechanism. Third-generation expandable prostheses are expensive, about Rs 20 lakh, which is not affordable for most patients in our country.

Our "go-to" modality for reconstruction has been the vascularized fibular graft. It is a versatile flap and can be used for reconstruction at a variety of sites.[1] We have used this graft for (a) intercalary resections, either alone or with recycled autograft (Capanna technique—combination of auto/allograft and vascularized fibula),[2] or for (b) reconstruction of combined epiphyseal-diaphyseal defects (humerus and radius). Monitoring of these flaps without skin paddle is a challenge. We use a triple-phase Tc99 MDP bone scan at 48 hours after surgery to assess viability and use Jones index to score the flap.[3] The fibula is usually harvested based on peroneal vessels. This, however, does not supply the proximal epiphysis. For longitudinal growth, the fibula should be harvested with the vessels supplying the epiphysis (epiphyseal transfer technique) that branches from the anterior tibial artery (first/second recurrent epiphyseal arteries or inferior genicular artery). Rarely due to small caliber they may not be demonstrable, in which case anterior tibial artery may be harvested in addition to peroneal vessels. Transposition of the ipsilateral fibula for tibial defects (Huntington's procedure or tibialization of fibula)[4] is an attractive option.

Postoperative radiation after biological reconstruction is a barrier to healing. All components of bone from epiphysis to osteoblasts, osteoclasts, periosteum, periosteum, vascularity, and quality of mineralized bone are detrimentally impacted by radiation, leading to increased problems with wound healing and bone union.[5] This represents a Hobson's choice between (a) delivery of radiation leading to issues with bone union or (b) avoiding radiation in biological reconstruction, leading to undertreatment that may compromise survival. We have attempted to circumvent this problem by using preoperative radiation in patients with Ewing's sarcoma in patients (a) who mandatorily need radiation (pathological fracture, large prechemotherapy tumor volume, etc.) and (b) who have biological reconstruction being performed.

Multiple choices exist of reconstruction for skeletal defects in children and should be individualized based on patient characteristics, need for additional therapy, patient affordability, and availability of expertise.

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Conflict of Interest
None declared.

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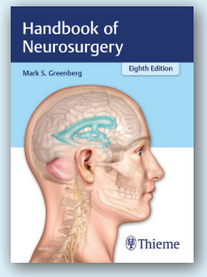

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