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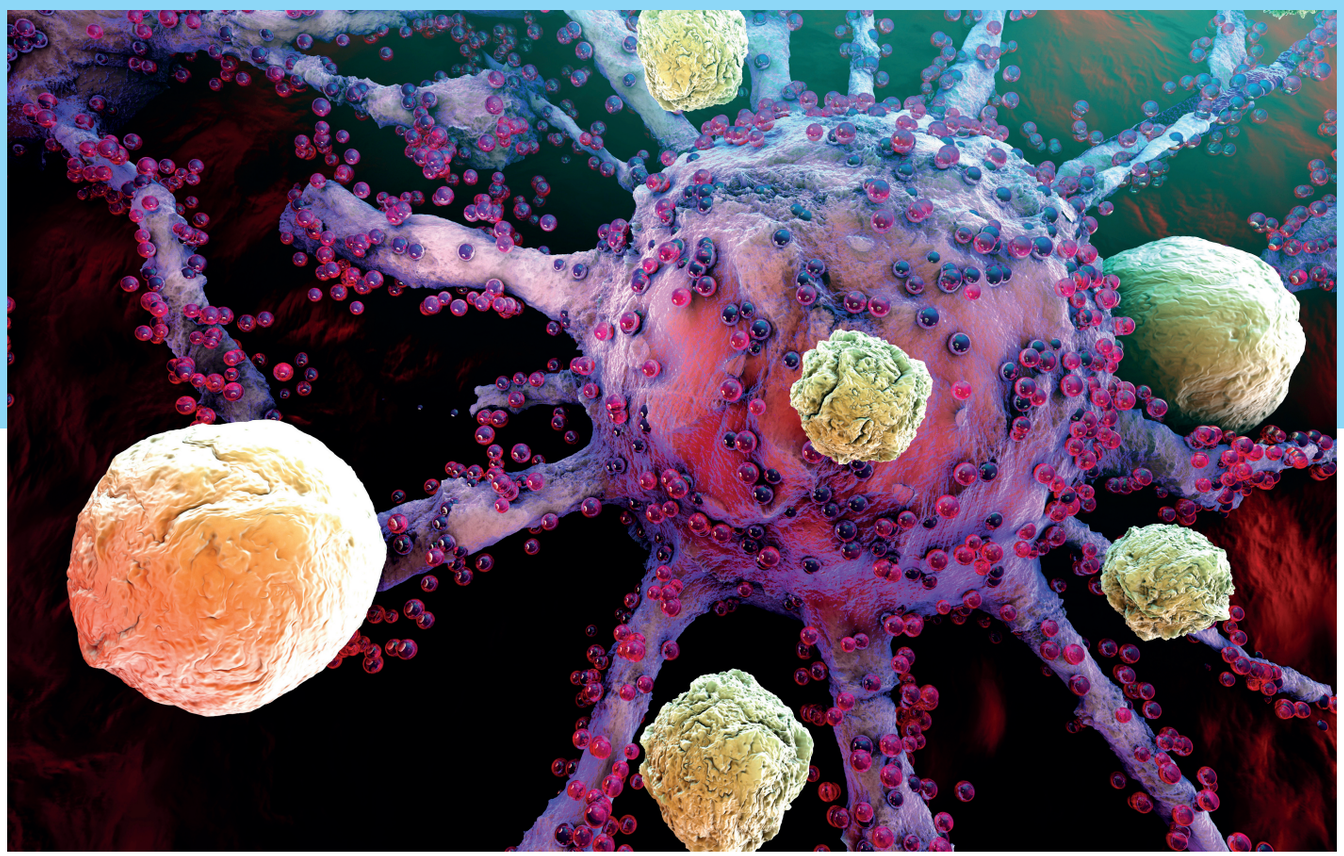

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Indian Journal of Medical and Paediatric Oncology

Volume 46 • Number 2 • Pages 119–232 • April 2025

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ISO-ISMPOCON 2025

Mahatma Gandhi
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Theme: WINNING THE BATTLE AGAINST CANCER - FROM INSIGHTS TO IMPACT!

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Octride Depot

(1 Month)

Dosage Form: Lyophilized powder for injection. **Composition:** Each vial of **Octride Depot** contains: Octreotide Acetate equivalent to Octreotide base 10 or 20 or 30 mg Excipients q.s. Each ml of **Diluent for Octride Depot** contains: Sodium carboxymethyl Cellulose IP 5 mg, Polysorbate 80 IP 1 mg, Mannitol IP 50 mg, Water for Injection IP 1 ml. **Description: Octride Depot** is a long acting dosage form consisting of microspheres of the biodegradable D, Llactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate release dosage form octreotide injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. **Octride Depot** is a depot formulation of octreotide, designed to be injected intramuscularly (intragluteally) once every four weeks. **Indications:** Octride Depot is indicated in patients in whom initial treatment with octreotide has been shown to be effective and tolerated. **Carcinoid Tumors:** Long term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors. **Vasoactive Intestinal Peptide Tumors (VIPomas)** Long term treatment of the profuse watery diarrhea associated with VIP secreting tumors. In patients with carcinoid syndrome and VIPomas, the effect of octreotide on tumor size, rate of growth and development of metastases, has not been determined. **Dosage and Administration:** For Intramuscular intragluteal use.Administer the entire contents immediately after reconstitution. For single use only. **Octride Depot** should be administered by a trained health care provider. It is important to closely follow the mixing instructions.Octride Depot must be administered immediately after mixing. Do not directly inject diluent without preparing suspension. **Octride Depot** should be administered intragluteally at four week intervals. Administration of Octride Depot at intervals greater than 4 weeks is not recommended.. Deltoid injections should be avoided due to significant discomfort at the injection site when given in that area. Octride Depot should never be administered intravenously or subcutaneously. The following dosage regimens are recommended. **Carcinoid Tumors and VIPomas** *Patients Not Currently Receiving Octreotide:* Patients not currently receiving octreotide should begin therapy with octreotide injection given subcutaneously.The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required. Octreotide injection should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide and who tolerate the drug may be switched to Octride Depot in the dosage regimen as described below *Patients Currently Receiving Octreotide Injection:* Patients currently receiving octreotide injection can be switched to Octride Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. Carcinoid tumor and VIPoma patients should continue to receive octreotide injection subcutaneously for at least 2 weeks in the same dosage they were taking before the switch. After two months, dosage may be adjusted as follows: • If symptoms are adequately controlled, consider a dose reduction to 10 mg for a trial period. • If symptoms are not adequately controlled, increase **Octride Depot** to 30 mg every 4 weeks. • Dosages higher than 30 mg are not recommended.*Elderly:* Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, *Pediatric use:* In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Octride Depot administered by IM injection every four weeks was approximately 3 mg/ml. *Hepatic impairment:* In patients with established liver cirrhosis, the starting dose should be 10 mg. Renal impairment: In patients with renal failure requiring dialysis, the starting dose should be 10 mg. In other patients with renal impairment, the dose should be similar to a non-renal patient.

Special Instructions for use 1. The lyophilized microspheres should be reconstituted immediately prior to administration 2. Diluent for **Octride Depot** is provided in prefilled syringe. The diluent prefilled syringe should not be used if any visible solid particles are seen. 3. Allow the **Octride Depot** vial and diluent prefilled syringe to reach room temperature (approximately 30 to 60 minutes). 4. Remove the tip cap of prefilled syringe and attach the 19 gauge needle (supplied) to the prefilled syringe. 5. Insert the needle through the center of the rubber stopper of the **Octride Depot** vial, using an aseptic technique. Gently inject the contents of the diluent prefilled syringe down the inside wall of the vial. Administer the suspension by taking care not to enter a blood vessel. 6. The injection should be given as soon as possible after mixing. 7. Suspension should be discarded if not used immediately. **Contra-indications:** Hypersensitivity to octreotide or any other component of the formulation. **Warnings and Precautions:** Octreotide may lead to gallbladder abnormalities or sludge. Blood glucose levels should be monitored .Antidiabetic treatment should be adjusted accordingly. Baseline and periodic assessment of thyroid function (TSH, total and/or free T4) is recommended during chronic octreotide therapy.In carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy.Octreotide may alter absorption of dietary fats..Monitoring of vitamin B12 levels is recommended. Patients on TPN and octreotide should have periodic monitoring of zinc levels. **Pregnancy & Lactation:** Octreotide should be used during pregnancy only if the therapeutic benefit outweighs the potential risks.Caution is advised when octreotide for injection (1 month Depot) is administered to a nursing woman. **Drug Interactions:** Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection. Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Octreotide inhibits the secretion of insulin and glucagon. Concomitant administration of bradycardia inducing drugs (e.g., beta blockers) may have an additive effect on the reduction of heart rate associated with octreotide. Dose adjustments of concomitant medication may be necessary. **Side effectsL Carcinoid tumors and VIPomas:** The commonly reported adverse events in patients with carcinoid tumors and VIPomas with an incidence of occurrence >15 % are abdominal pain, arthropathy, back pain, dizziness, fatigue, flatulence, generalized pain, headache, musculoskeletal pain, myalgia, nausea, pruritus, rash, sinusitis, upper respiratory tract infection (URTI), vomiting, biliary abnormalities including jaundice, gallstones, sludge and dilatation, hyperglycemia and sinus bradycardia.Other adverse events observed are hypoglycemia,conduction abnormalities, arrhythmias, hyperpyrexia, cerebral vascular disorder, rectal bleeding,ascites, pulmonary embolism, pneumonia and pleural effusion. Myocardial infarction has been observed in the post marketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under. **Overdosage:** No overdose has occurred in any patient to date. Doses of 2.5 mg (2500 mcg) of octreotide injection subcutaneously have, however, caused hypoglycemia, flushing, dizziness, and nausea. **Clinical Pharmacology:** Octreotide Depot is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. **Mechanism of Action :** Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. **Pharmacokinetics:** After a single IM injection of the long acting depot dosage the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour and reaching a plateau about two to three weeks post injection.Following multiple doses of octreotide depot given every 4 weeks, steady state octreotide serum concentrations were achieved after the third injection. Octreotide depot has not been studied in patients with renal impairment and hepatic impairment. **Incompatibilities:** Octride Depot is to be used as a single dose container, without any dilution with other products.Therefore, no compatibility data with other products have been generated. **Storage & Handling:** Store at 2°C to 8°C, protected from light. Do not freeze. Keep out of reach of children.

Expiry Date : Refer product label for expiry date. Do not use after expiry date. **Presentation:** Octride Depot is available as single use vials containing octreotide 10 mg or 20 mg or 30 mg, as lyophilized powder for injection, supplied with 2 ml of diluent in one prefilled syringe, two 19 gauge needles and two alcohol swabs. **D102/072012/V2**

1. Data on file

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05th March 2025 — Last date for submission of application

Result Date — **12th March 2025**

For more information please contact:
Mr. Srinivas on +91 98483 42649 | Email: mofteam@outlook.com

Indian Society of Medical and Paediatric Oncology (ISMPO)—Breast Cancer in Young Guidelines

Jyoti Bajpai[1] Shruti Sanjay Gandhi[2] Senthil Rajappa[3] Rima Pathak[4] Shalaka Joshi[5] Atul Batra[6] Manisha Singh[7] Joydeep Ghosh[8] Bharath Rangarajan[9] Gaurav Prakash[10] Biswajit Dubashi[11] Syed Nisar Ahmad[12] Rinoy Sreedharan[13] Shivashankara Swamy Mathighatta Shivarudraiah[14] Bhawna Sirohi[15] Chirag Desai[16] Prakash Chitalkar[17] Sudeep Gupta[18] Hemant Malhotra[19] Shyam Aggrawal[20]

[1] Department of Medical Oncology, Tata Memorial Centre, Parel, Mumbai, Maharashtra, India
[2] Department of Medical Oncology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, India
[3] Department of Medical Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Banjara Hills, Hyderabad, Telangana, India
[4] Department of Radiation Oncology, Tata Memorial Centre, Parel, Mumbai, Maharashtra, India
[5] Department of Surgical Oncology, Tata Memorial Centre, Parel, Mumbai, Maharashtra, India
[6] Department of Medical Oncology, All India Institute of Medical Sciences, Dr. B.R.A. Institute Rotary Cancer Hospital, New Delhi, India
[7] Department of Medical Oncology, Mahavir Cancer Sansthan and Research Center, Patna, Bihar, India
[8] Department of Medical Oncology, Tata Medical Centre, Kolkata, West Bengal, India
[9] Department of Medical Oncology, The Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India
[10] Department of Medical Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[11] Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
[12] Department of Medical Oncology, Sher-e-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India
[13] Department of Obstetrics and Gynaecology, Indira IVF Centre, Mumbai, Maharashtra, India
[14] Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Center, Delhi, India
[15] Department of Medical Oncology, Balco Medical Centre, Vedanta Medical Research Foundation, Raipur, Chhattisgarh, India
[16] Department of Medical Oncology, Sterling Hospital, Ahmedabad, Gujrat, India
[17] Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, India
[18] Department of Medical Oncology, Tata Memorial Centre, Parel, Mumbai, Maharashtra, India
[19] Department of Medical Oncology, Sriram Cancer Center, Mahatma Gandhi Medical College Hospital, Jaipur, Rajasthan, India
[20] Department of Medical Oncology, Sir Ganga Ram City Hospital, Delhi, India

Address for correspondence Jyoti Bajpai, MD, DM, ECMO, Department of Medical Oncology, Tata Memorial Centre, Parel, Mumbai 400012, Maharashtra, India (e-mail: drjyotibajpai25@gmail.com).

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Abstract

Breast cancer (BC) is the most common type of cancer globally and in India. In India, BC is more common among younger women compared with Western counterparts. Younger women with BC tend to have a less favorable outcome as they are more likely to have aggressive tumors. Younger women are not well represented in BC management studies as the median age at diagnosis is in the late 50s to early 60s. This can lead to difficulty in using risk-stratification models and molecular tools among young BC patients and may result in overtreatment. Therefore, Indian Society of Medical and Pediatric Oncology gathers and organizes available evidence from published literature to create a guide specifically for young BC patients in low- and middle-income countries like India.

Keywords
- breast cancer in young
- breast cancer
- National guidelines

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Introduction

Breast cancer (BC) is the most common type of cancer globally and in India.[1] According to data from Globocan 2020, BC accounted for 13.5% of all cancer cases and 10.6% of all deaths in India. The incidence of BC in India is expected to rise from 25.8 per 100,000 women in 2020 to 35 per 100,000 women by 2026.[1] By the year 2025, it is estimated that there will be an annual increase of 230,000 new BC patients with a marked increase in young women with BC (YBC) cases as per the National Cancer Registry Program.[2]

In India, BC is more common among younger women compared with Western counterparts.[3] This may be due to the country's population pyramid which has a large proportion of young people. Women diagnosed with BC at or younger than 40 years of age are defined as YBC globally although some extend the age limit to 45 years.[3,4] Similarly, women younger than 35 years of age with BC are defined as having very YBC.[4]

YBC tends to have a less favorable outcome as they are more likely to have aggressive tumors of high grade, basal-like or HER2-enriched, and higher prevalence of germline mutations.[1] Germline mutation profiling is recommended for these women and they may need genetic and fertility counselling, surveillance, and risk-reducing surgeries.[5] Diagnostic delays among younger women can lead to advanced disease and add to the psychosocial and financial burden.[6]

YBC women are not well represented in clinical trials as the median age at diagnosis is in the late 50s to early 60s. This can lead to difficulty in using risk stratification models and molecular tools among young BC patients and may result in overtreatment.[7] Prospective trials specifically for YBC women are needed to ensure appropriate treatment. Examples of such studies include POSH cohort study (United Kingdom), Helping Ourselves, Helping Others: The Young Women's Breast Cancer Study (United States and Europe). These studies show that in young patients, a greater proportion of luminal B and estrogen receptor (ER)-negative tumors were present.[5,8]

Well-designed multicenter prospective trials dedicated to YBC patients should be conducted globally, with India being well-suited to frame appropriate study questions due to its higher proportion of YBC cases. As a first step in our collaborative effort, we aimed to gather and organize available evidence from published literature to create a guide specifically for YBC patients in low- and middle-income countries like India.

Methodology

The ISMPO-BCY recommendations were adapted from current guidelines from the National Comprehensive Cancer Network and ESMO-BCY guidelines.[9] A group of 20 YBC experts from the entire country were invited. Special subgroups of two to three experts were formed to provide recommendations after thorough literature search for specific questions. These recommendations were then reviewed and updated by all 20 experts via email. Members with potential conflicts of interest were instructed to abstain from voting on certain questions. The recommendations were discussed and any areas of disagreement or controversy were addressed before final approval by all experts. Then final voting for each recommendation was done by all 20 experts (►**Tables 1**–**7**, ►**Supplementary Tables S1** and **S2** [online only]).

General Considerations When Caring for Young Women with Breast Cancer

When treating a BC in young (BCY) woman, it is important to have a multidisciplinary team (MDT) that includes specialists from various fields such as breast and plastic surgery, medical and radiation oncology, pathology, radiology, breast care nursing, genetics, physical therapy, fertility, sexual therapy, and psychology. The best care for these patients is delivered in specialized breast clinics dedicated to BCY women with early BC (EBC) or advanced-stage BC (ABC). Treatment decisions should be based on the same factors irrespective of the age of patient. The experts emphasized the need for online tools and patient support groups in local languages to help overcome barriers to accessing support such as childcare, work schedules, and distance from health care services.

The experts also noted that there is still a lack of evidence-based standards for certain issues in the treatment of YBC

Table 1 Levels of evidence and grades of recommendation

Levels of evidence (LoE) I. Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity II. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity III. Prospective cohort studies IV. Retrospective cohort studies or case–control studies V. Studies without control group, case reports, experts' opinions
Grades of recommendation (GoR) A. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C. Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional D. Moderate evidence against efficacy or for adverse outcome, generally not recommended E. Strong evidence against efficacy or for adverse outcome, never recommended

Table 2 General guidelines

Guidelines	LoE, GoR	Consensus
In India, BC is the most common cancer in women. However, several issues in the treatment of young patients (<40) with BC are yet to be answered.	Expert opinion	100%
Online programs and patient support groups should be developed and promoted in several local languages to overcome barriers to accessing support.	Expert opinion	100%
There should be specialized multidisciplinary breast cancer clinics for YBC (EBC, or ABC).	Expert opinion	100%
Every case should be ideally discussed by the MDT to plan the treatment and address specific issues.	Expert opinion	100%
Young age should not be the sole reason to prescribe a more aggressive treatment than other age groups. The following factors should impact the choice of treatment: tumor stage, histological grade, biological characteristic of the tumor (ER/PR, HER-2 receptor status, proliferative markers [e.g., K_i-67], genetic status [if available], patient performance status, and comorbidities).	Expert opinion	100%
Systematic research is needed in the identification of age-specific molecular, biological, and genomic aberrations for tailored therapeutic interventions.	Expert opinion	100%
In India because of low per capita income, high expenses on health care, and long waiting lists in publicly funded institutes, planning treatment in routine practice requires careful consideration of the strength of evidence for long-term clinical benefit and cost-effectiveness. Therefore, safe and effective strategies should be developed.	Expert opinion	100%
Young male breast cancer		
Young male breast cancer should be treated as per national guidelines.	Expert opinion	100%
The standard adjuvant ET is Tamoxifen		
An AI alone should not be used; if needed, combine it with LHRH analog.	Expert opinion	100%
Clinical trials should allow young male breast cancer to participate.	Expert opinion	95%

Abbreviations: ABC, advanced-stage breast cancer; AI, aromatase inhibitors; BC, breast cancer; EBC, early breast cancer; ET, endocrine therapy; GoR, grades of recommendation; LoE, levels of evidence; MDT, multidisciplinary team; YBC, young women with breast cancer.

Table 3 Assessment and treatment guidelines early and advanced breast cancer

Guidelines	LoE, GoR	Consensus
Screening, diagnosis, and imaging for staging and follow-up		
No clear role of screening for early detection of BC in healthy, average risk young women	[I, A]	100%
Opportunistic screening with USG and MRI breast may be considered in higher risk individuals like an individual with genetic predisposition, very dense breast, RT for childhood or young-adulthood malignancy	Expert opinion	100%
Young women with BRCA1/2mutation carriers and other high-risk factors including predisposing mutation (e.g., p53, PALB2, CHEK2) should undergo annual surveillance with MRI and mammography with or without USG	[II, A]	100%
Gynecological surveillance every 6 monthly can be considered for BRCA1/ 2 mutated women and other cancer susceptibility gene carriers (e.g., RAD51C, p53, BRIP1) who have not undergone RRSO	Expert opinion	95%
Methods of diagnosis and staging evaluation should be as per older women	[III, C]	100%
Tools for awareness, early detection, and surveillance should be developed	Expert opinion	100%
Genetic counselling and testing		
Genetic counselling should be offered to every young female with BC, preferably before the start of treatment according to national/international guidelines. For those who are not ready to consider genetic issues at diagnosis, access to genetic counselling should be offered again at follow-up to address issues of surveillance and other primary tumors	[III, B]	100%
Genetic testing should be done according to personal and family history	[III, B]	90%
In ideal situations comprehensive panels testing should be done, however, where not feasible minimum BRCA1/2 is recommended	[II, C]	100%
Loco-regional treatment		
A young patient with EBC should get treated with surgery like older patients, preferably with BCS as there is no difference in overall survival as compared with mastectomy	[I, A]	100%

(*Continued*)

Table 3 (*Continued*) Assessment and treatment guidelines early and advanced breast cancer

Guidelines	LoE, GoR	Consensus
Oncoplastic repair techniques should be discussed with all patients treated with BCS in view of maximizing cosmetic results. Attention to oncological principles is necessary while planning oncoplastic BCS	[II, C]	100%
All clinic-radiologically node-negative patients should have axillary staging procedure just like in older women	[I, B]	100%
In case of positive axillary node on SNB or LAS, a complete AXLND should be offered	[I, B]	95%
A young patient with either invasive or preinvasive BC need not undergo risk-reducing bilateral mastectomy if not carrying any high-risk mutations	[I, B]	100%
Planning of loco-regional treatment after NACT should be independent of age	Expert opinion	100%
In case of locally advanced tumors (LN+ TNBC or HER2 positive T >3 cm), NACT should be considered	[II, B]	100%
Appropriate identification method of tumor bed biopsy scars, clip placements is necessary before starting chemotherapy or after 1–2 cycles to facilitate post-chemotherapy surgery	[II, B]	100%
Tumor bed delineation with intra-operative clip placements is mandatory in case of BCS, so as to facilitate radiation boost delivery. This is even more important in the setting of oncoplastic BCS	[II, B]	100%
Post-chemotherapy axillary surgery should involve a complete AXLND, especially if node was involved pre-chemotherapy	[II, B]	95%
Post-chemotherapy BCS in LABC is safe in carefully selected cases	[II, B]	100%
Adjuvant treatment systemic treatment Endocrine therapy		
Before the start of either chemotherapy or ET, all young patients should be counselled regarding associated risks, treatment-related amenorrhea, or premature menopause	Expert opinion	100%
Detailed descriptions of all the available strategies to preserve fertility like techniques, timing, possible complications, success rates, costs, and ethical implications should be included in fertility counselling	Expert opinion	100%
Some important factors should be considered while choosing between the available FP techniques like the patient's age and ovarian reserve, type of anticancer therapy planned, availability of a partner at the time of diagnosis, the time available before the initiation of anticancer treatments, and the possibility that cancer metastasized to the ovaries	Expert opinion	100%
Addition of GnRH/LHRH analogues during chemotherapy is recommended irrespective of ER/PR status and other methods of FP in view of OFS	Expert opinion	100%
Apart from clinical trials, neoadjuvant ET should not be used in young patients	Expert opinion	100%
All patients with HR-positive disease should receive adjuvant ET	[I, A]	100%
Tamoxifen alone for 5 years is indicated for clinically low risk patients and 10 years in high-risk patients (higher risk of recurrence (i.e., young age, high-grade tumor, lymph node +) and tolerance is not a question	[I, A]	100%
Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively postmenopausal	[I, A]	100%
The addition of a GnRH agonist (or ovarian ablation) to tamoxifen or an AI is indicated in patients at higher risk of relapse	[I, A]	100%
For a woman who becomes definitively postmenopausal (as is confirmed on biochemical testing), switching to AI after 5 years of tamoxifen and for high-risk patients should be considered	[I, A]	100%
The addition of GnRH agonist (or ovarian ablation) to ET is indicated in a patient with high risk of relapse	[I, A]	100%
AIs are contraindicated without ovarian suppression in premenopausal women	[I, A]	100%
To check menopausal status for patient on GnRHa, hormone levels should be measured at least twice at 3-monthly intervals as there are concerns that ovarian function is not suppressed (at baseline and during the course of treatment)	Expert opinion	100%
In patients with HR +/HER2 −, high-risk BC 2 years of adjuvant CDK4/6 inhibitors can be considered in combination with endocrine therapy doi: 10.1093/jnci/djx074	[I, B]	100%

Table 3 (*Continued*) Assessment and treatment guidelines early and advanced breast cancer

Guidelines	LoE, GoR	Consensus
Chemotherapy		
The indication and choice of ACT in young patients should be the same as that of older patients	Expert opinion	100%
The standard duration of treatment (minimum 4 and maximum of 8 cycles) should be preferably dose dense	[I, A]	100%
The addition of platinum in TNBC and BRCA+ patients increases the pCR rates and may be considered when NACT is indicated. But its long-term outcomes are still inconclusive	[I, B]	100%
There are no data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended	[I, A]	100%
Counselling regarding impact of addition of platinum on fertility and possibility of compromising dose and duration of standard chemotherapy drugs should be done	[I, B]	100%
For patient with TNBC with gBRCA mutation addition of adjuvant olaparib should be considered	[I, A]	100%
For patients with TNBC not achieving a pCR after standard NACT, the addition of adjuvant chemotherapy in the form of 6–8 cycles of oral capecitabine should be considered	[I, A]	100%
In patients with TNBC who are planned for preoperative chemotherapy, the addition of pembrolizumab (with the chemotherapy and for completion of 1 year following surgery) can be considered in selected high-risk young patients where approved if cost is not a constraint	[I, A]	90%
Adjuvant olaparib after completion of (neo)adjuvant chemotherapy provides significant benefit in DFS in women harboring a germline BRCA1/2 mutation who have high risk (stage II–III, HER2-negative TNBC:pT2Nx or pTxN1–3 or residual disease after NACT; HR + :pTxN2–3 or significant residual disease after NACT; EBC	[I, A]	90%
Anti-HER2 therapy		
Indication of anti-HER2 therapy including pertuzumab should be the same irrespective of age	[I, A]	100%
Weekly paclitaxel for 12 weeks with trastuzumab for 1 year without anthracyclines can be considered in highly selected patients with small, node negative, HER2+ BC	[II, B]	100%
General considerations in the adjuvant setting		
In view of long-life expectancy, careful attention should be paid to possible long-term toxicities of adjuvant treatment	Expert opinion	100%
Adjuvant bisphosphonates can be considered in young women receiving OFS	[I, B]	100%
IBC in young should be managed same as older patients	Expert opinion	100%
Assessment and treatment general guidelines in advanced breast cancer		
In a young patient with ABC, therapeutic recommendations should not differ from those for older patients with the same disease characteristics and extent	Expert opinion	100%

Abbreviations: ABC, advanced-stage breast cancer; ACT, adjuvant chemotherapy; AI, aromatase inhibitors; AXLND, axillary lymph node dissection; BC, breast cancer; DFS, disease-free survival; EBC, early breast cancer; ET, endocrine therapy; FP, fertility preservation; MRI, magnetic resonance imaging; OFS, ovarian function suppression; SNB, sentinel lymph node biopsy; TNBC, triple-negative breast cancer; USG, ultrasound.

Table 4 Additional considerations in women with hereditary-associated breast cancer

Guidelines	LoE, GoR	Consensus
For BC survivors and asymptomatic carriers of a BRCA1/2 mutation, RRSO should be discussed from the age of 35 years provided that the woman has completed the family	[II, B]	100%
For BRCA1 mutation carriers, RRSO is recommended between ages 35 and 40 and for BRCA2 mutation carriers around age 40, after considering patient's preferences and family history. No definitive evidence of improvement in BC survival by RRSO. However, it reduces the incidence of ovarian cancer by 95%	[II, B]	100%
Indications and timing of RRSO for other highly penetrant mutations should follow available international/national guidelines	[II, B]	100%
The radiotherapy treatment of EBC is independent of BRCA or any other constitutional genetic status, except for germline TP53 and ATM mutations, for which a very high risk of secondary cancers has been described after RT. Radiation therapy should be carefully discussed on an individual basis for these patients	[III, B]	100%

Abbreviations: BC, breast cancer; EBC, early breast cancer; GoR, grades of recommendation; LoE, levels of evidence; RRSO, reducing salpingo-oophorectomy.

Table 5 Recommendations for BCP and pregnancy after BC

Guidelines	LoE, GoR	Consensus
After the first trimester, standard chemotherapy can be offered to the majority considering the tumor stage and biology	Expert opinion	100%
Systemic therapy like ET, anti-HER2 therapies, immunotherapy, and bone-modifying agents should be avoided in all trimesters	[I, A]	100%
The patients with HR+ disease should complete at least 18–24 months of ET before attempting pregnancy (if they cannot wait till the completion of ET). The ET should be completed as planned after delivery and breastfeeding	[I, B]	100%
Patients on systemic therapy postdelivery should not breastfeed	Expert opinion	100%
Pregnancy after BC should not be discouraged even in patients with HR+ disease. The decision about pregnancy should depend on the patient's prognosis based on the initial stage and biology	[I, B]	100%

Abbreviations: BC, breast cancer; BCP, breast cancer diagnosed during pregnancy; ET, endocrine therapy; GoR, grades of recommendation; LoE, levels of evidence.

Table 6 Special situation: neuroendocrine breast cancer

Guidelines	LoE, GoR	Consensus
Chemotherapy agents can be selected based on histopathological characteristics inclusive of the percentage of tumor cells demonstrating neuroendocrine features and differentiation. A) >90% of tumor cells demonstrate neuroendocrine features: NEN A1: Well-differentiated—NET A2: Poorly differentiated—NEC: large-cell/small-cell variants: platinum/etoposide-containing regimens	Expert opinion	100%
B) <90% neuroendocrine differentiation: IBCs-NST with neuroendocrine differentiation taxane-based and/or anthracycline chemotherapy		
Endocrine and anti-HER2 therapies may be considered in HR+ and/or HER2+ carcinomas	Expert opinion	100%

Abbreviations: GoR, grades of recommendation; LoE, levels of evidence; NEC, neuroendocrine carcinoma.

patients. In India, low medical insurance coverage, financial insecurity, and inconsistent reimbursement decisions by insurance companies can lead to inadequate treatment and follow-up for YBC patients. Therefore, careful consideration must be given to the strength of evidence for long-term clinical benefit and cost-effectiveness when planning treatment.

Screening and Diagnostic Imaging for Staging and Follow-Up

There is no clear role for screening mammography in healthy young women with an average risk for BC. However, opportunistic screening with ultrasound (USG) or magnetic resonance imaging (MRI) may be used in specific settings as mentioned in ►**Table 3**. The experts recommend that diagnostic imaging and staging should generally follow the same guidelines as for older women. Breast USG is the first diagnostic approach for young and pregnant/lactating women. Tomosynthesis or contrast-enhanced digital mammography and/or MRI may be needed to determine the extent of the disease. Separate data for tomosynthesis in young women are not available.

Genetic Counselling and Testing

The experts recommend that genetic counselling should be offered to all BCY women, regardless of family history or tumor subtype. Genetic testing should follow local guidelines and take into account availability of resources and reimbursement policies. Patients should be provided with adequate information before undergoing genetic testing by a trained health professional and made aware of the potential impact of the results on their treatment and follow-up as well as on family members. While *BRCA1/2* are the most commonly mutated genes, addition of tests for other moderate- to high-penetrance genes is on the discretion of the genetic counsellor. The choice of laboratory for multi-gene panel testing is crucial and should include high-penetrance genes such as *BRCA1/2, p53*, and *PTEN* as well as moderate- to high-penetrance genes such as *CDH1, CHEK2, PALB2, RAD51C, BRIP1*, and *ATM*. Practice should be guided by national/international guidelines.[10] In ideal situations, multigene panels testing should be done, however, where not feasible minimum *BRCA1/2* is recommended as cost is a constraint. For those denying genetic counselling at diagnosis, access to such facilities should be offered again during follow-up, so as to address issues such as risk of other primary tumors, risk stratification for relatives, and surveillance.

Loco-regional Treatment

Surgery

While young age is a known risk factor for local recurrence after breast conservation surgery (BCS), mastectomy does

Table 7 Supportive and follow-up care guidelines

Guidelines	LoE, GoR	Consensus
Young women are at increased risk of psychosocial issues (premature menopause, treatment-related amenorrhea, weight gain, hair loss) that should be addressed regularly in routine cancer treatments and follow-up with the active involvement of patient and family members	[II, B]	100%
All young women should be counselled regarding the risk of getting pregnant while on treatment despite developing amenorrhea and the need for adequate nonhormonal contraception if they are sexually active	[I, B]	100%
All young women should be counselled/referred to specialist consultation if interested in FP before the commencement of any therapy	Expert opinion	100%
In asymptomatic patients, routine laboratory or imaging tests other than follow-up mammography are not recommended	[II, A]	100%
Annual bone density evaluation is recommended for patients on AIs or OFS	[I, A]	100%
Young patients should be counselled and motivated to adopt a healthy lifestyle: ● Regular exercise and maintain body weight for age ● Healthy and balanced diet ● Avoid smoking and cessation counselling in smokers Limit alcohol intake	Expert opinion	100%
At follow-up visits, in addition to cancer-related history and physical examination, the patient should receive a detailed history regarding physical or psychosocial sequelae of treatment and menopausal symptoms. Clinical examination is complemented with a mammogram (bilateral if BCS has been done) every 12–24 months	Expert opinion	100%
The follow-up frequency in absence of symptoms should be every 3–6 months for the first 3 years after therapy, 6–12 monthly for the next 2 years and annually thereafter up to 10 years and then 2 yearly	[II, A]	100%
Patients with a significant family history of cancer or known BRCA mutation should be kept on lifelong 6 monthly or annual follow-up as they have a much higher risk of contralateral BC and ovarian cancer even after risk-reducing surgeries	Expert opinion	100%

Abbreviations: BC, breast cancer; BCS, breast conservation surgery; FP, fertility preservation; GoR, grades of recommendation; LoE, levels of evidence; OFS, ovarian function suppression.

not improve overall survival (OS) in YBC patients unless clinically indicated.[11] Appropriate oncoplastic techniques should be used to optimize cosmetic outcomes after BCS.[12] However, in the Indian setting, care should be taken not to compromise oncological principles when planning oncoplastic BCS. If BCS is contraindicated, a modified radical mastectomy may be performed. In carefully selected patients, skin and nipple-sparing techniques can be used with immediate whole breast reconstruction.[13] Breast reconstruction immediately following mastectomy offers the same survival rates as mastectomy without reconstruction when performed by an expert. Reconstruction can be offered to interested patients but delays in starting adjuvant treatment due to surgical complications should be avoided as much as possible. Secondary reconstruction post-mastectomy may be preferred for those with locally advanced BC (LABC) or inflammatory BC (IBC) cancer who have had a poor response to neoadjuvant systemic treatment. The timing and technique of breast reconstruction should be discussed preoperatively on an individual basis, especially if post-mastectomy radiation therapy (RT) is indicated. Patients with EBC and no signs of cancer in their lymph nodes (LNs) should undergo an axillary staging procedure, either a sentinel LN biopsy or a lymphatic mapping and sentinel node sampling. If cancer is found in the LNs, a complete axillary LN dissection (AXLND) up to level 2/3 is recommended. After neoadjuvant chemotherapy (NACT), AXLND is the standard of care. Conservative axillary procedure in this setting should not be offered outside trial setting. Further research is needed to determine the role of conservative management after NACT. For patients with LABC or those with a poor tumor-to-breast ratio for BCS, NACT may be used. Before starting NACT, it is important to evaluate the tumor using imaging and mark its location with biopsy scars or clips. The surgical plan is determined based on how well the patient responds to NACT. In some cases, BCS may be safe.

Radiation Therapy

The indications for postoperative RT in YBC are the same as in older women. The field of irradiation should be determined based on the initial staging and posttreatment pathological staging. According to available literature, moderate hypofractionation (40–42.6 Gy/15–16 fractions) can be used in young women just like in other age groups.[14] A tumor bed boost is recommended for most young patients due to their age and other factors such as tumor grade. This can be delivered either sequentially or simultaneously.

Partial breast irradiation (PBI) or accelerated PBI should not be performed outside of clinical trials due to a lack of evidence. The decision to use postoperative RT should not

depend on *BRCA* status. The safety of RT in patients with moderate pathogenic gene variants such as *ATM* is uncertain and limited, so the risks and benefits should be discussed on an individual basis. In addition, in patients with *TP53* mutation, for whom RT is otherwise contraindicated to the high risk of secondary malignancies, role of RT should be discussed in case of higher chances of loco-regional recurrence. Avoiding RT may be considered if the patient agrees to close follow-up.

Adjuvant Systemic Treatment

The decision to use adjuvant chemotherapy (ACT) in YBC should be based on the same factors as in older patients. These include the extent of the disease, the biological characteristics of the tumor, and patient characteristics. Age alone should not be the criteria to overtreat BCY.

Gene Expression Signatures

Gene expression tests like Oncotype Dx, MammaPrint, Prosigna, Endopredict, and Breast Cancer Index can provide additional information about an individual's risk of recurrence and the potential benefit of chemotherapy.[7,15] However, it is important to note that women under 40 are underrepresented in studies evaluating these tests, particularly in studies of node-positive disease. In TAILORx study, researchers evaluated the use of the 21-gene Oncotype Dx recurrence score in women with HR+, HER2− BC. Patients were grouped into low, intermediate, or high risk of recurrence based on their score. Only 30% of those with a low score were premenopausal and only 4% were under 40.[16] In MINDACT study, researchers evaluated the 70-gene signature and randomized patients based on clinical and genomic risk. Patients with low clinical and genomic risk did not receive chemotherapy while those with high clinical and genomic risk did. Patients with discordant risk profiles were randomized to determine whether clinical or genomic risk would be used to decide on chemotherapy. Due to limited data and statistical power, it is difficult to draw clear conclusions about whether the small benefit reported with chemotherapy in patients with discordant risk would have been greater in younger women. Only 6.2% of patients in the study were under 40.[17]

In WGS PlanB study, patients with up to three involved LNs and a low Oncotype Dx recurrence score had a good outcome without ACT. However, no subgroup analysis for patients under 40 has been presented.[18]

All patients in WGS ADAPT ER+/HER2 with 0 to 3 involved LN and a low recurrence score (RS) of 0–11 received ET alone (mostly tamoxifen in pre- and aromatase inhibitors (AI) in postmenopausal patients), and those with intermediate RS (12–25) received 3 weeks of ET prior to surgery. Patients whose surgical specimen had Ki67 $\leq$10% were considered endocrine-responders and received ET alone (of whom 23.3% were $\leq$50 years), while those with Ki67 >10% were classified as endocrine nonresponsive and received chemotherapy along with ET (of whom 64.7% were $\leq$50 years). Based on clinical and immunohistochemical (IHC) factors, the ENREP algorithm (https://enrep.info) can help estimate endocrine responsiveness, as derived from the ADAPT data.[19]

The Rx-PONDER study showed that premenopausal women with a recurrence score of 25 or lower and one to three positive LNs who received both chemotherapy and ET had longer invasive disease-free survival (DFS) and distant relapse-free survival than those who received only ET. However, postmenopausal women with similar characteristics did not benefit from ACT.

In conclusion, it may be appropriate to consider omitting ACT in BCY with favorable clinical and pathological features, including low gene expression profiles. However, commercially available genomic assays for HR+ EBC have not been developed to predict which type of ET is most appropriate based on genomic risk. Therefore, these tests should not be used to select the type or duration of ET at this time point. For Asian ethnic women, CanAssist Breast (CAB) is a validated and cost-effective test.[20] This test predicts risk of recurrence using Army Intelligence algorithm by incorporating IHC staining information of five biomarkers (CD44-a stemness marker; pan-Cadherin-cell adhesion, N-Cadherin, and invasion markers; ABCC11 and ABCC4-drug exporters) along with three clinical parameters (tumor size, grade, and node status). CAB classifies patients into low risk or high risk (>15.5) based on recurrence score on a scale of 1 to 100. Despite the fact that CAB uses biomarkers which are different from Oncotype DX, Sengupta et al[21] demonstrated that this test has 83% concordance with Oncotype DX in selecting patients with low risk of recurrence. The cost-effectiveness analysis by Bakre et al[22] shows that with CAB there is a savings of 41% on expenditure incurred due to chemotherapy compared with expenses in the absence of a prognostic test. However, one must be cognizant about the fact that data are more robust for established tests like Oncotype DX or MammaPrint; however, this can be considered as a cost-effective alternate where there are constraints.

Preoperative Endocrine Therapy

Experts generally do not recommend ET alone as (neo) adjuvant for YBC outside of clinical trials.[23] The International Breast Cancer Study Group conducted trials evaluating the efficacy of the gonadotropin-releasing hormone (GnRH) antagonist Degarelix versus the GnRH agonist Triptorelin as a preoperative treatment in premenopausal patients receiving Letrozole. The results showed a partial response rate of 45%, which is comparable to evidence in postmenopausal women.[24] Ovarian function suppression (OFS) was achieved quickly and more effectively with Degarelix than with Triptorelin. This observation may warrant further research to determine if this intervention could improve disease control.

Therefore, experts recommend personalizing therapy based on factors such as early childbirth and co-morbidities. In some cases, patients may not be able to receive chemotherapy due to nononcological conditions such as cardiac or renal dysfunction or hematological disorders. In these cases, hormonal therapy (HT) with OFS may be considered

preoperatively to achieve effective disease control before local therapy.

Adjuvant Endocrine Therapy

Studies that looked at the use of OFS in combination with Tamoxifen or Exemestane in premenopausal women with BC showed that for women at lower risk of relapse, there was no additional benefit to using OFS. However, for women at higher risk of relapse, using OFS with Tamoxifen or Exemestane improved outcomes compared with using Tamoxifen alone.[24,25] According to the SOFT and TEXT data, the experts confirmed that if GnRHa is given in combination with Tamoxifen or an AI, it should be given for 5 years.[26] After 5 years of adjuvant ET, the risk of recurrence continues for over 20 years. Therefore, the recommendation for extending Tamoxifen beyond 5 years in high-risk patients if tolerated is based on the ATLAS and aTTom trials.[27,28] The ASTRRA, randomized phase III study showed that 2 years of adding OFS to Tamoxifen significantly improved the 5-year DFS (3.6% absolute improvement), compared with Tamoxifen alone, and therefore OFS with Tamoxifen should be considered in women with late resumption of ovarian function after chemotherapy, or who remain premenopausal.[29] The use of an AI alone is not recommended in premenopausal women and that caution should be taken when using an AI in premenopausal women who became postmenopausal during treatment due to the potential for recovery of ovarian function.[30] The experts confirmed that hormone levels should be measured at least twice at 3-month intervals to ensure ovarian function is suppressed. Estradiol assays are not standardized and, especially at very low levels of Estradiol, hence gas chromatography/mass spectroscopy method should be preferred to monitor therapy.[31] Based on SIFT-EST sub-study data results, there are concerns about suboptimal OFS with tri-monthly formulations of GnRHa and therefore monthly formulations are preferred in women under 35 years of age and those receiving an AI.[32]

The method of OFS can be surgical or medical and requires balancing the patient's wish for potentially preserving fertility with the need for compliance with frequent injections and cost.[33,34] The possibility of surgical complications of oophorectomy and the side effects of permanent menopause in early age are significant issues from the perspective of survivorship. Cost considerations play a role in India as well as lower adherence and early discontinuation of adjuvant ET in younger patients are associated with lower OS.[35] According to the SOFT/TEXT trial, the rate of early discontinuation was approximately 20%.[26] There are multiple reasons for treatment discontinuation such as side effects, perception of recurrence risk and estimated impact of therapy, social support, patient–doctor relationship, and continuity of follow-up care.[36] Efforts should be made to address these barriers to treatment adherence and motivate patients by emphasizing the real prospects of benefit with continued HT.

GnRH Agonists and Ovarian Function Preservation

The effect of OFS on fertility preservation (FP) varies according to age group and type of chemotherapy regimen and hence at best considered adjunct to established FP measures. As per available data, there is no significant impact on disease outcomes with temporary OFS with GnRHa during chemotherapy.[37] Therefore, the experts confirmed that the use of GnRHa concomitant with (neo-)ACT should be offered to patients who wish to preserve ovarian function only after adequately discussing the possibility of additional toxicity and benefits; however, its use during chemotherapy does not replace established FP methods.

Fertility Preservation for YBC Patients

Fertility becomes an important consideration for survivors of YBC. In a survey conducted in our country, it was found that most practitioners were partly aware of FP options but did not regularly offer them to patients due to concerns about losing time for treatment and patients not being willing at the moment. There is also lack of MDT coordination in this direction. The FP options available in our country are listed in ►**Supplementary Table S2** (online only).

This guideline briefly addresses some of the main concerns related to FP in YBC patients:

- Safety of Controlled Ovarian Stimulation (COS) in NACT candidates: no clear evidence to suggest that COS for oocyte/embryo cryopreservation before NACT causes significant delay in treatment or has detrimental prognostic effect even though the whole process takes around 15 to 20 days.[38] Use of Tamoxifen protocol to prevent high Estradiol levels may be preferred in some cases.[38]
- Ovarian cryopreservation is still not a mainstream method in India and is available at select centers: no case series about pregnancy achieved post-tissue reimplantation. The advantage of the process is no wait time, unlike COS. It should be considered only if the oocyte or embryo freezing is not possible for women $<$36 years.
- BRCA mutation may have a negative impact on women's reproductive potential even before starting therapy. Baseline investigations and extensive counselling are mandatory.[39]
- Interruption of therapy to attempt pregnancy: no optimal cut-off is defined, however in the POSITIVE trial[40] after 2 years of therapy ET was interrupted to allow pregnancy. A washout period of 3 months for ET should be considered for conception. However, the patient and family must be adequately counselled about the pros and cons of therapy interruption and therapy must be resumed after pregnancy and lactation based on the practice in some of the trials. A gap of 12 months is ideal before the end of chemotherapy and conception.[41]

Therefore, increasing awareness about FP amongst the oncology fraternity in India and fertility professionals along with research is the need of the hour so that YBC survivors have a fair chance of fertility later on in life.

Neo/adjuvant Chemotherapy

Although BCY is associated with more unfavorable pathologic features and aggressive biology, age should not be a lone factor to determine the role of NACT/ACT. We have discussed previously the role of gene expression signatures in

identifying patients with HR+ BC who may not need chemotherapy. Notably, in the SOFT and TEXT studies, for patients who did not receive chemotherapy (8 and 21% node positive in each trial, respectively) the 8- and 9-year rate of freedom from BC exceeded 90%, respectively, with similar favorable outcomes in the Austrian Breast and Colorectal Cancer Study Group 12 trial, in which 95% of women did not receive chemotherapy.[26,42] There is a lack of research for BCY patients in investigating different chemotherapy regimens. Experts confirmed that sequential regimens have equal or better efficacy over combination regimens and are also better tolerated in BCY.[43] The indication for dose-dense chemotherapy regimen is independent of age.[44] Both a sequential regimen of Anthracycline-based chemotherapy followed by adequately dosed Cyclophosphamide/Methotrexate/Fluorouracil or weekly paclitaxel and a combination of a Taxane and Cyclophosphamide may be valid alternatives. In the last EBCTCG meta-analysis involving Taxane- or Anthracycline-based regimens, proportional risk reductions were not significantly altered according to age.[45,46] The standard duration of treatment should include four to eight cycles of treatment, as used for older women.

The data from an Indian study strongly indicate need for early detection of triple-negative BC (TNBC) in young patients and augmentation of therapy in addition to standard Taxane and Anthracycline-based chemotherapy in view of overall inferior outcomes.[47–49] The phase III KEYNOTE 522 study compared Pembrolizumab with chemotherapy versus placebo with chemotherapy followed by a year of pembrolizumab or placebo, respectively. The most recently updated data shown benefit of pCR (64.8% vs. 51.2%, p ¼ 0.00055) and for EFS (91.3% vs. 85.3%, hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.43–0.93) favoring the pembrolizumab arm.[50] The IMPASSION-031 randomized trial studied NACT with or without atezolizumab followed by a year of atezolizumab or placebo. pCR was superior for the atezolizumab arm, (58% vs. 41%; $p = 0.0044$),139 but outcome data are awaited.[51]

Both the BrighTNess and Indian study by Gupta et al, trials have shown improved pathological CR rates and for patients with TNBC with the addition of Carboplatin.[52,53] Given the over-representation of triple-negative subtypes in these population, young women were well represented in both.[52,53] Data on the introduction of platinum agents in the adjuvant setting is still pending. For patients with TNBC who have not achieved a pCR after standard preoperative regimens, the addition of six to eight cycles of Capecitabine may be considered, as done in other age groups.[54] Subgroup analysis of the CREATE-X trial in TNBC patients having residual disease after NACT suggested adjuvant capecitabine significantly improves survival outcomes in younger patients.[54] The role of 1 year of adjuvant Olaparib in HER2-negative EBC with germline BRCA1/2 mutations which significantly improved invasive DFS (iDFS; 3-year rate, 85.9% vs. 77.1%; HR: 0.58; 99.5% CI: 0.41–0.82; $p < 0.001$) and OS (4-year rate, 89.8% vs. 86.4%; HR: 0.68; 98.5% CI: 0.47–0.97; $p = 0.009$) is additionally relevant to young women.[55]

The addition of 2 years of Abemaciclib can be considered in patients with HR +/HER2-negative, high-risk BC (i.e., those with ≥4 positive LNs, or 1–3 positive LNs with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a K_i-67 score of ≥20%).[56] The recently published NATALEE trial demonstrated that patients who received ET plus ribociclib had an improvement in iDFS compared with ET alone (HR: 0. 748; 95% CI: 0.618–0.906; $p = 0.0014$).[57]

Adjuvant Anti-HER-2 Therapy

Compared with older women, HER2+ YBC have comparable outcomes when controlling for other known prognostic factors. YBC also derive equivalent benefits from adjuvant Trastuzumab.[4] Thus, YBC with node-negative HER2+ and tumors size <2 cm may be effectively treated with the de-escalated regimen of adjuvant weekly Paclitaxel with Trastuzumab for 12 weeks followed by 9 months of Trastuzumab, which has demonstrated excellent long-term DFS and OS.[58] In addition, lower rates of chemotherapy-related amenorrhea was observed in this study compared with standard alkylator-based chemotherapy regimens (only 9% of women age ≤40 reporting prolonged chemotherapy-related amenorrhea).[58] Additionally alternative Taxanes (i.e., Docetaxel, Paclitaxel, Albumin-bound paclitaxel) may be substituted for selected patients due to medical necessity like hypersensitivity reaction. If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2. NACT combined with HER2-directed therapy is preferred for young women with larger and/or node-positive HER2-positive tumors. Subcutaneous formulations of Trastuzumab (Hyaluronidase-oysk the subcutaneous formulation) and Trastuzumab plus Pertuzumab have demonstrated similar pCR rates as the intravenous formulations of these therapies when combined with chemotherapy in the neoadjuvant setting may be particularly attractive for young women who need to fit BC treatment into complex personal and professional commitments.[59,60] Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous Pertuzumab and intravenous Trastuzumab are given as part of systemic therapy. In addition, all these three subcutaneous injections have different dosing and administration instructions compared with the intravenous products. In young women with residual disease after NACT, adjuvant T-DM1 (Ado-Trastuzumab emtansine) was associated with superior 3-year iDFS compared with Trastuzumab among the 296 patients <40 years enrolled in the KATHERINE trial (86.5% vs. 74.9%; HR: 0.50; 95% CI: 0.29–0.86).[61] Martin et al demonstrated benefit of Neratinib for high-risk HER2+ patients when given for a year after completion of 1 year of Trastuzumab. In addition, a significant benefit was seen in the HR+ subgroup. Most common side effect of Neratinib like diarrhea should be managed prophylactically.[62]

There is no evidence of the role of Neratinib after 1 year of adjuvant Trastuzumab and Pertuzumab or after post-adjuvant TDM1. Hence experts agreed on discussion on Neratinib if available, as in other age groups, in patients at high risk of relapse (e.g., node +, HR +); the increased toxicity needs to be clearly communicated to patients (►**Supplementary Table S1** [online only]).

Scalp cooling devices can be considered in patients receiving Anthracyclines or Taxanes to reduce the incidence of chemotherapy-induced alopecia and superior hair regrowth.[63]

Adjuvant Bisphosphonates

Six monthly adjuvant bisphosphonates can be considered for young females receiving OFS with HT. A recent case–control study has also shown that there are no major teratogenic effects of bisphosphonate exposure on pregnant females except for increased rates of neonatal complications and spontaneous abortions.[64]

Side-Effects of Adjuvant Therapy

In view of long-life expectancy, the experts reinforce the careful surveillance for possible long-term toxicities of adjuvant treatment (e.g., secondary cancers, cardiovascular toxicity, irreversible ovarian failure, weight gain, cognitive functions, and bone health).

Advanced Breast Cancer Loco-regional Relapse

Treatment of locoregional relapse is same as in older women. The primary treatment of an in- breast-tumor recurrence is a completion mastectomy in case of previous BCS and wide excision of chest wall recurrence with clear margins (is required chest wall resection) in case of a post-mastectomy recurrence. Further adjuvant therapy is warranted in the form of ET for HR+ cancers and chemotherapy/targeted therapy for HR– and HER2+ cancers.[65]

Special Situations

Inflammatory Breast Cancer

IBC is rare subtype of LABC with a poor prognosis. It is characterized by diffuse erythema and edema occupying at least one-third of the breast, with or without an underlying mass with a history of fewer than 6 months and pathological diagnosis of IDC. High index of suspicion is required to diagnose these cases in young women as the features may mimic infectious mastitis and breast abscess. The MDT approach is critical in the care of patients with IBC[66] and all eligible patients should be enrolled in clinical trials, given the rarity of the disease. The treatment of nonmetastatic IBC is similar to nonmetastatic noninflammatory LABC, which includes NACT, followed by loco-regional treatment. The only difference is SLNB and BCS should not be preferred in IBC even with a very good response to NACT. The experts confirmed that women who have achieved a partial response to NACT should undergo modified radical mastectomy with axillary dissection and post-mastectomy radiation. Immediate reconstruction following surgery should be avoided as IBC is associated with poor prognosis and a high risk of early recurrence.[65] About one-third of patients with IBC are metastatic at diagnosis and should be managed as per older BC patients. Radiotherapy can be used to palliate inoperable IBC.

BRCA Mutation Carriers

Experts confirmed that the decision regarding therapeutic mastectomy when BCS is feasible and contralateral prophylactic mastectomy depends on multiple factors (e.g., patient age, disease stage, previous breast biopsies, genetic predisposition or family history of BC, fear of recurrence, and concern with cosmetic symmetry).[67] Advancement in modern MDT has led to a reduction in the incidence of contralateral BC from approximately 0.6% to 0.2–0.5% per year.[68] Improvement in survival with contralateral prophylactic mastectomy is still variable in available data.[68,69] Therefore, the experts reinforced MDT and individualized approach in such cases. For a high-risk young patient, MRI breast is preferred for surveillance whenever available.[70] There is no definitive evidence of improvement in survival by risk reducing salpingo-oophorectomy (RRSO). Timing and indications of RRSO for BRCA1/2 mutated and other highly penetrant mutations should follow available international/national guidelines. Salpingectomy (removal of the fallopian tubes) alone is not the standard of care; clinical trials are ongoing. The experts recommended that standard prognostic factors should be followed to decide about treatment in early disease as there are still no definitive conclusions on the best chemotherapy regimen for BRCA-associated BC patients in the neo/adjuvant setting. Based on TNT trial, the superiority of a platinum agent, compared with Taxanes, was confirmed in the ABC setting for BRCA-associated TNBC.[71] And the Olympia trial has established the role of adjuvant Olaparib for 1 year after curative treatment in BRCA-mutated BC patients as mentioned earlier.[52] The superiority of Olaparib including a superior RR and progression-free survival with a more favorable toxicity profile was demonstrated in the OlympiAD study with OS benefit of 7.9 months (22.6 vs. 14.7) amongst patients who had not received prior chemotherapy in the metastatic setting.[72] The EMBRACA study a with similar design proved the superiority of Talazoparib.[73] A somatic BRCA1/2 pathogenic gene variants in breast tumors can be found in a small proportion of patients not harboring germline mutations.[74] But at present, the clinical utility and therapeutic usage of these mutations in BC are not well established and are the subject of ongoing research. Therefore, somatic BRCA1/2 testing should not be used as an alternative to germline testing.

Young Male Breast Cancer

About 1% of all BCs occurs in males.[75] Young male BC is a disease of the elderly. But in India, the data available have shown that male BC is more frequently found in the younger age groups. According to National Cancer Institute's Surveillance, Epidemiology, and End Results Database,[76] more than 90% of the young male BCs are ER+. Similar results also have been shown by an Indian study with an ER/PR positivity rate of around 80%.[75] According to various Indian studies, young male BC is diagnosed more commonly at the advanced stage.[75] Experts recommend routine management of young male BC in accordance with international recommendations/guidelines. Experts also suggest to include young male BC early as well as advance in clinical trials.

Pregnancy-Associated Breast Cancer

BC diagnosed during pregnancy (BCP) or postpartum is known as pregnancy-associated BC (PABC).[77] BCP management needs MDT and precision care. Treatment depends

upon disease stage, receptor status, gestational age, and performance status.[77–81] Diagnostic delays are common, and reduction of such delays requires clinical and self-examination of the breast and obstetrician's awareness of examining breast lumps during pregnancy. [81] Chest X-rays with abdominal shielding, abdominal and pelvic USG, and non-contrast skeletal MRI have been recommended for staging studies.[80,81] Histopathology is recommended to confirm a diagnosis with receptor status which carries therapeutic and prognostic importance. Experts recommended BCP management as per standard BC management, with careful consideration of the trimester of pregnancy, maternal and fetal safety.[79,82] Termination of pregnancy generally does not improve outcomes and is not recommended unless there is a pressing obstetric and/or oncological reason. Outcomes of treatment are variable, but disease stage and biology-matched outcomes are comparable to age-matched nonpregnant BC in several studies, including in the first Indian gestational registry in which a 7-year follow-up data in a cohort of 104 PABC cases had shown comparable oncological and obstetrical outcomes.[77] Premature birth has emerged as an important negative predictor of cognitive development, thus avoiding iatrogenic preterm birth is recommended unless there is a compelling obstetric reason. Pregnancy after BC can also be considered in women with HR and/or BRCA mutation-positive disease under trained oncology care. Patients on ongoing systemic therapy should not breastfeed. Other women can breastfeed and should seek appropriate professional care.[83]

Neuroendocrine Neoplasms of the Breast in Young Women

The recent World Health Organization Classification 2019 unified the neuroendocrine neoplasm (NEN) of the breast as those in which >90% of tumor cells demonstrate neuroendocrine features. NENs are a heterogeneous group and were further classified as neuroendocrine tumors (NETs) if well differentiated and as neuroendocrine carcinomas of the breast (NECB) when poorly differentiated. NECBs are further subdivided into small and large cell carcinomas. Those with <90% neuroendocrine differentiation is classified as invasive breast carcinoma of no special type (IBCs-NST) with neuroendocrine differentiation.[84]

Most of NECB patients are ER and/or PR positive, implying that NECB is part of the luminal-like type.[84]

The most common clinical features of NECB are similar to those of invasive breast carcinoma of no special type (IBC-NST). Compared with IDC of no special type, NECB is more likely to present with systemic metastasis at diagnosis. The radiologic characteristics of NECB are not specific. Due to rarity, as of now, there is a lack of high-quality guidelines or clear consensus for these NECBs, and evidence is sparse based on case reports and retrospective studies. However, at best, chemotherapy agents can be selected based on the histopathological characteristics of NECB. In general, poorly differentiated, small-cell NECs or large-cell NECs are treated with platinum/etoposide-containing regimens and other types of NECB with Taxane-based and/or Anthracycline chemotherapy. Although these tumors are known to express hormone and HER2 receptors, there is limited literature on the response of these tumors to endocrine and anti-HER2 therapy.[85]

Operable tumors should be resected first as per the standard surgical options in IBCs-NST as there is limited evidence regarding NACT in NECB. Patients with a large tumor size (>5 cm) with a strong desire to preserve the breast, locally advanced NECB, or inoperable NECB may receive NACT.[85]

Goserelin and Letrozole can be considered in situations where a patient with a strong desire to conserve breast with contraindications/refusal for chemotherapy under close observation after multidisciplinary joint clinic discussion. In addition, Palbociclib and other cyclin-dependent kinases (CDK) 4/6 inhibitors combined with Fulvestrant may be considered in patients with high-grade NECB who are resistant to platinum-based chemotherapy and HT.[85,86]

NETs Gr 1 and 2 are treated with somatostatin receptor analogs. There are case reports of response to Lutetium peptide receptor radiotherapy in NEBC.

RT and surgery are indicated as per the standard options in IBCs-NST. As there is no specific recommendation for NEBC.[84]

Long-term follow-up is recommended as NECBs may metastasize even years after treatment of the primary tumor.[87]

Supportive and Follow-Up Care

Expert panel confirmed that follow-up and supportive care in young women should follow the same guidelines as in older women. It should be emphasized that BC care nurses and other supportive care staff can play a critical role in providing survivorship care, and support for young patients and their families. The panel also reiterated that standardized patient-reported outcome measurements may allow timely collection of treatment side effects, preparing the development of targeted interventions. Electronic devices as well as online applications are convenient and efficient tools for gathering information from patients to allow real-time integration of patient-reported outcome data in the electronic medical record and earlier interventions by the health care team.[88]

Psychosocial Issues

Experts confirmed that psychosocial issues should be regularly addressed during routine treatment as well as during follow-up involving patients and family members in the early course of treatment. In addition to social issues like a return to work, financial loss, and psychosocial issues, FP, contraception, premature menopause, sexual functioning, pregnancy after BC, bone health, cognitive impairment, and lifestyle changes are to be addressed. There is a great need for dedicated research/clinical trials to address these concerns of YBC. As of now, the multidisciplinary approach remains the backbone of care to ensure a holistic and comprehensive management planning.

Conflict of Interest

None declared.

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Ethical Dilemmas and the Moral Distress Commonly Experienced by Oncology Nurses: A Narrative Review from a Bioethics Consortium from India

Manjeshwar Shrinath Baliga[1,2,3] Seema Chauhan[4] Ani Grace Kalaimathi[5] Lal P. Madathil[1,2,3] Thomas George[6] Russell Franco D'souza[1,7] Princy Louis Palatty[2,8]

[1] Department of Education, International Program, International Chair in Bioethics, World Medical Association Cooperating Centre (Formerly UNESCO Chair in Bioethics University of Haifa), Haifa, Israel
[2] The Bioethics SAARC Nodal Centre, International Network Bioethics at Amrita Institute of Medical Sciences, Kochi, Kerala, India
[3] Bioethics Education & Research Unit at Mangalore Institute of Oncology, Mangalore, Karnataka, India
[4] College of Nursing, All India Institute of Medical Sciences, Gorakhpur, Gorakhpur, Uttar Pradesh, India
[5] Tamilnadu Nursing Council, Chennai, Tamil Nadu, India
[6] Department of Internal Medicine, Coney Island Hospital, Brooklyn, New York, United States
[7] Directorate of the Asia Pacific Division and Education Department, Melbourne, Australia
[8] Department of Pharmacology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Ernakulam, Kerala, India

Address for correspondence MS Baliga, Senior Radiobiologist, Mangalore Institute of Oncology, Pumpwell, Mangalore, India 575002 (e-mail: msbaliga@gmail.com; msbaliga.mio@gmail.com).

Princy Louis Palatty, MD, The Bioethics SAARC Nodal Centre, International Network Bioethics at Amrita Institute of Medical Sciences, Kochi, Ernakulam, Kerala 682041, India (e-mail: drprincylouispalatty@gmail.com).

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Abstract

Nurses working in oncology frequently have to make tough moral choices, such as how to break bad news or how to make sure a dying patient receives good palliative or end-of-life care. In the context of patient care, this may limit the ethical and moral options available to nurses. This can cause moral dissonance and ethical insensitivity on the job and can be very stressful. To be able to meet ethical problems in trying times calls for capacity to recognize and know how to manage the concerns. The purpose of this article was to describe common ethical challenges and to present some methods that may be helpful when confronting them. This narrative review discusses the ethical standards that oncology nurses should uphold and implement in their daily work. Many common ethical dilemmas are also explored, and the study hopes to shed light on how novice nurses, such as students and fresh recruits, may experience when caring for cancer patients and their family caregivers. Importantly, this review also addresses aspects of how nurses can improve their skills so that they can deal with the ethical quandaries and moral discomfort that arise on a daily basis in cancer care.

Keywords
- ethical dilemmas
- moral distress
- oncology nurses
- bioethics

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Introduction

Nurses are important members of society because of the unique tasks they do in promoting health, preventing sickness and injury, assisting in rehabilitation, and offering support to patients in need in both hospital and community setups.[1] Nurses' primary concern is holistic health, which includes the physical, social, emotional, and spiritual requirements of their patients, and they work relentlessly to advance their patients' best interests.[1] They play a key role in ensuring everyone's well-being across the spectrum of positive health and are involved in the therapeutic decision-making process to advocate for and provide advice to the patients and their family caregivers. On a daily basis, nurses face a lot of ethical dilemmas in clinical practice, and their judgments must be guided by moral principles. Nurse, as a crucial stakeholder in health care delivery, should adhere to these principles when dealing with patients, their families or caregivers, and other health care professionals and the following principles as a set of guideline.[1]

From historical perspective, Florence Nightingale, the "*Mother of Modern Nursing*," established nursing as a respectable and noble profession, and the "*Nightingale Pledge*," a modified Hippocratic Oath formulated in 1893, is largely credited with establishing the code of ethics.[1] The American Nurses Association (ANA) formulated the code of ethics in the 1950s and has amended it many times.[2] In 2015, nine additional interpretative statements or clauses were added to the code of ethics to clarify nursing practice.[3] The 2015 ANA Code of Ethics includes instructive comments that might help nurses in their daily work.[2,3] The recent version of ANA has nine provisions: the first three (1–3) address core values, the next three (4–6) on duty and loyalty, and the last three (7–9) on nursing duties outside patient interactions.[4] Most importantly, the Code covers frontline care, research, management, and public health nursing.[4] The ANA Code of Ethics for Nurses sections are addressed and briefly explained herewith:

Provision 1: *The nurse practices with compassion and respect for the inherent dignity, worth, and unique attributes of every person*.

The code requires nurses must know how to treat patients and families professionally while respecting their rights and coworkers' participation in care and work and emphasizing the worthiness of all individuals in the treatment paradigm.[4]

Provision 2: *The nurse's primary commitment is to the patient, whether an individual, family, group, community, or population*.

This implies that nurses should prioritize the patient and accept their wishes. They must report any outside or personal conflicts of interest that may impact patient care while also understanding professional constraints and outcomes.[4]

Provision 3: *The nurse promotes, advocates for, and protects the rights, health, and safety of the patient*.

This provision mandates that nurses must understand patient privacy and care, and prohibits nurses from treating patients while intoxicated, including with approved medicines. Nurses conducting clinical trials must understand informed consent and patient disclosure; have clear clinical and documentation skills, maintain competency standards, and report suspected medical malpractice that could damage patients. Finally, the nurse must meet institutional performance requirements, self-evaluate, undergo professional revalidation, and complete extra study when required.[4]

Provision 4: *The nurse has authority, accountability, and responsibility for nursing practice; makes decisions; and takes action consistent with the obligation to provide optimal patient care*.

Nursing requires thoughtful, planned, and implemented decision-making. Professional authority must handle individualism and patient ethics, and nursing responsibilities must be delegated with consideration for the work and its outcome. The nurse's accountability in those circumstances is reflected in their authoritative and responsible nursing care.[4]

Provision 5: *The nurse owes the same duties to self as to others, including the responsibility to promote health and safety, preserve wholeness of character and integrity, maintain competence, and continue personal and professional growth*.

The provision requires self-care as well as coworker care, and an ideal nurse will practice safe health care at home and at work. Nurses must be honest, seek for professional improvement, maintain and increase proficiency, and adapt to changes in care, trends, and innovations that contribute to personal growth.[4]

Provision 6: *The nurse, through individual and collective effort, establishes, maintains, and improves the ethical environment of the work setting and conditions of employment that are conducive to safe, quality health care*.

Ethical care criteria, as well as the obligation to disclose any deviations from appropriateness, should be stated out for nurses both inside and outside of their workplaces. Awareness of safety, quality, and environmental variables, as well as the proactive actions of nurses as individuals or teams, can lead to the best patient care outcomes.[4]

Provision 7: *The nurse, in all roles and settings, advances the profession through research and scholarly inquiry, professional standards development, and the generation of both nursing and health policy*.

According to this provision, nurses should engage in scholarly activities and research initiatives aimed to upheld practice standards and professional development. The nursing committees and boards should influence health policy and professional standards through participation and contribution. Also, professional practice guidelines should dynamically evolve as practice changes over the time.[4]

Provision 8: *The nurse collaborates with other health professionals and the public to protect human rights, promote health diplomacy, and reduce health disparities*.

The World Health Organization constitution (1946) states that health is a right, although health disparities persist between nations and cultures. Nurses must preserve health as a right for everyone, improve treatment through interdisciplinary teamwork, continuous nursing education, and a highly attainable standard of health. Nurses face rare

situations that require diplomacy and persuasion to defend patient rights and reduce health disparities.[4]

Provision 9: *The profession of nursing, collectively through its professional organization, must articulate nursing values, maintain the integrity of the profession, and integrate principles of social justice into nursing and health policy.*

Bioethics is founded on two pillars: values and social justice. Nurses must continue to serve on committees and groups in order to communicate and assess values for correctness and the survival of the profession. In these groups, they must uphold social justice and should strive to retain nursing integrity, have political knowledge, collaborate with others, and contribute to global health policy.[4]

Bioethics Principles

In addition to the guiding principles of the ANA code addressing nursing ethics, Beauchamp and Childress' ethical principles serve as the cornerstone of medical ethics.[4,5] The four main concepts of *autonomy, beneficence, nonmaleficence*, and *justice* serve as the foundation for all ethical interactions and behavior in nursing and across the health care sciences.[6] Nurses have a responsibility to avoid potential harm, and to consider the values and preferences of their patients, their families, and the greater community.[7,8]

Respect for Autonomy

Patients' autonomy, which is underscored by the Nuremberg code, is essential in medical ethics because it enables mentally competent adult patients to make their own treatment decisions.[4,5,9–11] Nurses must ensure that patients have access to all pertinent medical information, educational resources, and treatment options.[12,13] The nurse should refrain from swaying the patient's decision and be forthright about the therapeutic benefits, disadvantages, and treatment-induced adverse effect.[4,11] Once the patient is aware of all essential data, nursing personnel, in collaboration with medical professionals, can develop a treatment approach that takes the patient's values and preferences into account.[4,11] When a patient refuses medication or treatment, nurse should be compassionate and ensure that he or she has provided informed assent.[4,11–13] If nurses are to adhere to an ethical code, they must restrict their actions to those permitted by law of the land while providing comprehensive, high-quality treatment to patients.[4,11] The autonomy of nurses as health care professionals is also essential to their capacity to think critically and communicate effectively in all aspects of their work.[4,12,13]

Beneficence

Beneficence, defined as "*kindness and generosity*," is a "compassionate action" motivated by a care for the well-being of others, and the ANA defines it as "*conduct influenced by empathy*."[4,5,11] To practice beneficence, nurses must lay aside their personal emotions and provide the finest care possible for their patients, as well as take measures to improve their patients' well-being with real care and deliver what is best for them.[4,11] This ethical notion can be observed in action when a nurse consoles a dying patient by holding their hand and administers prescriptions on time.[4,11]

Nonmaleficence

Nonmaleficence, or "*do no harm*," reflects the first principle of the Hippocratic Oath, "*Primum non nocere*," and is the most commonly acknowledged principle in the field of nursing ethics.[4,5,11] Nurses are supposed to provide safe and effective care in all ways possible—without injuring their patients.[4,11] Quite often, the recommended treatment is no therapy at all, and it is preferable that the benefits, dangers, and consequences of any medical attempt be thoroughly weighed and that inferior care be avoided.[4,11] However, when a patient chooses to refuse a potentially life-saving drug, a nurse's obligation to "*do no harm*" as this may conflict with the latter's *right to autonomy***.** In addition, nurses are required to report any pharmacological therapy that is causing the patient imminent physical or mental harm, such as suicidal or murderous ideas. As a result, nurses must take care not to inadvertently harm patients.[4,11]

Justice

The concept of justice, a comprehensive ethical ideal focused on fairness, equality, and impartiality in dealing with patients and the general public is "*gold standard*" in health care.[4,5,11] In accordance with the nursing code of ethics, nurses place a high value on impartiality. Therefore, it is the responsibility of the nurse to provide care based solely on evidence, irrespective of the patient's age, race, religion, socioeconomic status, or sexual orientation.[4,11] Regardless of their circumstances, patients have the right to be treated equally and impartially. Moreover, when individuals are treated fairly, it encourages their acceptance and active participation, which increases the likelihood of improved health outcomes.[4,11]

Empathy

Empathy which is termed as "*an individual's capacity to understand or feel what another person is experiencing from within the other person's frame of reference*" is important in both nursing and health care ethics.[4,5,11,14,15] Among health care workers, the nurses have a long period of interaction with the patient and their family carers and therefore are better able to connect with them and understand how they are handling difficult situations.[16] Empathizing with patients is crucial to open up a line of communication about their concerns and preferences. An empathetic approach helps nurses to provide compassionate care and reduces patients' anxiety and distress in serious illness, pre- and postsurgical phases, or during protracted rehabilitation

process.[14] Empathetic dealing is shown to enhance understanding and expression of patient's thoughts, increase the level of contentment, improve treatment adherence, and help overall improvement in the treatment paradigm.[16,17]

Veracity or Truthfulness

In nursing, honesty is an ethical requirement and the *foundation of the principle of veracity and the nurse-patient relationship*.[14] The Code acknowledges the responsibility of transparency as one established in concern for patients and their independence, therefore an act of "*benevolent deceit*,"[14] in which a professional does not tell a patient something because they believe it will harm them, is equally immoral. The nurse must always be truthful as this allows patients to express their autonomy about future care, demonstrating its relevance to the idea of autonomy. Honesty allows for the establishment of fair standards for medical care, and nurses have an ethical obligation to be frank when addressing a patient's illness, available treatments, and associated expenses.[14] Patients can utilize their autonomy (or parents/caregivers can use parental authority) to make decisions that are in their best interests if they are provided accurate information. The nurse's truthful information gives patients access to accurate and dependable information, allowing them to make informed decisions about their health care that could possibly have a long-term impact on their life.[18]

Fidelity

Fidelity termed as "*faithfulness to a person, belief, or cause*" and in colloquial terms as being "*loyal and supportive*" is vital.[14] In nursing care fidelity is an important principle and it is obligatory that the nurse adheres to her word and delivery of patient care in accordance to the high standards set by the nursing profession and keeping up with the latest evidence-based practice.[14]

Accountability

The ANA defines accountability as "*being answerable to oneself and others for one's own acts*" and upholds the "*principles of integrity and respect for the dignity, value, and self-determination of patients*" and that nurses must take responsibility for their acts and adhere to a code of ethics in order to be held accountable.[14,19] The ANA makes it abundantly apparent that nurses, not providers, regulations, or directives, are responsible for the clinical judgments and actions associated with nursing practice.[14] It is also suggestive that accountability must include five concepts of *obligation*, *willingness*, *intent*, *ownership*, and *commitment*.[14] On a personal level accountability includes delivering and incorporating commitment to excel, get trained in best practices and its clinical application, take onus for errors committed and learn from constructive comments, to support other health care workers, and nurses honor commitments and being a positive role model.[14]

Professionalism

Professionalism which is defined as "*an individual's adherence to a set of standards, code of conduct, or collection of qualities that characterize accepted practice within a particular area of activity*" is an important aspect in health care ethics.[14,20,21] Nurses should be committed to their patients' rights regarding their treatment, be fair to them, and able to engage with them in a healthy unbiased and unprejudiced manner.[22] The nurse-patient relationships need to have well-defined boundaries and the best interests of the vulnerable populations need to be safeguarded, without expecting sexual, personal, or financial gain.[14] Nurses have to provide patients with accurate and comprehensive information before and after they give their consent to treatment and should make extra efforts to protect the privacy and confidentiality of the patients.[22] Nurse should teamwork with other health care providers to improve clinical proficiency, lessen the likelihood of adverse events, increase patient safety, limit wasteful spending, and improve outcomes for the patient.[22]

Nursing Ethics in Cancer Care

Cancer treatment and care is unquestionably the most challenging work in the medical sciences, and nurses who work in surgical, radiation, gynecological, pediatric, geriatric, medical, and palliative oncology units are responsible for clinical assessment, education, coordination, direct frontline therapy, symptom management, and supportive care.[23–25] Some also provide essential care, including bone marrow transplants and community-based cancer screening, diagnosis, and prevention.[23–25] In numerous nations, nurse-managed ambulatory oncology clinics provide long-term follow-up, chemotherapy screening, supportive care, fatigue treatment, and symptomatic relief. Oncology nurses with genomics training provide consultations and cancer risk assessments.[23–25]

The majority of oncology nurses regularly interact with patients who are experiencing physical and mental distress as a result of their illness, including but not limited to feelings of despondency, unhappiness, dread, loneliness, and intense and condemning feelings of human vulnerability.[26] The need to provide information about the patient's diagnosis, prognosis, risks and benefits of treatment, and disease progression prospects makes it difficult for nurses to approach these patients.[27] Clinically, the physician is responsible for informing patients about their diagnosis, treatment options, and any associated risks in order to obtain informed consent, while the nurse's duty is to provide planned care with empathy.[27]

In addition to clinical care, nursing objectives include moral responsibilities, such as preserving patients' autonomy, providing dignified physical and emotional care, and promoting the total patient welfare.[28] Despite the fact that ethical concepts and principles are the foundation of cancer nursing practice, nurses frequently face difficulties in fulfilling their professional fundamental obligations and

responsibilities.[29] Unresolved conflicts can lead to feelings of frustration and helplessness, which can lead to impaired patient care, job dissatisfaction, disagreements within the health care team, exhaustion, and burnout.[29]

Stressful issues in clinical oncology include pain management and supportive care, quality of life, moral conflicts with unsuccessful treatments, resuscitation protocols, information sharing ambiguity, end-of-life care, mortality, and respect for the dying.[30,31] Rules, principles, norms, and guidelines provide nurses with a foundation for their work, but they may not always provide the best solutions for patients because moral dilemmas frequently lack a definitive right or incorrect solution. During end-of-life care, nurses must strike a balance between patient care and encouraging family members to accept the fact and psychologically assist them during the difficult period. These are a few of the most frequent nursing concerns in an oncologic setup.

Nurses Dilemma during Breaking Bad News

Bad news, or "information that radically transforms the patient's life world," is common in oncology.[32] The doctor/oncologist usually tells the patient and family the awful news.[33,34] A nurse's ethical dilemmas begin with the diagnosis, as some families may exercise their right to autonomy by asking the nurse who is in regular contact with the patient to conceal about the illness, raising concerns about mental health, self-harm, or suicide.[35,36] This is ethically challenging since the nurse must choose between maintaining their ethical beliefs and honoring a patient's confidentiality and telling the patient.[36] The nurse must assess social, religious, and cultural elements, ascertain patient's emotional condition, communicate the facts, show empathy, and encourage future planning. The nurse must also decide how much cancer information is to be shared without discouraging the patient, which can be ethically difficult during active care.[35,36]

Nurses Dilemma during Treatment Period

Nurses must perform a full physical, cognitive, and emotional assessment, help patients set goals of care, educate patients and their families about treatment goals and side effects, and obtain informed consent for tumor board or oncologist-recommended treatment.[33] Nurses must address physical deformities, fertility loss, and sexuality issues while keeping professional boundaries within the patient's comfort zone.[35,36] Nurses in culturally traditional societies need to be sensitive to cancer treatment surgery on the breast, vaginal region, or penis.[35,36] In traditional orthodox cultures, nurses struggle to explain sexuality or reproduction difficulties after therapy, especially to reproductive-age patients.[35,36] The nurse must professionally address patients' and caregivers' concerns about clinical prognosis, treatment cost, benefits and risks, and alternative therapies without intruding on attending physicians' domain.[37,38] Handling these situation can be complicated and creates a dilemma which can be difficult to handle.

Nurses Dilemma during Change from Curative to Supportive/Palliative/Hospice Care

Localized or early-stage cancers are curable, and the treatment goal is to achieve complete remission and disease-free status.[35,36] During treatment, doctors may decide that further treatment is futile due to the aggressiveness of the cancer, suboptimal benefits and outcomes of the chosen modalities, or tumor recurrence or metastasis based on clinical trajectories and radiological endpoints and shift to palliative care.[35,36] At such stage, palliative care's main purpose is to limit unfavorable effects so the patient dies with less pain[35,36] The situation becomes complex when the nurse is aware that, despite all the efforts, the patient's cancer is not responding to the treatment, and the future prospects for the condition is not favorable. For nurses who have delivered care to patients and offered comfort to their family members, it can be highly difficult when doctors discuss palliative care or treatment choices with restricted curative advantages and related expenses prior to prescribing a treatment plan.[37] Addressing these dilemmas can be difficult as nurses are expected to demonstrate both expertise and empathy without compromising patient care and institutional rules of professionalism.

Nurses Dilemma during the Course of Palliative Treatment and Care

Palliative cancer treatments mostly using radiation and/or chemotherapy improve the quality of life for patients with advanced disease by effectively managing symptoms and relieving discomfort.[38] Patients receiving palliative therapy sometimes have misconceptions about their overall prognosis, the aim of palliative treatment, and often have unrealistic hopes of their cancer being cured.[38] This affects their ability to make informed judgments, treatment options, and further complicates the situation.[38] For palliative care nurses are required to assist patients in their recovery by attending to their physical, mental, and spiritual health as well as supporting family caregivers, these situations can be particularly difficult to deal with from a moral standpoint and can cause frustration and burnout.

Nurses Dilemma during End of Life Situation

The end of life, "*the last few hours or days of an individual*," is extremely distressing for patients and their family caregivers.[39–42] In oncology, at this stage all curative treatment are stopped and palliative or hospice care is initiated.[43] Nurses treating end-of-life patients must control pain and uncomfortable symptoms while offering medical, emotional, social, and spiritual care to mentally cognisant patients and their families.[43] Nurses will also have to inform family members of the patient's poor prognosis and discuss death,[44] which is extremely difficult and worse especially when the patient is a child or principal support for the family.[45–47] To complicate, at times the inability to alleviate pain and

approaching end-of-life care aggravate the ongoing ethical challenges for the oncology nurses and lead to moral discomfort. Professionally, obeying the treating doctor's judgment for passive euthanasia, do-not-resuscitate, and life-sustaining drug orders may increase distress.[48,49] Nurses must communicate the patient's approaching death while satisfying family needs and safeguarding dignity, societal, and religious beliefs and this can be mentally exhausting.[48,49]

Mitigation of Ethical Dilemma and Moral Distress in Nurses

Globally, nurses working in oncology invariably face ethical challenges and the universal belief is that eliminating them is no longer possible. Considering this, emphasis is now on training nurses to recognize them and effectively addressing these. Today, the goal is to inculcate skills to identify, build resilience, learn to cope, and prevent moral distress and burnout. The important aspect is that reports suggest that majority of ethical dilemmas included difficult situations at the end of life and are linked to putting off or avoiding tough conversations, having conflicting commitments, and not allowing others to voice their ethical opinions which consequently lead to moral distress and moral injury.[50,51] The end result is that when disagreements over ethics arise care of critically ill patients gets more complicated and compromised. These events negatively affect patient care, which can subsequently lead to staff burnout, job departure, and will ultimately affect the hospital system. In lieu of this, across the world emphasis is now on interventions to mitigate ethical dilemma and moral distress in oncology nursing and the four R's to respond strategically to moral distress[52] and ethical deliberation[53–55] are historically found to be useful. In addition to these, a meta-analysis published by Morley et al have highlighted that interventions like "*facilitated discussions, specialist consultation services; an intervention bundle; multidisciplinary rounds; self-reflection and narrative writing*" are all effective in mitigate ethical dilemmas, disagreements, and the resulting moral distress.[56] Importantly, encouraging open discussion is reported to reduce the frequency and severity of disputes, emotional suffering, and moral distress.[54–57]

In addition to the above said aspects it is also desired that hospital administrators can prevent and resolve ethical dilemmas by enhancing communication, creating opportunities for ongoing education to competent and trained personnel on the topic, and implement structured training to resolve ethical disputes among nurses and other health care workers through case-based vignettes.[57] More importantly,

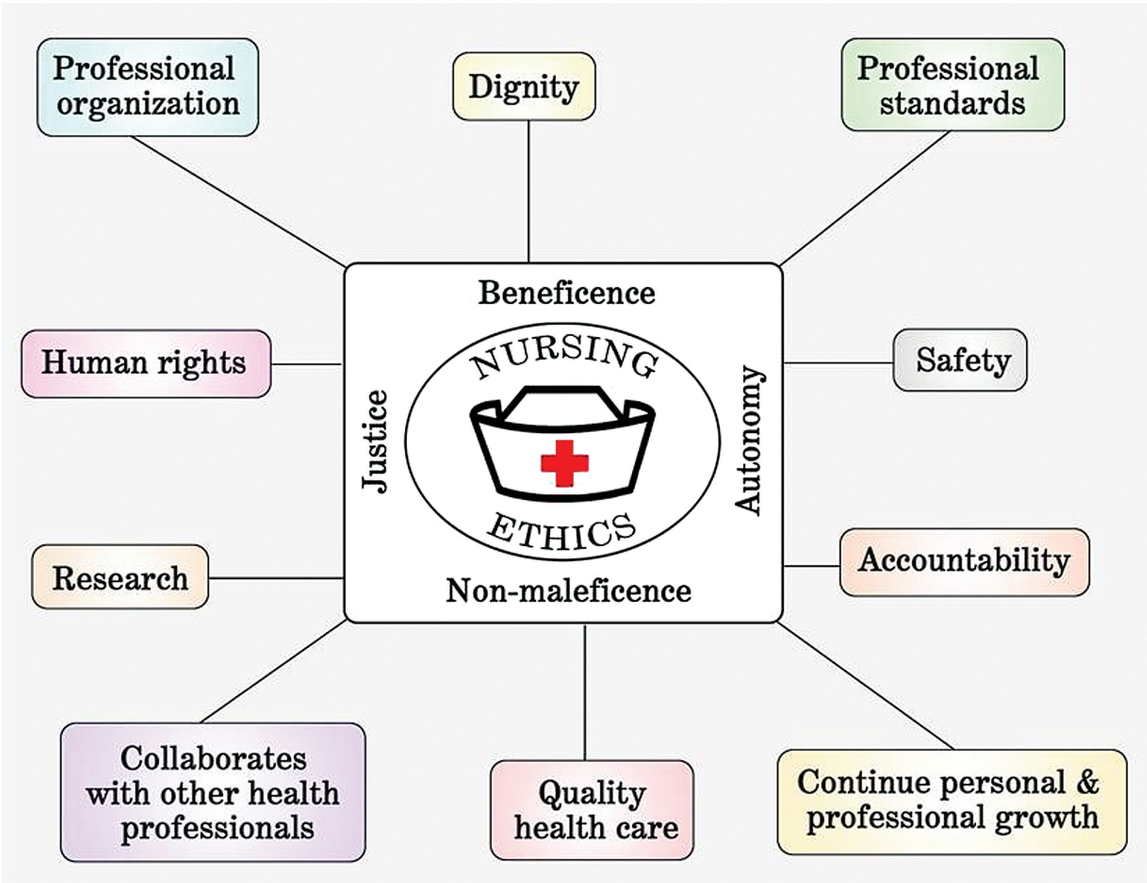

Fig. 1 Various principles and aspects important in nursing ethics.

health care providers and hospital administrators should invest the necessary resources, time, and energy into improving cancer care services and should also look for ways to strengthen professional health care teams.[52–57]

Deputation of nurses for structured short-term training in oncology and palliative care programs at cancer care and hospice centers can also be help in acquainting them with the clinical and ethical issues prevailing and on how to handle them from experienced peers. Adding training in medical ethics in oncology, palliative care, and end of life aspects in curriculum of nursing education and refresher courses for the working professionals is another important approach to help reach objective in the health care students.[54] It is anticipated that a concerted and sincerely planned efforts in these lines will be beneficial for the nurses and will help them identify the issues, build resilience, and assist coping with ethical dilemmas and moral distress. The outcome of these objectives will significantly help the nursing fraternity in their personal and professional endeavors, and consequentially help improve patient care and service to society.

Conclusion

Nurses who care for cancer patients bear a heavier moral burden, and ethical difficulties abound in this field, and are vulnerable because they are constantly exposed to pain, death, and bereavement. Nurses must be taught basic ethical principles, recognize moral, cultural, religious, and spiritual concerns, and have a plan in place to address them through collaborative decision making in order to improve cancer care. The aforementioned activities should be carried out in accordance with the ethical principles of beneficence and nonmaleficence, while respecting the patient's autonomy and promoting social justice (►**Fig. 1**). These concepts should be taught to nursing students and inculcated into their daily practice. As a curriculum component, bioethics education must include cancer, and nurses must have stronger basics in essential principles from the outset of their job training. Creating and maintaining a common ethical decision-making process with key stakeholders throughout the treatment process should also be included. Specific learning outcomes should be incorporated into nursing educational activities. This will help to establish a competent and morally conscious oncology workforce.

Patient Consent

Patient consent is not required due to the retrospective nature of the study.

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Conflict of Interest

None declared.

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Global Burden of Testicular Cancer and Its Risk Factors

Sharyu Mhamane[1] Sonali Bagal[1] Samyukta Shivshankar[1,2] Prithviraj Kadam[1] Gagan Prakash[3] Atul Budukh[1,2]

[1] Centre for Cancer Epidemiology, Tata Memorial Centre, Navi Mumbai, Maharashtra, India
[2] Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India
[3] Division of Urologic Oncology, Department of Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Atul Budukh, PhD, Department of Epidemiology, Tata Memorial Centre, Homi Bhabha National Institute, Centre for Cancer Epidemiology, ACTREC, Sector 22, Utsav Chowk, CISF Road, Kharghar, Navi Mumbai, Maharashtra 410 210, India (e-mail: atul.budukh@gmail.com; budukham@tmc.gov.in).

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Abstract

Testicular cancer (TC) is a rare cancer accounting for 5% of total urologic tumors. It occurs in distinct age groups of adolescents and young adults unlike other cancers peaking in the older age groups. About 95% of TC arises from germ cells. The histological classification of TC consists mainly of seminomas and nonseminomas. Based on GLOBOCAN 2022, the continent with the highest incidence rate was Europe (Age-adjusted rate-6.4), while Africa (0.59) had the lowest incidence. The highest mortality rates were estimated for Latin America and the Caribbean (0.58) followed by Europe (0.35) while the lowest was for the Asian continent (0.14). The highest prevalence of TC was in Europe followed by Oceania and Northern America, while Africa had the least prevalence of TC cases among all. A myriad of risk factors is associated with TC; Cryptorchidism is the strongest associated risk factor of TC increasing the risk by fivefold. Other risk factors identified include family history increasing the risk by four- to eightfold, increased adult height, infertility (1.6- to 2.8-fold), pesticide exposure (threefold), and gr/gr deletion (threefold). Clinically, TC generally presents as a painless scrotal swelling often mistaken as a hydrocele and the bulk of disease growing in the retroperitoneum can be asymptomatic even after growing to a huge size. This article aims to present the global burden of TC and also discusses its etiological risk factors.

Keywords
- testicular cancer
- epidemiology
- GLOBOCAN
- etiology
- cryptorchidism

Introduction

The burden of testicular cancer (TC) has doubled in the past 40 years. Coded as C62 as per the International Classification of Disease-Oncology–3rd Edition, it accounts for 5% of urologic tumors, globally.[1–3] Despite being rare, it is an important public health issue due to its impact on the quality of life in men.[4] Due to data scarcity, the epidemiology of TC is not explored to its full potential, unlike other cancer sites.[5] However, increased attention is required due to its grim consequences affecting the quality of life in men due to treatment of TC such as cytotoxicity and cardiometabolic issues affecting the most productive years of adolescents and young adults.[6]

Depending on the cell type from which the cancer has originated, TC is divided into two types; those from the germ cells and the other arising from the nongerm cells of the testis.[7] Around 95% of TC arises from germ cells, while the remaining 5% arises from sex cord or stromal cells and miscellaneous nonspecific stromal cells.[8] Of these, 95% of

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testicular germ cell tumors (TGCTs) are further divided based on the histologic features into seminomas, nonseminomas, and spermatocyte seminomas.[4]

The burden of TC is observed to peak in the age group 15 to 40, thus it is predominantly regarded as the cancer of adolescents and young adults.[5,6,9] There is a lack of clear appearance of signs and symptoms of TC with the exception of a unilateral lump or painless swelling; detecting TC cases in the early stage is a challenge. This calls for a clear understanding of the etiology as well as the current epidemiology of TC. This article aims to add to the literature on TC emphasizing its epidemiology and etiology.

Burden of Testicular Cancer

The current epidemiology of TC across continents is described in terms of incidence, mortality, prevalence, and survival. ►**Table 1** presents the burden of TC in different continents as per GLOBOCAN 2022.[10]

Incidence and Mortality

Literature indicates an increasing incidence of TC worldwide.[2] There exists a geographical difference in the incidence of TC.[11] Based on GLOBOCAN 2022, a total of 72,040 incidence cases of cancer were recorded with a global incidence age-adjusted rate (AAR) for TC of 1.7 per 100,000 population. The continent of Europe has the highest incidence rate of TC with 6.4 per 100,000, followed by Northern America (5.5) and Oceania (5.5), Latin America, and the Caribbean (3.8), while the lowest incidence rates were estimated for Africa (0.59) and Asia (0.76).

Similarly, for mortality, a total of 9,068 deaths due to TC were estimated, with a global mortality AAR of 0.21. Though the overall death rate due to TC is low, of all the continents highest mortality of TC was noted for Latin America and the Caribbean (0.58), followed by Europe (0.35), Northern America (0.26), and Africa (0.23), while continents of Oceania (0.20) and Asia (0.14) recorded the lowest mortality rates for TC. The 5-year prevalence proportion for TC shows that there are 297,454 prevalent cases of TC with a global estimate of 7.5 cases per 100,000 proportions. The highest prevalence is in Europe (30.2), followed by Northern America (26.7), Oceania (25.7), and Latin America (16.3), while the lowest were in Asia (3.0) and Africa (1.3).[10]

Based on the Human Development Index (HDI), which is defined as a summary measure of average achievement in key dimensions of human development of the country,[12] the highest burden is recorded in European and Nordic countries such as Norway, the Netherlands, Denmark, and Slovenia where the burden has doubled in past two decades, while the comparatively lower burden of TC is observed in the African and Asian countries belonging to comparatively lower and medium HDI, respectively.[2,6]

The incidence and mortality of TC across all continents is presented in ►**Figs. 1** and **2**.[10]

Survival

The data on the survival of TC is scarce. According to the Surveillance, Epidemiology and End Results organization, a very high 5-year overall survival rate of 95% was observed for all-stage TC and 99.2% for localized TC in the United States.[2] The increase in survival was attributed to the introduction of platinum-based chemotherapy regimens and guidelines to help standardize tumor management, thus increasing the 5-year survival rates from 63% to more than 90% during the last three decades.[10,13] Improved survival can also be attributed to increased awareness, wider use of ultrasonography at the primary level, and centralization of care and guidelines.[14]

In the Context of Cancer Registries Represented in CI5 XII

Based on the data from Cancer Incidence in Five Continents Volume XII, the range of incidence rates for TC in cancer registries from different continents is presented in ►**Table 2**. Of the total 589 cancer registries represented in CI5 XII, the cancer registry with the highest AAR for TC was the Chile, Valdivia Cancer Registry with AAR of 15.5 per 100,000 population. This registry belongs to the South, Central America and the Caribbean continent. The lowest incidence rate for TC was recorded in the Eldoret, Kenya registry in the African continent and the Nebraska Cancer Registry in the North American continent.[15]

Table 1 Burden of testicular cancer in different continents as per GLOBOCAN 2022

Continents	Incidence		Mortality		Prevalence	
	Cases	AAR per 100,000	Deaths	AAR per 100,000	Previous cases	Proportion per 100,000
Africa	3,139	0.59	1,080	0.23	9,026	1.3
Latin America and Caribbean	13,650	3.8	2,103	0.58	53,322	16.3
North America	10,546	5.5	565	0.26	49,417	26.7
Asia	19,388	6.4	3,660	0.35	70,947	30.2
Europe	24,070	5.5	1,611	0.20	109,109	25.7
Oceania	1,247	0.76	49	0.14	5,633	3.0
Total	72,040	1.7	9,068	0.21	297,454	7.5

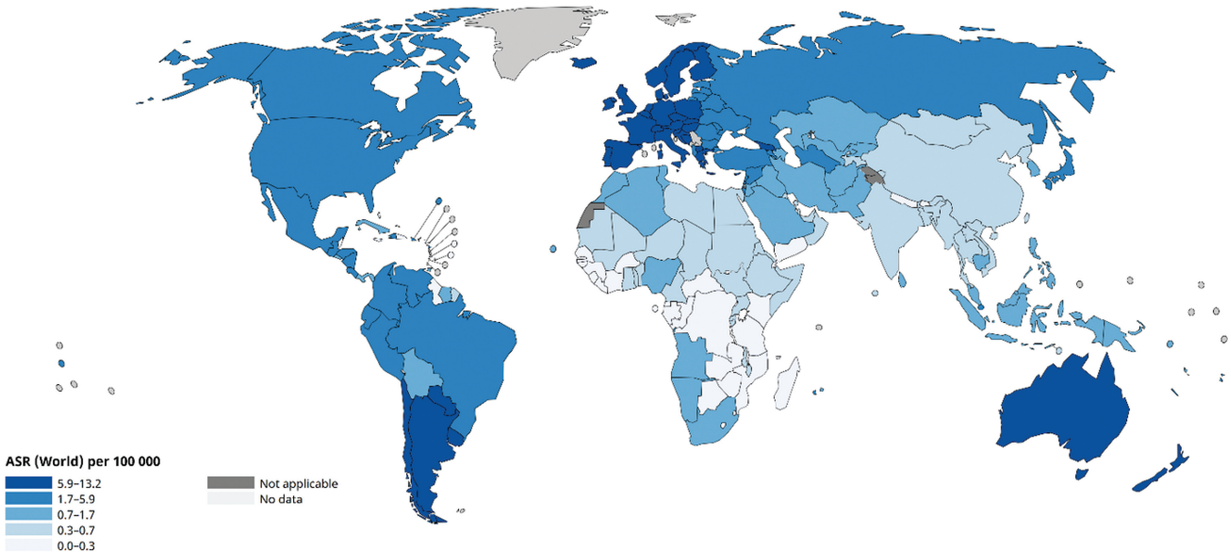

Fig. 1 Age-standardized rate (world) per 100,000, incidence of testicular cancer as per GLOBOCAN 2022.

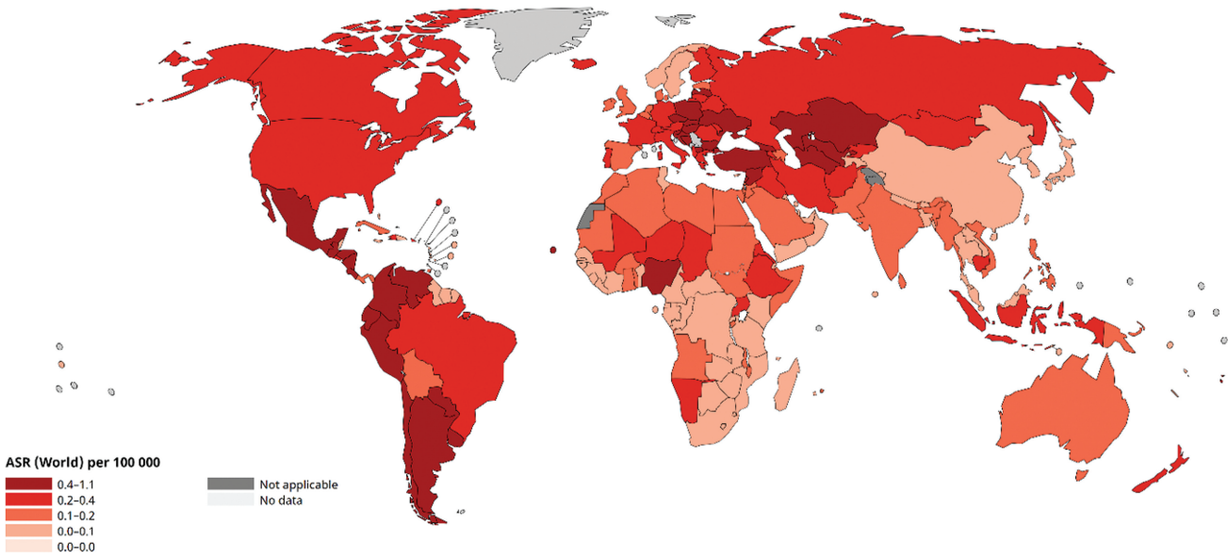

Fig. 2 Age-standardized rate (World) per 100,000, mortality of testicular cancer as per GLOBOCAN 2022.

As per GLOBOCAN 2020, Chile reported the highest mortality for TC. A retrospective study based on a 41-year follow-up at a Chilean cancer institute noted that approximately 40% of the patients who were registered with TC as the cause of death had unspecific information in their death certificates, thus owing to the high burden of TC in Chile to the erroneous labeling of TC as the cause of death.[16]

In Context of Indian Cancer Registries

Of the 72,040 new incident cancer cases of TC (Age-standardized incidence rate [ASIR] 1.7 and Cum.risk: 0.13) recorded worldwide, India recorded 4,456 new cancer cases (ASIR: 0.57). By the year 2050, India is estimated to observe a 24.4% increase in the proportion of TC cases, which is slightly higher than the estimated global increase of TC cases by 22.7%.[10]

Published data from the Indian cancer registries were used for the year 2013 to 2019 to understand the difference in the incidence rate of TC. The incidence rate was higher than the national rates in Wardha, Maharashtra (0.8), Trivandrum, Kerala (0.8), Dibrugarh, Assam (0.8), Bhopal, Madhya Pradesh (0.8), and New Delhi (0.7).

As per CI5 XII, the rates for seminomas germ cell tumors among Indian cancer registries ranged from 0.5 to < 0.1 per 100,000 with the highest recorded in Wardha (0.5), Trivandrum (0.4), Kamrup urban district (0.4), Barshi, Paranda, and Bhum (0.4), and lowest in Mizoram (< 0.1) cancer registry.

Table 2 Testicular cancer incidence rates as per cancer registries represented in CI5 Volume XII

Continent	Number of registries represented in CI5	Range of testicular cancer incidence rate			
		High		Low	
		Name of registry	AAR	Name of registry	AAR
Africa	14	France, La Réunion	2.8	Kenya, Eldoret	0
America, Central and South, and Caribbean	27	Chile, Valdivia	15.5	Brazil, Recife	0.7
America, North	175	Canada, Yukon	13.2	USA, Nebraska: Black	0.3
Asia	230	Türkiye, Trabzon	6.3	China, Yiyuan County China, Yongkang City China, Yunmeng County	0.1
Europe	123	Switzerland, Graubünden Glarus	14.4	Russian Federation, Arkhangelsk	1.7
Oceania	20	Australia, Tasmania	9.9	USA, Hawaii: Filipino	1.9

Similarly, for nonseminomas, the rates ranged from 0.4 to <0.1 per 100,000 with the highest recorded in Chandigarh (0.4), Bhopal (0.3), New Delhi (0.3), and Kollam (0.3), while lowest in Mizoram (<0.1) cancer registry.[15]

Worldwide, 9,068 deaths (Age-standardized mortality rate [ASMR]: 0.21 per 100,000) have occurred due to TC. Of these, 1,050 deaths (ASMR: 0.14) were recorded in India. By the year 2050, India will observe a 45.5% increase in mortality, which is slightly higher than the 40% increased proportion estimated globally.[10] This increasing burden of mortality indicates focused attention towards early diagnosis, treatment, and survival of TC cases in the forthcoming decades.

For India, as per GLOBOCAN 2022, the prevalence of TC estimated for 5-year period is 2.0 proportion per 100,000 population.[10]

Globally, a wide variation is observed in the epidemiology of TC. The attribution of these variations can be to the differences in the environmental and genetic factors, health infrastructure such as diagnostics and treatment availability, as well as reporting infrastructure.[14]

The high burden in high HDI countries is a result of lifestyle factors as well as the robust diagnostic infrastructure availability, while declining mortality rates are attributed to improved treatment modalities. The global variation of TC is also associated with the HDI, gross domestic product, alcohol drinking, overweight, sedentary lifestyle, obesity, and hypercholesterolemia. Understanding the risk factors is of prime importance while understanding the overall epidemiology of TC.[14]

Risk Factors of Testicular Cancer

There is a myriad of factors that contribute to the etiology of TC. These risk factors can be broadly divided into biological, lifestyle, genetic, and environmental factors.

Biologic Factors

Cryptorchidism

Cryptorchidism, synonymous with un/maldescended testis is the most common congenital malignancy in males and is diagnosed in approximately 1% of boys who reach 1 year of age. In this condition, the testis lies above the external inguinal ring either within the inguinal canal or within the abdomen.[17–19] The testes failing to descend normally in the scrotum elevates the local temperature, which is posited to be procarcinogenic. This in addition to the hormonal conditions predisposes to both cryptorchidism and TC. Among all the other risk factors, it is the most established and strongest risk factor associated with TC.[20] History of cryptorchidism is associated with an almost fourfold increased risk of developing TC (odds ratio [OR]: 3.99, 95% confidence interval [CI]: 2.80–5.71).[21] While men whose cryptorchidism was resolved before the age of 15 had reduced risk by twofold.[22] Other conditions being explored for their role in TC development include Down syndrome and Klinefelter syndrome.[6]

Age

The natural history of TC is seen to have a distinct age group peak for the disease, unlike other cancers presenting at older age. The risk disposition of TC is within the reproductive age group[9] of 20 to 35 years, while the older age peaks between 50 and 55 years.[2,4,6] A peak in the reproductive age group could be attributed to sex hormones (androgen levels) as well as high estrogen levels in utero.[4,9]

Family History

Familial risks for TC are among the highest of all cancers. However, data are limited for histological types of TC and possible familial associations of TC with other cancers.[23] Individuals whose fathers had TC were four to six times more likely to develop TC, this risk, however, almost doubled to 8 to 10 times if the brother had TC.[6,24]

Perinatal and Physical Factors

Studies have emphasized early exposure could be a potential risk factor. Though the majority of the studies present inconclusive results, the likely factors that contribute include low birth weight, maternal exposure to estrogen, maternal smoking, gestational weight gain, inguinal hernia, birth defects, and serum cholesterol levels.[4,6,25]

An increase in height was associated with an increased risk of TC in several studies.[25–28] A 5-cm increase in adult height was associated with a 3% increased risk of TC.[26] Controversial results about body mass index (BMI) exist[4]; however, majority of studies conclude that increased BMI increases the risk of TC.[7,19]

Hormonal and Reproductive-Related Factors

A meta-analysis including eight studies from Western countries concluded that there was no significant association between vasectomy and the risk of TC (OR: 1.10, 95% CI: 0.95–1.30).[29] However, infertility in men increases the risk of TC by 1.6 to 2.8 times.[24]

A study found a nonsignificant inverse association between an increasing number of children fathered 5 years before diagnosis and risk of TC (OR per additional child 0.78, 95% CI: 0.58–1.04).[30]

Lifestyle-Related Factors

Diet

Increased caloric intake was associated with a higher risk of TC, all types, especially nonseminoma cancer.[19] This particularly explains the high burden of TC in Scandinavian countries that have a higher intake of dairy products. Dairy in addition to fish and meat was also postulated to be the source of intake of organochlorines responsible for increased risk of TC.[31] Fruit and vegetable consumption is regarded to be protective against cancer in general, and hormone-related cancers in particular, by reducing the enterohepatic recirculation of estrogens.[32] Various studies in animals reported that cocoa and theobromine, the main stimulant of cocoa, exert toxic effects on the testis, inducing testicular atrophy and impaired sperm quality.[33]

Physical Activity

A recent meta-analysis of studies presents controversial and inconclusive results for physical activity (PA) and its effect on the risk of TC.[14] However, older studies have found moderate effects of PA on TC. The conflicting results on the relationship between PA and TC risk should not be taken as a lack of relation; further research using strict methodology is needed to get definitive findings.[4]

Occupational Factors

Literature comprised several studies on occupational exposures, potential carcinogens and their impact on TC risk. Exposures reported in most studies were of pesticides, textile dust, aliphatic, alicyclic hydrocarbons, organic solvents, endocrine disrupting factors such as polychlorinated biphenyls, organochlorines, nonionizing radiation, radiofrequency emitters, electrical machines, and high voltage lines. Exposure to organochlorine pesticides like cis-nonachlor, trans-nonachlor, and p,p′-dichlorodiphenyldichloroethylene was observed to cause an increasing risk of TGCTs with increasing concentration in blood. Relative risks were higher for seminoma than nonseminoma.[4,27,34–37]

Occupations assessed in the literature included agriculture work, gardening, chemical manufacturers, metal trimming, welding, industrial production of glue, railway traffic supervisors, firefighters, electrical engineers, and programmers. For police officers, a positive association was found with TC (OR = 1.31), which was mostly attributed to hand-held radar[38]; however, a similar study among military personnel had inconclusive results.[4] Similarly, regarding the use of cellular and cordless telephones, no increased risk of TC was reported[39] Among farmers, the risk of TC due to pesticides increased by threefold, with organochlorines responsible for the catapulted risk.[33] Understanding the exposures is important due to their potential to influence the risk of TC by interfering with the hormonal pathways of the body.

Social and Behavioral Factors

Recent literature have shared findings of increased risk of TC among individuals belonging to low-income group. For diagnosis, lower levels of education and SES are risk factors for later stage TC diagnosis and hence higher TC mortality.[25] The behavioral factor for TC risk encircles the consumption of alcohol and substance use. A meta-analysis stated 62% increased odds of developing TC due to cannabis use. These studies are mainly conducted in developed countries.[40,41]

Genetic and Environmental Factors

The presence of the "gr/gr" deletion in the Y chromosome was associated with a twofold increased risk of TGCT (OR: 2.1, 95% CI: 1.3–3.6, $p = 0.005$), and a threefold increased risk among patients with a family history of TC (OR: 3.2, 95% CI: 1.5–6.7, $p = 0.0027$). The gr/gr deletion was more strongly associated with seminoma (OR: 3.0, 95% CI: 1.6–5.4, $p = 0.0004$) than with nonseminoma.[42] The rarity of the condition of TC is attributed to the lack of reliable studies with large samples to confirm the genetic background and its role in TC. Though the role of genetics is undeniable, large-scale studies providing clear evidence are required to comprehend the role of genetics in the development of TC.[4]

Environmental exposures to toxins through industrialization contribute majorly to the increased risk of TC. The testicles' anatomical placement in the scrotum may be crucial in the development of cancer since they are mostly exposed to environmental pollutants such as intense heat, γ-radiation, and electromagnetic fields.[43,44] The environmental genotoxins majorly consist of endocrine disruption with estrogenic, antiandrogenic, and mixed estrogenic antiandrogenic properties,[45] organochlorines, and polychlorinated biphenyls, these derivatives are similar to those found in pesticides.

Testicular dysgenesis syndrome (TDS) comprises hypospadias, undescended testis, spermatogenesis, and TGCT. It has a common fetal origin attributed to the fetal androgen production deficiency in addition to the failure in normal differentiation of the fetal cells, similar to that of TC, thus TDS have been associated with TC.[46,47] However, there is a lack of detailed studies on the effect of TDS or one of its components

on the oncological outcomes of TC. The etiology of TDS and TC is linked to environmental exposures and genetic susceptibility.[48] Fetal exposures to "di-n-butyl phthalate" are the most likely to be responsible for TDS and TC.[49,50]

The majority of the environmental exposure evidence-based studies are conducted in small cohorts gauging mainly occupational exposure. Thus, large sample size-based studies are requisite to understand the environmental exposures and their impact on the risk of TC.

Anatomically, the testis is present outside the body and is prone to environmental temperature. Occupational exposure to extreme conditions has been demonstrated to significantly increase the risk of TGCT.[51] Temperature exposure at workplaces is hypothesized as a potential association with the increased risk of TC.[52]

The summarization of risk factors identified from the study is mentioned in ►**Table 3**.

Table 3 Summary of identified risk factors

Risk factors identified	References
Cryptorchidism[a]	17–22
Age	2,4,6
Family history • *TC in father and brother*	6,23,24
Perinatal or maternal factors • *Low birth weight, maternal exposure to estrogen, maternal smoking, gestational weight gain, inguinal hernia, birth defects, serum cholesterol levels*	4,6,25
Physical features • *Increased height, increased BMI*	6,19,26–28
Hormonal or reproductive factors • *Infertility, vasectomy (-), increasing sibship size (-)*	4,9,24,29,30
Diet • *Dairy products, cheese, cocoa, fruits, and vegetable (-)*	19,32,33
Physical activity	14
Occupational factors • *Pesticides, textile dust, aliphatic, alicyclic hydrocarbons, organic solvents, endocrine disrupting factors such as polychlorinated biphenyls, organochlorines, nonionizing radiation, radiofrequency emitters, electrical machines, and high voltage lines*	4,27,33–39,52
Socioeconomic factors • *Lower levels of education and socioeconomic position*	25
Genetic factors	42
Environmental exposure • *Extreme heat exposure, γ-radiation and electromagnetic fields, organochlorines, and polychlorinated biphenyls* • *Testicular dysgenesis*	37,44–52

Abbreviations: BMI, body mass index; TC, Testicular cancer.
Note: (-) indicates an inverse risk of TC.
[a]Factors supported by strong evidence.

Discussion

Considering the rarity of the condition and the distinct age group in which it occurs, that is, the reproductive age group consisting of adolescents and young adults affects productivity and incurs a financial burden on the country. The highest incidence has been observed in Central Europe (Denmark, Norway, and Germany) and generally in Caucasian populations of developed countries.[53] In addition to this, in low- and middle-income countries (LMICs) there is an increase in the proportion of cancer burden projected in the coming years, thus addressing the issue of TC is crucial.[40] Understanding the epidemiology of TC will help in resource allocation and developing health policies and diagnostic guidelines.

The first imaging modality that is recommended for examining the TC is scrotal ultrasonography. Orchiectomy serves as both a diagnostic and a therapeutic measure if a tumor is found. Platinum-based chemotherapy has revolutionized the treatment of TC and is considered a significant success in the area of oncology due to its high cure rate.[24,40] However, some studies emphasize the toxicity induced due to the treatment of TC and the compromised long-term quality of life.[6,24] Radiation and chemotherapy increases the risk of secondary malignancies and cytotoxicity. Survivors of TC have a fivefold increased risk of cardiovascular disease, metabolic syndrome, pulmonary toxicity, nephrotoxicity, and ototoxicity.[54] Thus, though the survival of TC has improved owing to the newer treatment regimens, the quality of life remains questionable.

Indian Context of Testicular Cancer

Compared with those in Western nations, patients in India who have TGCTs typically present at an advanced stage and with a greater International Germ Cell Cancer Collaborative Group risk. Compared with the West, patients with TC had worse results in LMICs like India. The late-stage presentations with significant nodal disease load, numerous therapy discontinuations, dosage compromise, and scrotal orchidectomy are held responsible for this.[40] There is a need for improvement in the care provided for TC by implementing evidence-based management and prevention strategies, especially in LMICs; however, there exists a severe paucity of data with limited to no data available on demographic features, management, and outcomes.[40] Cancer registries are excellent tools to gauge and record the burden of cancer in any given geographical region.[55,56] India has a total of 52 population-based cancer registries and more than 250 hospital-based cancer registries.[57,58] These registries can be employed to understand the population-level pattern of TC and to study the clinical management of TC, thus improving the disease prognosis and quality of life of the patients.

The beneficial effects of centralization of care on the outcome of TC has been established. With the existing health policies in India, centralization of cancer care is difficult and that could be another reason for an inferior outcome seen here.[59]

Conclusion

The current epidemiology of TC shows lower rates of TC in low HDI countries as compared with other high HDI countries. Developed countries are shielded with their robust health care system and newer and improved treatment regimens. Unfortunately, this is not the scenario in the health care systems of resource-constraint settings; therefore, reliance on preventive and early detection is the effective strategy to tackle the issue of TC. Since TC is a rare condition and data are scarce, efforts should be taken to maintain a proper database of cases that deals with the treatment and management of TC. This database can be employed to conduct several studies to understand the etiology and management of TC.

This study found that there are several risk factors related to studies of TC. However, the majority of the studies have been conducted on selected samples or small cohorts, thus yielding inconclusive results. An extensive approach that considers both biological and epidemiologic risk factors is required to precisely determine each person's risk of TC and, consequently, to tailor appropriate prevention and management strategies.[4] Therefore, understanding the epidemiology is essential to plan cancer management strategies. To accurately study the changes in incidence and outcomes of TC and all tumor types, the availability of high-quality cancer registry data is required.[9]

Patient Consent

This a review article based on published literature, therefore patient consent was not required.

Authors' Contributions

S.M.: Writing original draft, data curation, and visualization.
S.B.: Writing - review and editing, data curation, and visualization.
S.S.: Writing - review and editing, data curation, and visualization.
P.K.: Writing - review and editing.
G.P.: Writing - review and editing.
A.B.: Conceptualization, writing - review and editing, and supervision.

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Conflict of Interest

None declared.

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Profile and Outcomes of COVID-19 Infection in Pediatric Patients with and without Cancer: A Case–Control Study

Puneet Kaur Sahi[1] Varun Kumar[1] Arpita Gupta[1] Mampy Das[1] Priyanka Meena[1] Divyanshi Divyanshi[1]

[1] Department of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India

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Address for correspondence Varun Kumar, MD, Department of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi 110002, India (e-mail: drkumarvarun11@gmail.com).

Abstract

Objectives Pediatric patients with cancer are considered a vulnerable population to the ill effects of coronavirus disease 2019 (COVID-19). We hereby studied the difference between clinical characteristics, lab parameters, and outcomes of COVID-19 among children suffering from cancer and those without cancer. We also analyzed risk factors for the occurrence of moderate-to-severe COVID-19 disease in pediatric cancer patients.

Materials and Methods This retrospective case–control study was carried out using the medical record review method over 6 months in a tertiary-care center in India. All patients below 18 years of age, with reverse-transcriptase polymerase chain reaction (RTPCR) confirmed COVID-19, were screened for enrolment. Patients were split into two groups: Group A comprised of patients with cancer, while group B consisted of patients without any underlying comorbidity. Patients with other comorbidity except cancer and inadequately recorded case sheets were excluded. Details regarding demography, clinical features, investigations, treatment, and outcomes were recorded.

Statistical Analysis Microsoft Excel and Statistical Package for the Social Sciences (SPSS) software, version 25 was used for data analysis. A *p*-value less than 0.05 was considered significant.

Results Two-hundred-five pediatric inpatients with RTPCR-established COVID-19 infection were screened and final analyses were performed on 97 patients, of which 31 children were classified into group A and 66 into group B. Median age of enrolled children was 5 years with 58.8% males. The prevalence of cancer as a comorbidity in pediatric inpatients with COVID-19 was 15%. Fifty-five percent of cancer patients had hematological malignancies, while 45% had solid tumors. Fever ($p = 0.001$) and gastrointestinal manifestations ($p = 0.0001$) were significantly less common among pediatric cancer patients. Children with cancer had significantly more leukopenia ($p = 0.003$), neutropenia ($p = 0.003$), and lymphopenia ($p = 0.005$). The case fatality rate was higher in children with cancer (3.2%) as compared to noncancer patients (1.5%, $p = 1.0$). Few risk factors for moderate-to-severe COVID-19 among children with

Keywords
- SARS-CoV-2
- pediatric cancer
- hematological malignancy
- risk factors
- severe disease
- solid tumors

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cancer included age less than 2 years ($p = 0.06$), undernutrition ($p = 0.33$), advanced stage of cancer ($p = 0.49$), and presence of coinfection ($p = 0.35$)

Conclusion Cancer is a significant comorbidity among pediatric COVID-19 patients. While children with cancer have less severe COVID-19, their case fatality rate is higher than those without cancer. Younger age, undernutrition, advanced stage of cancer, and presence of coinfections may predispose to the development of moderate-to-severe COVID-19 among pediatric cancer patients.

Introduction

Ever since the declaration of the coronavirus disease 2019 (COVID-19) pandemic, there have been many publications about COVID-19 infection in children. Most of the studies indicate that COVID-19 infection in the pediatric age group is generally mild and many remain asymptomatic. However, pediatric patients with cancer have been considered a vulnerable population to the harmful effects of COVID-19 due to their immunosuppressed state and also due to reprioritization of healthcare services.[1] To date, studies on COVID-19 in pediatric patients suffering from cancer show an asymptomatic, mild or moderate disease. However, attributable mortality in children with malignant disease is reported to be at least 10 times higher as compared to those children without comorbidities.[2] Indian data on COVID-19 in children with cancer shows low mortality due to COVID-19 infection per se.[3] However, there is limited data on the clinicoepidemiological and laboratory profile of COVID-19 in Indian children especially in the form of a case–control study.

The following research was conducted to understand the difference between clinical characteristics, lab parameters, and outcome of COVID-19 infection among pediatric patients with and without cancer. We also analyzed risk factors for the occurrence of severe COVID-19 disease in pediatric patients with cancer.

Materials and Methods

Study Design and Participants

This is a retrospective observational case–control study conducted using the medical record review method. The research was conducted after acquiring approval from the Institute's Ethics committee, over 6 months from April 2021 to September 2021, in the Department of Pediatrics of a tertiary care center in India.

Inclusion Criteria

All patients below 18 years of age with a definite diagnosis of COVID-19 through a positive nasopharyngeal and/or oropharyngeal reverse-transcriptase polymerase chain reaction (RTPCR) test were screened for enrolment.

Exclusion Criteria

Patients with any comorbidity except cancer and those with inadequately recorded case sheets were excluded.

The study cohort was split into two groups for comparison. Group A comprised pediatric patients with any form of cancer as comorbidity (newly diagnosed or already on treatment), while group B consisted of pediatric patients without any underlying comorbidity.

Primary Outcome

To analyze the Difference between clinical characteristics, lab parameters, and outcome (discharge/death) of COVID-19 infection among pediatric inpatients with and without cancer.

Secondary Outcome

To identify the Risk factors for the occurrence of severe COVID-19 disease in pediatric patients with cancer.

Data Collection

The following recorded data was reviewed for all enrolled patients

1. Demographic details: age, gender, place of current residence
2. Malignancy-related details: Baseline disease, disease stage, date of diagnosis, disease status (active or in remission), date of last chemotherapy/radiotherapy/surgery
3. COVID-19-related details: clinical manifestations, complications, disease severity at presentation, treatment received, duration of hospital stay, and outcome.
4. Details of coinfection: disease status, treatment received, and outcome.
5. The blood investigations including complete blood count, kidney function test, liver function test, coagulation profile, and radiological investigations including chest X-ray and/or computed tomography chest scan were recorded.
6. Outcome details: Discharge/transfer out to another facility as per existing hospital policy at that time or death.

Ethical Consideration

The research was reviewed and approved by the Institute's Ethical board, Maulana Azad Medical College & Associated Lok Nayak Hospital, GB Pant Hospital, Guru Nanak Eye Center, New Delhi-110002, registered (Registration number ECR/329/Inst/DL/2013/RR-2019) with Drug controller general of India, Directorate General of Health Services, New Delhi. All actions executed in this study 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. Complete data anonymity was maintained.

Study Definitions

Confirmed COVID-19 Case[4]

A patient with RTPCR established severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, identified in the nasopharyngeal or oropharyngeal swab.

Disease Severity Classification[5]

Mild: Simple upper respiratory tract infection (fever, cough, sore throat, nasal congestion,) devoid of any respiratory distress and maintaining saturation of more than or equal to 95% without oxygen support. All RTPCR positive patients with isolated symptoms of fever, lassitude, or anorexia were classified into mild disease.[5]

Moderate: Pneumonia with features of fast breathing and maintaining saturation of 90-94% on room air.

Severe: Severe pneumonia with signs of fast breathing and breathlessness and maintaining saturation less than 90% on room air. In patients with severe pneumonia, the presence of the following signs was considered a severe disease: central cyanosis, feed refusal, apathy, and seizures. Acute respiratory distress syndrome, sepsis, or septic shock were considered severe diseases.

Additionally, patients with isolated gastrointestinal (GI) manifestations were classified into mild (no dehydration) or severe (severe dehydration).[6] Those with isolated central nervous system symptoms such as seizures, altered sensorium, or meningitis were classified into severe categories.[6]

Abnormal laboratory parameters were classified as follows[7]: anemia: hemoglobin less than 11 gm/dL, leukopenia: total leucocyte count (TLC) less than 4,000/ µL; leucocytosis: TLC more than 11,000 cells/ µL; neutrophilia: absolute neutrophil count (ANC) more than7,700/µL; neutropenia: ANC less than 1,500/ µL; lymphopenia: for age less than 12months, absolute lymphocyte count (ALC) less than 3000/ µL, for age more than or equal to 12 months, ALC less than 1000/ µL; lymphocytosis: for age less than 10 years, ALC more than 8,000/µL, for age more than or equal to 10 years, ALC more than 4,000/ µL; hypoalbuminemia less than 3.5 g/dL; hyperbilirubinemia more than 1.0 mg/dL elevated urea more than 40 mg/dL; elevated creatinine more than 0.9 mg/dL; elevated ferritin more than 60 ng/mL (till 9 years) and more than 300 ng/mL (10–12 years); elevated procalcitonin 0.5 ng/mL, increased IL-6 more than7 pg/mL; increased D-dimer more than 1 mg/mL.

Statistical Analysis

The data obtained from the medical records were coded into MS Excel spread sheet and evaluated using MS Excel and Statistical Package for the Social Sciences 25 (SPSS). The categorical variables were denoted as percentages and analyzed using chi-squared test or Fisher's exact test as deemed fit. Continuous variables were denoted as mean with standard deviation (normal distribution) or median with interquartile ranges (non-normal distribution). The significant difference amongst non-normally distributed variables was analyzed using Mann–Whitney U tests or Kruskal–Wallis test as necessary. A *p*-value less than 0.05 was taken as statistically significant.

Results

A total of 205 admitted pediatric patients with RTPCR confirmed COVID-19 infection were screened for enrolment in this study. Patients with comorbidities other than cancer ($n = 59$) and those with inadequately recorded case sheets ($n = 49$) were excluded. Final analyses were performed on 97 patients out of which 31 children were classified into group A (children with cancer) and 66 into group B (children without any comorbidity). The study flow is shown in ►**Fig. 1**.

Cancer Type and Prevalence

The prevalence of cancer as a comorbidity in admitted pediatric patients with COVID-19 in this study was 15%. Overall, the median age of enrolled children was 5 years with an interquartile range of 2 to 11 years and 58.8% of them were males. The baseline characteristics, COVID-19 disease severity, and outcomes of the enrolled patients are detailed in ►**Table 1**.

The disease severity by type of cancer in the COVID-19 children is depicted in ►**Fig. 2**. Seventeen patients (54.8%) had hematological malignancies (HM; acute myeloid leukemia = 1, B-cell acute lymphoblastic leukemia = 11, T-cell acute lymphoblastic leukemia = 1, Hodgkin Lymphoma = 3, non-Hodgkin Lymphoma = 1), whereas 14 patients (45.1%) were diagnosed to have solid tumors (retinoblastoma = 3, Ewing sarcoma = 4, choroid plexus tumor = 1, hepatoblastoma = 1, juvenile ossifying fibroma = 1, Wilms tumor = 1, teratoma = 1, posterior fossa mass = 1, neuroblastoma = 1).

Chemotherapy Details

Out of 31 cancer patients, 14 children (45.1%) were receiving intensive chemotherapy, and 15 children (48.3%) were on nonintensive chemotherapy regimens. Two patients (6.45%) were not receiving any chemotherapy. Among the two patients, one was undergoing palliative care, while the other was yet to begin chemotherapy.

Disease Severity

Amongst the enrolled patients, 33% were asymptomatic, 46.4% had mild, 10.3% had moderate, and 10.3% had severe disease overall. Group-wise details are mentioned in ►**Table 1**.

Coinfections

Three patients (9.7%) with cancer had another coinfection (febrile neutropenia = 1, sepsis = 1, tubercular meningitis = 1), whereas 12 children without cancer (18.2%) were diagnosed to have another coinfection (disseminated tuberculosis = 2, pulmonary tuberculosis= 2, abdominal tuberculosis= 1, tubercular lymphadenitis= 1, tubercular meningitis= 1, liver abscess= 2, septic arthritis= 1, enteric fever= 1, scalp abscess = 1; $p = 0.37$).

Clinical Manifestations

Overall, the most common symptoms were fever (47.4%), cough (23.7%), and vomiting (16.5%). There was a significantly higher number of patients in group B who manifested with fever ($p = 0.001$) and vomiting ($p = 0.034$). Among group A,

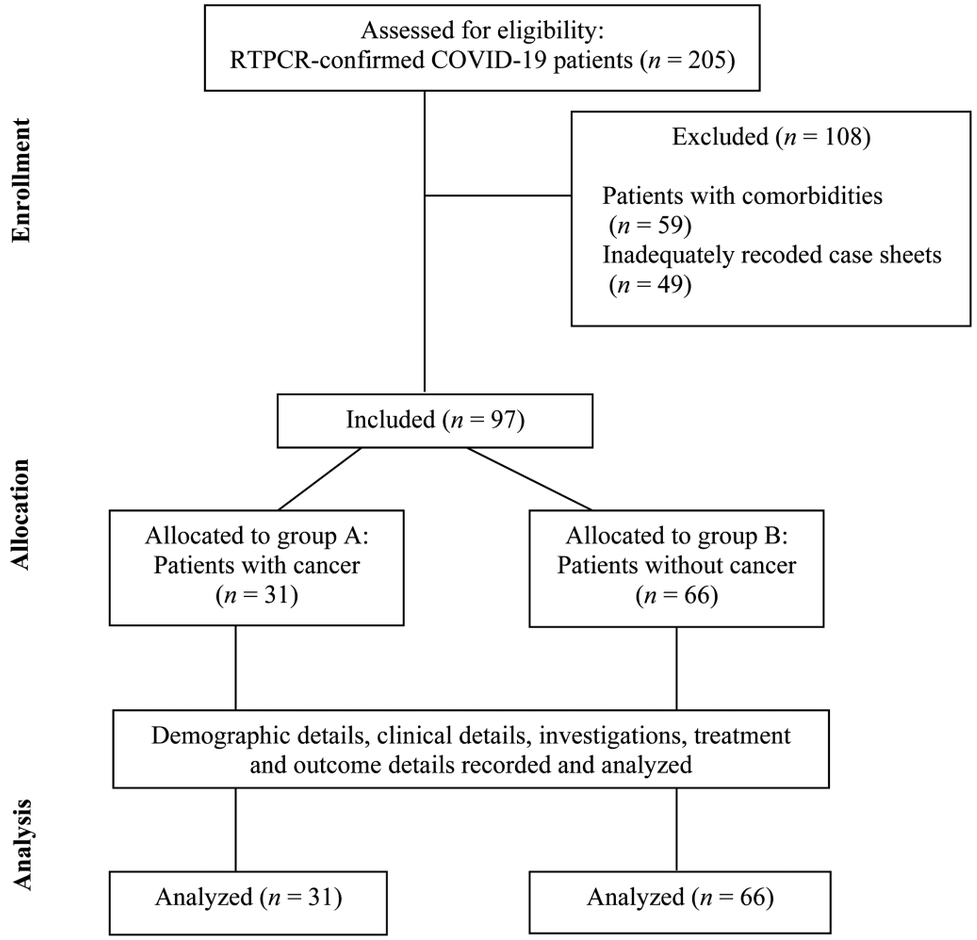

Fig. 1 Study flow. COVID-19, coronavirus disease 2019; RTPCR, reverse-transcriptase polymerase chain reaction.

most common symptom complex at presentation was respiratory (25.8%) followed by neurological (12.9%) as compared to group B patients which showed GI (48.5%) followed by respiratory manifestations (37.9%). Group B patients had significantly higher GI manifestations ($p = 0.0001$). There was no statistically significant difference concerning respiratory, neurological, bleeding, and skin manifestations. A comparison of symptoms and symptom complex is detailed in ►**Table 2**.

Laboratory Investigations

Group A had significantly a greater number of patients who had leukopenia ($p = 0.003$), neutropenia ($p = 0.003$), and lymphopenia ($p = 0.005$). There was no significant difference between the rest of the checked laboratory parameters between the two groups (►**Table 3**).

Radiological Investigations

Among group A, chest X-ray was done for 21 patients out of which 5 showed infiltrates and 1 showed hilar lymphadenopathy. Among group B, a chest X-ray was done for 23 patients, in which 8 showed infiltrates, 3 exhibited hilar lymphadenopathy, and 1 showed pleural effusion.

Oxygen Requirement

Only two patients (6.45%) in group A required oxygen (nasal prongs = 2), while eight patients (12.1%) required oxygen in group B (ventilator support = 1, high-flow nasal cannula = 1, nasal prongs = 2, simple mask = 3, oxygen hood =1; $p = 0.49$).

Mean Duration of Hospital Stay

The mean duration of hospital stay among group A was 11.6 ± 6.8 days as compared to 9.6 ± 5.4 days among group B ($p = 0.33$).

Outcome

The case fatality rate among cancer patients was 3.2% as compared to 1.5% in noncancer patients. However, there was no difference in mortality rate as both the groups had one death each. In both groups, the death was attributed to severe COVID-19 infection. There was no death due to progression of cancer or complications of chemotherapy, during the period of study. Among group A, the expired patient was a 12-month-old female child who was diagnosed to have sacrococcygeal teratoma with hepatic metastasis with severe COVID-19 pneumonia. While in group B, the

Table 1 Baseline characteristics, disease severity, and outcomes of enrolled patients ($N = 97$)

Parameter	Total patients ($N = 97$)	Patients with cancer (group A) ($n = 31$)	Patients without comorbidity (group B) ($n = 66$)	*p*-Value
Median age in years	5	6	5	
(IQR)	2–11	4–11	1.1–10.7	
Sex (%)				0.31
Male	57 (58.8)	21 (67.7)	36 (54.5)	
Female	40 (41.2)	10 (32.3)	30 (45.5)	
Underweight (%)	30 (30.9)	15 (48.4)	15 (22.7)	0.01
Severity of COVID-19 (%)				0.18
Asymptomatic	32 (33.0)	15 (48.4)	17 (25.7)	
Mild	45 (46.4)	12 (38.7)	33 (50.0)	
Moderate	10 (10.3)	2 (6.4)	8 (12.1)	
Severe	10 (10.3)	2 (6.4)	8 (12.1)	
Number of patients with coinfection (%)	15 (15.5)	3 (9.7)	12 (18.2)	0.37
Duration of hospital stay in days (mean ± SD)	10.2 ± 5.9	11.6 ± 6.8	9.6 ± 5.4	0.33
Outcome (%)				1.0
Death	2 (2.0)	1 (3.2)	1 (1.5)	
Discharge	95 (97.9)	30 (96.8)	65 (98.5)	

Abbreviations: COVID-19, coronavirus 2019; IQR, interquartile range; SD, standard deviation.

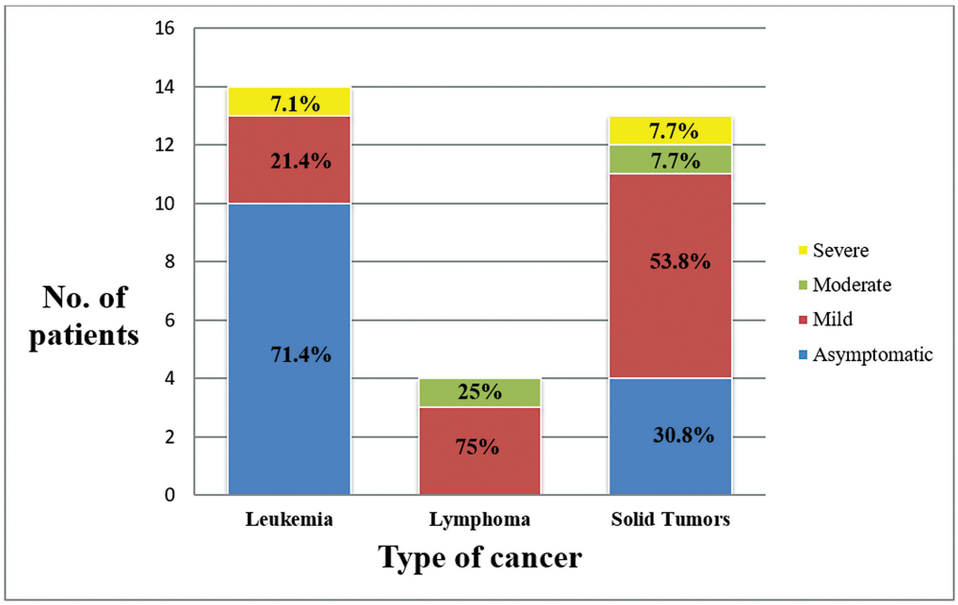

Fig. 2 Disease severity by type of cancer.

expired patient was a 9-year-old male child with tubercular meningitis stage-3 and multiorgan dysfunction.

Risk Factors

Risk factors for moderate-to-severe COVID-19 disease among cancer patients are detailed in ►**Table 4**. Poor nutritional status, higher cancer stage, and presence of coinfections seemed to be associated with moderate-to-severe COVID-19. However, these results were statistically not significant.

Discussion

To our knowledge, this is one of the few studies to directly compare the clinical, biochemical, radiological, and outcome profiles of COVID-19 infection in children with and without cancer.

In our study, we found that 15% of the hospitalized pediatric patients with COVID-19 had cancer as a comorbidity. A previously published meta-analysis showed the

Table 2 Pediatric COVID-19 symptoms and symptom complex at presentation

Parameter	Total ($N = 97$) *N* (%)	Patients with cancer (group A) ($n = 31$) *N* (%)	Patients without comorbidity (group B) ($n = 66$) *N* (%)	*p*-Value
Symptoms				
Fever	46 (47.4)	7 (22.6)	39 (59.1)	0.001
Cough	23 (23.7)	5 (16.1)	18 (27.3)	0.34
Coryza	10 (10.3)	3 (9.7)	7 (10.6)	1.0
Vomiting	16 (16.5)	1 (3.2)	15 (22.7)	0.034
Diarrhea	10 (10.3)	1 (3.2)	9 (13.6)	0.16
Pain abdomen	6 (6.2)	0 (0)	6 (9.1)	0.17
Anorexia	2 (2.0)	0 (0)	2 (3.0)	0.56
Lethargy	4 (4.1)	0 (0)	4 (6.1)	0.30
Excess irritability	6 (6.2)	2 (6.4)	4 (6.1)	1.0
Seizures	2 (2.0)	0 (0)	2 (3.0)	0.56
Headache	7 (7.2)	2 (6.4)	5 (7.6)	1.0
Fatigue	13 (13.4)	5 (16.1)	8 (12.1)	0.75
Bleeding manifestations	2 (2.0)	2 (6.4)	0 (0)	0.10
Rash	7 (7.2)	2 (6.4)	5 (7.6)	1.0
Symptom complex				
Respiratory manifestations	33 (34.0)	8 (25.8)	25 (37.9)	0.34
GI tract manifestations	34 (35.0)	2 (6.4)	32 (48.5)	0.0001
Neurological manifestations	19 (19.6)	4 (12.9)	15 (22.7)	0.38
Bleeding manifestations	2 (2.0)	2 (6.4)	0 (0)	0.10
Skin manifestations	7 (7.2)	2 (6.4)	5 (7.6)	1.0

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal.

worldwide prevalence of COVID-19 in adult patients with cancer to be around 4.6%.[8] Other studies have variably reported the prevalence of COVID-19 in patients with cancer to be between 2.6 and 11%.[8,9] Studies done in children hospitalized with COVID-19 in India have reported cancer as a comorbidity in as many as 7-15%.[1,10] The reasons for a high proportion of cancer as comorbidity in children with COVID-19 may be manifold. Due to the nature of their disease and related therapy, children with cancer are at high risk of developing viral infections.[11] Likewise, it is logical to expect higher infectivity of COVID-19 in children with cancer. At our center, we found an even higher proportion of children having cancer as comorbidity. Additional factors that may have contributed to this include a referral bias as our hospital is one of the few public sector hospitals in the area dealing with pediatric cancer patients. Moreover, our hospital was designated as an exclusive COVID-19 treating center during the pandemic; thus, all children with COVID-19 with any comorbidity were referred to us. Another reason for the difference in this prevalence may be the difference in admission criteria for COVID-19 children in various centers.

Overall, the median age, gender, and distribution of disease severity of the enrolled cohort were similar to the previously published literature.[3] However, children with cancer were significantly underweight as compared to children without cancer that may be due to their underlying disease or therapy-related anorexia leading to malnutrition.

In this study, a greater proportion of admitted pediatric cancer patients with COVID-19 had HM (54.8%) as comorbidity as compared to solid tumors (45.1%). This result corroborates with the data reported in the global registry which showed that among pediatric patients with COVID-19, 67.1% had HM, while only 32.9% had solid tumors.[12] It has been reported that patients with HM have a more severe course of COVID-19 as compared to solid tumors and consequently a higher hospitalization rate.[13] Patients with HM have been shown to have delayed seroconversion, prolonged viral shedding, higher viral load, and immune disturbance following COVID-19 infection compared to patients with solid tumors.[14,15] Furthermore, patients of COVID-19 with HM have been shown to have remarkably lower percentages of monocytes, double-positive T cells, natural killer cells, and B-cells.[16,17] These patients also have impaired CD4 T-cell and B-cell reaction to SARS-CoV-2 and lower levels of anti-COVID-19 antibodies in comparison to patients suffering from solid cancer.[18] All these factors are likely to contribute to higher hospitalization rates of children with COVID-19 with HM compared to those with solid tumors.

Table 3 Laboratory investigations of pediatric COVID-19 patients at presentation

Parameter	Proportion of children having abnormal values		
"N" observed/ "N" tested	Patients with cancer (group A) ($n = 31$)	Patients without comorbidity (group B) ($n = 66$)	*p*-Value
Anemia	15/23	17/27	0.88
Leucopenia	11/23	2/27	0.003
Leucocytosis	3/23	10/27	0.10
Neutropenia	9/23	1/27	0.003
Neutrophilia	2/23	9/27	0.045
Lymphopenia	11/23	3/27	0.005
Lymphocytosis	1/23	2/27	1.0
Neutrophil: lymphocyte ratio >3.03	4/23	8/27	0.34
Thrombocytopenia	10/23	9/27	0.65
Azotemia	1/17	5/21	0.20
Hyperbilirubinemia	3/19	5/20	0.69
Transaminitis	11/21	11/20	0.89
Hypoalbuminemia	5/13	6/11	0.70
Raised INR	2/4	5/11	1.0
Raised D-dimer	3/5	6/6	0.18
Raised interleukin-6	2/2	4/5	1.0

Abbreviations: COVID-19, coronavirus disease 2019; INR, international normalized ratio.

Table 4 Risk factors for moderate-to-severe COVID-19 disease in cancer patients

Risk factors	Asymptomatic or mild disease $N = 27$	Moderate or severe disease $N = 4$	*p*-Value
1. Age • <2 years • 2–10 years • >10 year	 1 (3.7%) 16 (59.3%) 10 (37%)	 2 (50%) 1 (25%) 1 (25%)	0.06
2. Cancer type • Solid tumors • Hematological	 11 (40.7%) 16 (59.3%)	 2 (50%) 2 (50%)	0.56
3. Cancer stage (solid tumors and lymphomas) • Stage 1 • Stage 2 • Stage 3 • Stage 4	 2 (15.3%) 1 (7.7%) 5 (38.5%) 5 (38.5%)	 1 (33.3%) 0 0 2 (66.7%)	0.49
4. Cancer risk stratification (leukemias) • Standard risk • Intermediate risk • High risk	 3 (21.4%) 7 (50%) 4 (28.6%)	 0 0 1 (100%)	0.53
5. Recent chemotherapy	21 (77.7%)	2 (50%)	0.55
6. Neutrophil: lymphocyte Ratio >3.03	3/19 (15.8%)	2/4 (50%)	0.19
7. Neutropenia	8 (42.1%)	1 (25%)	0.63
8. Presence of coinfection	2 (7.4%)	1 (25%)	0.35
9. Underweight	12 (44.4%)	3 (75%)	0.33

Abbreviation: COVID-19, coronavirus disease 2019.

In terms of severity, most of the patients in both groups were either asymptomatic or had a mild disease that is consistent with data from other studies and larger Registries.[3,12] Higher proportion of patients without cancer had severe disease (12.1%) as compared to patients with cancer (6.2%). However, this difference was statistically nonsignificant. More severe disease in noncancer patients may be explained by the pathophysiology of COVID-19 that involves the host's immune response to the viral antigen leading to cytokine-induced tissue damage.[19] Most of the cancer patients are immunosuppressed, rendering them incapable of mounting an adequate immunological response to infection and hence making them less likely to manifest symptoms.

In both groups, fever, cough, and fatigue were common symptoms among patients. However, noncancer group had significantly a greater number of patients who presented with fever and GI tract manifestations. It has been shown that SARS-CoV2 enters host cells via the angiotensin-converting enzyme receptor 2 and transmembrane protease serine 2 that are found in the type II alveolar cells of the lung, in enterocytes of colon and ileum, and in the glandular cells of the stomach, duodenum, and rectal epithelium.[20] Thereafter, COVID-19 invaded cells release many chemokines and inflammatory mediators causing a cytokine storm and aggregation of immune system cells in the GI tract.[21] Patients with cancer often have chemotherapy-induced mucositis.[22] This may interfere with the entry of the virus into the GI tract. Also as previously stated, patients with cancer are unable to mount a cytokine storm in response to COVID-19 due to their weakened immune responses. These two factors may be responsible for a low prevalence of GI manifestations in children with cancer.

In our study, 47.8% of children with cancer had lymphopenia and 39.1% had neutropenia. This is comparable to the global data which shows that 41.3% of pediatric cancer patients had lymphopenia and 32.3% had neutropenia.[12] In terms of laboratory parameters, COVID-19-infected children with cancer had significantly more leukopenia ($p = 0.003$), neutropenia ($p = 0.003$), and lymphopenia ($p = 0.005$). It has already been shown in previous studies that the most common hematological manifestation of COVID-19 among children is leucopenia.[23] Pediatric cancer patients with COVID-19 may be prone to develop severe leukopenia due to their underlying immunosuppressed state, chemotherapy, and also due to the additive effect of COVID-19.

Both groups received similar treatment as per the prevailing Indian Council of Medical Research protocol. There was no difference with respect to oxygen requirement and outcome. Mean period of hospital stay among cancer patients was higher (11.6 ± 6.8 days) as compared to noncancer patients (9.6 ± 5.4 days), although this difference was statistically non-significant. A higher mean duration of hospital stay among cancer patients reflects increased morbidity in them. As demonstrated in previously published literature, patients with cancer have delayed seroconversion, prolonged viral shedding, and a higher viral load following COVID-19 infection.[14] Since our discharge criteria included RTPCR negativity, hence patients with cancer had a longer mean duration of hospital stay as they took a longer time to become RTPCR negative.

The case fatality rate among cancer patients was 3.2% as compared to 1.5% in noncancer patients. The mortality rate among pediatric cancer patients in this study is similar to that reported in the Global Registry of COVID-19 in childhood cancer (3.62%). Similar to our study, a greater mortality risk in pediatric cancer patients has also been reported in a systematic review.[24] However, most studies have not reported COVID-19 as an exclusive cause of death in cancer patients. An increased risk of mortality among cancer patients may be attributable to the fragile health status of the individuals due to underlying disease, the type and stage of cancer, ongoing immunosuppressive therapy, and poor nutrition.[25]

We also tried to explore the risk factors for moderate-to-severe COVID-19 among cancer patients in terms of cancer type, staging/risk stratification, intensity of chemotherapy, neutropenia, nutritional status, and presence of coinfections. In our study, chemotherapy was continued for all cancer patients except two patients among which one was under palliation and another was a sick newly diagnosed cancer patient. There was no significant difference observed in terms of severity or outcome based on recent chemotherapy use. Similar to our study, recent chemotherapy was not associated with worse clinical outcomes in many other studies including adult cancer patients with COVID-19.[13,26] Contrary to our results, few studies from adult cancer patients who had COVID-19 show that recent chemotherapy was associated with poor clinical outcome.[27] This may be due to the older age group of the enrolled cohort and a higher incidence of other comorbidities such as hypertension and type 2 diabetes in adult patients. However, it is well known that interruptions or delays in starting therapy lead to relapses and an increase in cancer-related mortality among pediatric oncology patients.[28] Also due to a low mortality rate among children with COVID-19, it has been suggested to continue cancer-related therapy in them.[3]

Our results show that among cancer patients with moderate-to-severe COVID-19 disease, a higher proportion of children was less than 2 years of age, was underweight, was in the advanced stage of their cancer, and had the presence of co-infections. Similar to our results, a previously published meta-analysis revealed that infants were at higher risk for severe COVID-19 and at higher risk for admission to critical care units.[29] It has been suggested in previous studies that COVID-19-induced cytokine storm can exacerbate malnutrition by causing muscle protein breakdown and albumin consumption. Malnutrition has also been considered as a risk factor for severe COVID-19 in children.[30] Another risk factor for severe COVID-19 is the presence of a coinfection. Children with coinfections often have a higher need for supportive therapy and have a higher duration of hospital stay.[31] However, these risk factors were not found to be statistically significant. Further large-scale studies are required to investigate these risk factors.

However, ours is one of the few studies to directly compare clinical characteristics and outcomes of pediatric COVID-19-infected patients with and without cancer while exploring risk factors for severe COVID-19 disease among pediatric cancer patients. It has certain limitations as well like small sample size and inability to follow up patients who were discharged. Another limitation is that the following data represents the inpatient population only and misses out on the disease characteristics of outpatient population.

Conclusion

Cancer is a significant comorbidity among pediatric patients with COVID-19. Most children with cancer have asymptomatic to mild symptoms of COVID-19. However, their case fatality rate is higher than in children without cancer. Fever and GI tract manifestations were found to be significantly less common among pediatric cancer patients. Among COVID-19 infected children with cancer, younger age, under-nutrition, advanced stage of cancer, and presence of coinfections predispose to the development of severe COVID-19. It may be reasonable to continue chemotherapy in COVID-19 infected children with cancer except those with identified risk factors for severe disease.

Authors' Contributions

P.K.S. conceptualized, drafted, and critically appraised the manuscript.

V.K. helped in data collection, reviewed literature, and drafted the manuscript. A.G. conceptualized, reviewed literature, and critically appraised the manuscript.

M.D., P.M., and Divyanshi helped in data collection and review of literature.

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Ethical Approval

Ethical approval was taken from the Institute Ethics Committee prior to commencement of this work.

Patient Consent

None declared.

Conflict of Interest

None declared.

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Docetaxel, Oxaliplatin with Capecitabine (TEX Regimen) in Metastatic Gastric and Gastroesophageal Adenocarcinoma: A Prospective Single-Arm Observational Study from a Tertiary Cancer Center in Kashmir

Sanudev Sadanandan Vadakke Puthiyottil[1] Faisal R. Guru[2] Syed Nisar Ahmad[2] Mir Ab Wahid[3] Choh Naseer Ahmad[4] Lone Mohammad Maqbool[5] Mohammad Hussain Mir[2] Banday Saquib Zaffar[2] Hashim Ismail Kunju[6] Bhat Gul Muhammed[2]

[1] Department of Medical Oncology, Government Medical College, Kozhikode, Medical College PO, Kozhikode, Kerala, India
[2] Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India
[3] Department of Surgical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India
[4] Department of Radiodiagnosis, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu & Kashmir, India
[5] Department of Radiation Oncology, Government Medical College, Baramulla, Kant Bagh, Baramulla, Jammu & Kashmir, India
[6] Department of Medical Oncology, Travancore Medical College, Thattamala PO, Kollam, Kerala, India

Address for correspondence Sanudev Sadanandan Vadakke Puthiyottil, MBBS, DNB, MNAMS, DM, DrNB, Department of Medical Oncology, Government Medical College, Kozhikode, Medical College PO, Kozhikode, Kerala, 673008, India (e-mail: drsanudev@gmail.com).

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Abstract

Background Metastatic gastric and gastroesophageal adenocarcinoma (MGGEAC) is a challenging disease with limited treatment options. The Taxotere, Eloxatin, and Xeloda (TEX) regimen has shown promising results in several clinical trials. There exists a dearth of data pertaining to the efficacy and tolerance of the treatment approach in the populace of Kashmir.

Materials and Methods This study was performed at the Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir. Patients with MGGEAC received treatment with biweekly TEX regimen that included docetaxel 50 mg/m^2-D1, oxaliplatin 85 mg/m2-D1, and capecitabine 1250 mg/m^2/day, twice daily orally, for 14 days. The effectiveness of the regimen was assessed based on the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), along with the prognostic factors, safety, and tolerability of the regimen.

Results The ORR was 63.5% after four cycles. The median PFS and OS were 9.1 and 13 months, respectively. Univariate and multivariate analysis showed that a higher number of sites of metastases is associated with poor PFS. The TEX regimen was well tolerated. The most observed grade 3 to 4 toxicities were neutropenia (36.7%), anemia (20%), fatigue (20%), and febrile neutropenia (16.7%).

Conclusion Using the TEX regimen in MGGEAC showed better response rates and a slightly longer PFS. A higher number of sites of metastases is a poor prognostic factor in MGGEAC, as seen in our study. The toxicity profile shows that the regimen is tolerable. We recommend a randomized controlled study comparing CapeOx with TEX to test this regimen further.

Keywords
- gastric cancer
- TEX regimen
- docetaxel
- oxaliplatin
- capecitabine
- prognostic score

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Introduction

Globally, gastric cancer accounts for 5.7% of new cases (5th most common) and 8.7% of deaths due to cancer per year (3rd most common).[1] Nonmetastatic gastric and gastroesophageal junction adenocarcinoma are managed by combined therapeutic modality (surgery, chemotherapy, and radiotherapy).[2] The 5-year overall survival (OS) of localized gastric cancer is 31% that has remained stable over the last three to four decades.[3] Metastatic disease has an extremely poor prognosis with a 5-year OS of less than 5%.[2] According to Globocan 2020, gastric cancer is the sixth most common cancer in India. India has a yearly estimate of 68,000 new cases of gastric cancer, which leads to around 50,000 deaths.[4,5] Kashmir has a high incidence of gastric cancer (4th most common), accounting for 7.6% of all cancers and it exceeds the national average in India.[6,7] The metastatic disease is managed primarily by palliative intent chemotherapy with surgery and radiotherapy reserved for selected indications. Systemic chemotherapy results in better response rates, slightly prolonged survival, and improved quality of life.[8]

Immunotherapy, either alone or in combination with chemotherapy, has now replaced chemotherapy as the first-line treatment for metastatic gastric and gastroesophageal adenocarcinoma (MGGEAC) in Western countries.[9–11] However, due to its high cost, chemotherapy remains the standard of care for patients in low-middle income countries like India. Platinum and 5-fluorouracil (5-FU)/analogue combination is considered the gold standard first-line regimen in this setting. The DCF regimen (docetaxel, cisplatin, 5-FU) slightly improves response rate and survival, but with higher toxicity, it provides an additional option for physically fit patients.[12,13] To reduce the toxicity, while maintaining the efficacy, different regimens were tried. One such regimen referred to as the fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) regimen has reported improved ORR with an acceptable toxicity profile.[14–16] The modification of this regimen with the substitution of 5-FU with capecitabine (Taxotere, Eloxatin, and Xeloda [TEX] regimen) has been tested by many investigators.[8,14,17,18]

In Kashmir, the diagnosis and treatment of MGGEAC are often challenging due to limited healthcare resources; however, efforts are being made to improve the management of these cancers in the region, including the development of specialized cancer centers and increased access to screening and diagnostic services.[6] Overall, MGGEAC represents a significant burden of disease in Kashmir, and improving awareness, prevention, and treatment strategies for these cancers in the region is a critical public health priority.

The aim of our prospective observational study is to assess the effectiveness, safety, and tolerability of the TEX regimen in treating MGGEAC in the Kashmir region. The study seeks to assess the ORR, PFS, and OS of patients with MGGEAC-treated with this regimen. This information can guide clinical practice and contribute to evidence-based treatment guidelines for patients with MGGEAC.

Materials and Methods

Patient Selection

This prospective observational study was conducted in MGGEAC patients registered at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu & Kashmir from November 2017 to December 2018. Patients who had been newly diagnosed with MGGEAC or were developing metastatic disease after receiving definitive treatment with radical surgery and chemoradiation, and who fulfill the following inclusion criteria, were included in the study. Inclusion criteria were (1) age more than 18 years and less than 70 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status less than 2, (3) no prior palliative chemotherapy, and (4) measurable disease and sufficient renal, hepatic, and bone marrow function. However, patients with uncontrolled medical illness, psychiatric illness, and pregnant or lactating women were excluded from the study.

Study Design and Treatment Protocol

Eighty-five patients were enrolled in the study. History with clinical examination was performed before enrolment. Baseline complete blood count, blood chemistries, electrocardiogram, and serum tumor markers (Carcinoembryonic antigen (CEA), CA19–9) were analyzed. All the enrolled patients underwent Oesophagogastroduodenoscopy (OGD) scopy and histopathological confirmation of disease. A contrast-enhanced computed tomography (CECT) scan of the thorax, abdomen, and pelvis was performed 2 weeks before starting the treatment. After enrolment, patients received the TEX regimen as follows: docetaxel 50 mg/m^2 (1 hour infusion), followed by oxaliplatin 85 mg/m^2 (2 hours infusion) on day 1, and capecitabine 1250mg/m^2/day twice daily for 14 days by oral route. The cycle was repeated every 14 days. Administration of prophylactic treatments, such as antiemetics and corticosteroids, was based on standard recommendations and physician assessment. Granulocyte colony-stimulating factor was used for secondary prophylaxis. Treatment continued as long as the disease progressed, there was unacceptable toxicity, or the patient refused treatment. Dose modifications were performed according to published guidelines.

Assessment of Response and Tolerability

The patients were evaluated for their response to chemotherapy after each treatment cycle. They underwent a CECT scan after completing four cycles of chemotherapy or earlier if the physician deemed it necessary. The scans were evaluated by at least two observers and confirmed by an independent radiologist. The assessment of radiological response was determined using the RECIST 1.1 criteria.[19] Results were stratified as complete response (CR), partial response (PR), stable disease, or progressive disease. The period of PFS was calculated from the commencement of chemotherapy until the first indication of disease progression or death. In the absence of any such events, the last follow-up date was considered as the end-point for PFS measurement. The OS period was calculated from the

beginning of chemotherapy until the patient's death due to any cause, or until the last follow-up date if the patient was still alive. Toxicity assessments were conducted in each cycle using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. OS and PFS were further evaluated with univariate and multivariate analyses. A prognostic score proposed by Chau et al, which includes ECOG performance status more than or equal to 2, SAP levels more than 100, presence of peritoneal metastases, and presence of liver metastases were calculated and patients were divided into three groups (no risk factors, one or two risk factors, ≥3 risk factors).[20]

Statistical Analysis

The utilization of descriptive statistics, such as median, frequency, and percentage, was employed to depict categorical variables encompassing age, gender distribution, treatment, and response to treatment. All patients were assessed for the ORR, which was expressed as a percentage and considered as the primary end-point. The secondary endpoints were PFS, OS, and safety. PFS and OS were evaluated using Kaplan–Meier survival methods, whereas univariate and multivariate comparisons analysis was done by log-rank test. IBM SPSS version 20.0 (SPSS Inc. Chicago, Illinois, United States) was used for statistical analyses.

Ethics

The Ethical Standards by the Institutions and National Research Committee, Helsinki Declaration of 1964, and subsequent amendments or equivalent standards have been complied with for all procedures undertaken in this study. The study was approved by the Institutional Ethics Committee of SKIMS, Soura, Jammu & Kashmir (Protocol number 65/2018 dated 07.07.2018), and conducted in compliance with protocol after written informed consent to participate in the study was taken from all patients before enrolment.

Results

Patient Demographics

The study enrolled a total of 85 patients between November 2017 and December 2018. The data from 85 patients diagnosed with gastric ($n = 61$) and gastroesophageal junction ($n = 24$) adenocarcinomas who underwent treatment with the TEX regimen was analyzed. Her2 neu tested positive in 8 out of 38 biopsy samples (►**Table 1**).

Efficacy

Median number of chemotherapy cycles delivered was eight cycles (1–15). After completion of four cycles of the TEX regimen, we evaluated a total of 85 patients and found that one of them achieved a CR, which corresponds to a percentage of 1.2%. Additionally, 53 patients showed a PR, representing a percentage of 62.4%. Thus, ORR was 63.5% (54/85). In 21 patients (24.7%), the disease remained stable. In addition, only 10 patients (11.8%) showed progressive disease (►**Table 2**). Maintenance capecitabine was received by 32 patients (37%) after getting a favorable response on the TEX regimen. Upon

Table 1 Patient dispositions and demographics

Baseline characteristics	No. of patients (percentage, if required)	
Total no. of patients evaluated	85	
Median age	60 (26–70 years)	
	≤ 60 years	55 (64.7%)
	> 60 years	30 (35.3%)
Sex	Male	70 (82.4%)
	Female	15 (17.6%)
ECOG PS	≤1	75 (88.2%)
	≥2	10 (11.8%)
Location of primary	GE junction/proximal	30 (35.3%)
	Body	24 (28.2%)
	Distal	27 (31.8%)
	No localization	4 (4.7%)
Prior surgery and chemoradiation	No	79 (92.9%)
	Yes	6 (7.1%)
Site of metastases	Nonregional node	38 (44.7%)
	Liver	36 (42.4%)
	Peritoneum	28 (32.9%)
	Lung	7 (8.2%)
No of sites of metastases	1	44 (51.8%)
	≥2	41 (48.2%)
Histology	Adeno	69 (81.2%)
	Signet	16 (18.8%)
Her2Neu (by FISH/IHC)	Positive	8 (9.4%)
	Negative	30 (47.1%)
	Not performed	47 (55.3)
Chau prognostic group	No risk factor	9 (10.6%)
	1/2 risk factor	69 (81.2%)
	3/4 risk factor	7 (8.2%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry.

Table 2 Tumor response to Taxotere, Eloxatin, and Xeloda (TEX) regimen after completion of four cycles

Number of eligible patients	85
No of patients performed response assessment scan	78
Radiologic response	Frequency (%)
Complete response	1 (1.2)
Partial response	53 (62.4)
Stable disease	21 (24.6)
Progressive disease	10 (11.8)
Overall response rate	54 (63.5)
Clinical benefit rate	75 (88.2)

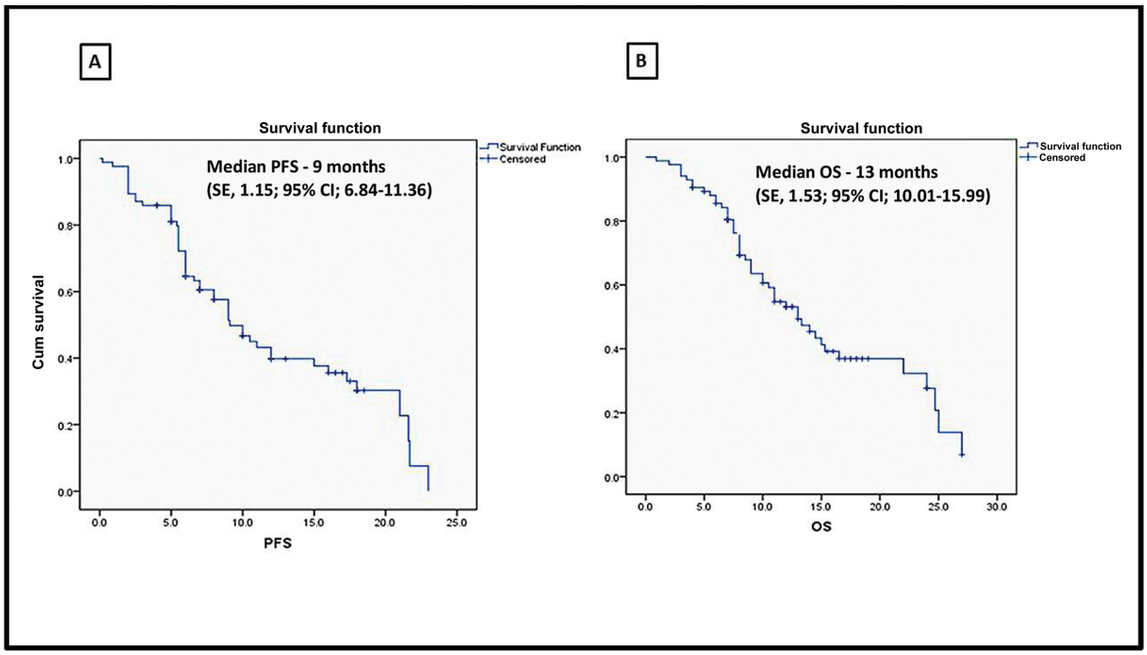

Fig. 1 Kaplan–Meier curve for progression-free survival (PFS) (**A**) and overall survival (OS) (**B**). CI, confidence interval; SE, standard error.

progression, 62% of patients (33/53) received second-line chemotherapy. The most common second-line chemotherapy used was single-agent irinotecan (70%).

Having observed clinical responses of the tumor against the TEX regimen after four cycles, next, we evaluated PFS and OS as secondary end-points of our study. The median follow-up period was 10.5 (3–27) months. The duration of median PFS was noted to be 9.1 months (standard error: 1.15, 95% confidence interval [CI]: 6.84–11.23 months). Similarly, the median OS noted was 13 months (standard error: 1.53; 95% CI: 10.01–15.99 months; ►**Fig. 1**).

Univariate Analysis of OS and PFS with Prognostic Factor Score

In the univariate analysis, a single metastatic site had shown better progression-free survival (PFS), which retained significance in multivariate analysis (8.5 vs. 2.7 months; *p*-value 0.035). ECOG performance status, presence of nonregional

Table 3 Univariate and multivariate analyses of PFS

Characteristics	PFS (months)	*p*-Value (univariate analysis)	*p*-Value (univariate analysis)
Age		0.338	0.986
≤ 60	6.271		
> 60	4.987		
Gender		0.681	0.731
Male	5.999		
Female	5.259		
ECOG PS		0.011	0.175
0.1	10.026		
≥2	1.232		
Location of primary		0.927	0.578
GE junction/ Proximal	6.134		
Body	6.020		
Distal	6.367		

(*Continued*)

Table 3 (*Continued*)

Characteristics	PFS (months)	*p*-Value (univariate analysis)	*p*-Value (univariate analysis)
No localization	3.996		
Histopathological reports		0.848	0.140
Adeno	5.820		
Signet ring cell	5.438		
TB		0.588	0.418
N	6.181		
> ULN	5.078		
ALP		0.126	0.233
< 100 U/L	7.015		
> 100 U/L	4.243		
Presence of nonregional nodal metastases		0.043	0.345
Yes	7.678		
No	3.580		
Presence of peritoneal metastases		0.149	0.324
Yes	3.672		
No	7.587		
Presence of liver metastasis		0.632	0.234
Yes	5.109		
No	6.150		
No. of sites of metastases		0.045	0.035 (HR: 0.017, 95% CI: 0.000–0.759)
1	8.525		
≥2	2.734		
Chau prognostic score		0.244	0.117
No risk factors	2.065		
1,2 risk factors	4.525		
3,4 risk factors	10.298		
Capecitabine maintenance		0.004	0.857
Yes	7.776		
No	3.483		

Abbreviations: ALP, Alkaline phosphatase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GE, gastroesophageal junction; HR, hazard ratio; PFS, progression-free survival; TB, total bilirubin; ULN, upper limit of normal.

lymph nodal disease, and capecitabine maintenance had significant effects on PFS in univariate analysis, whereas none of these factors showed significance in multivariate analysis. For OS, capecitabine maintenance had shown significance in univariate analysis, but not shown significance in multivariate analysis (►**Tables 3** and **4**).

Assessment of Safety Profile

Next, we checked for TEX regimen safety and tolerability. Neutropenia was the most observed grade ¾ toxicity (36.7%). Anemia and fatigue were the second most common toxicity, affecting 20% of the participants. Febrile neutropenia and sensory neuropathy were reported in 16.7 and 8.3%, respectively. There were no deaths related to the treatment. Twenty-four of the patients required dose reductions (►**Table 5**).

Discussion

Systemic treatment in MGGEAC aimed to improve survival, pain control, quality of life, and nutritional intake. The Cochrane meta-analysis[13] showed that systemic chemotherapy improves median survival and response rate compared with placebo. The combination chemotherapy regimen is superior to single-agent chemotherapy in terms of survival

Table 4 Univariate and multivariate analyses of OS

Characteristics	OS (months)	*p*-Value (univariate analysis)	*p*-Value (multivariate analysis)
Age		0.479	0.341
≤ 60	7.760		
> 60	6.689		
Gender		0.953	0.344
Male	7.284		
Female	7.164		
ECOG PS		0.053	0.111
0,1	10.996		
≥2	3.453		
Location of primary		0.992	0.760
GE junction/proximal	6.834		
Body	7.220		
Distal	7.633		
No localization	7.209		
Histopathological reports		0.486	0.147
Adeno	8.014		
Signet ring cell	6.434		
TB		0.670	0.109
N	6.715		
> ULN	7.733		
ALP		0.726	0.826
< 100 U/L	7.579		
> 100 U/L	6.869		
Presence of nonregional nodal metastases		0.088	0.290
Yes	9.183		
No	5.265		
Presence of peritoneal metastases		0.471	0.124
Yes	6.126		
No	8.322		
Presence of liver metastasis		0.987	0.813
Yes	7.244		
No	7.204		
No. of metastases		0.080	0.312
1	10.209		
≥2	4.239		
Chau prognostic score		0.851	0.280
No risk factors	6.215		
1,2 risk factors	6.569		
3,4 risk factors	8.888		
Capecitabine maintenance		0.001	0.874
Yes	10.064		
No	4.384		

Abbreviations: ALP, Alkaline phosphatase; ECOG PS, Eastern Cooperative Oncology Group performance status; GE, gastroesophageal junction; OS, overall survival; TB, total bilirubin; ULN, upper limit of normal.

Table 5 Adverse events

Toxicity	Any grade Number (%)	Grade 3 and 4 Number (%)
Hematological		
Neutropenia	31 (51.7%)	22 (36.7%)
Anemia	35 (58.33)	12 (20%)
Thrombocytopenia	17 (28.3%)	8(13.3%)
Febrile neutropenia (Grade 3 and 4 only)	–	10 (16.7%)
Nonhematological		
Fatigue	35 (58.3%)	12 (20%)
Sensory neuropathy	17 (28.3%)	5 (8.3%)
Diarrhoea	17 (28.3%)	4 (6.7%)
Mucositis	12 (20%)	4 (6.7%)
Hand foot syndrome	24 (40%)	4 (6.7%)
Anorexia	24 (40%)	3 (5%)
Nausea and vomiting	18(30%)	3 (5%)

and response rate with slightly increased toxicity.[21] There is no ideal first-line chemotherapy regimen, which could be either a doublet of a platinum agent with 5-FU/analogue, or a triplet of docetaxel combined with platinum and 5-FU/analogue. The selection is based on patient performance status, general health, comorbid illnesses, and patient preference.[22]

Docetaxel-based triplet regimens for advanced gastric cancer have become more common following the results of the V-325 trial of Van Cutsem et al 2006, which concluded that the use of DCF resulted in improved clinical outcomes and survival compared with only CF regimen,[14] but with higher frequency of adverse events (82% severe neutropenia, 29% febrile neutropenia and 49% severe gastrointestinal adverse events).

To reduce the toxicity of the DCF regimen, while maintaining its efficacy, researchers introduced a modified DCF regimen.[23–25] Another approach was to substitute cisplatin with oxaliplatin and 5-FU with capecitabine, which is called TEX regimen.[14,18] A comparison of the REAL-2 meta-analysis and ML17032 trial has revealed that capecitabine-based combinations offer improved OS when compared with 5-FU.[26] Al-Batran et al data showed decreased toxicity with oxaliplatin compared with cisplatin-based chemotherapy.[27]

A trial using the FLOT regimen[15] for MGGEAC reported an ORR of 57.7%, median PFS, and OS of 5.2 and 11.1 months, respectively. Grade 3/ 4 toxic effects were neutropenia (48.1%), leukopenia (27.8%), diarrhea (14.8%), fatigue (11.1%), and febrile neutropenia in 3.8%.

According to Srinivasalu et al,[28] ORR, 1-year PFS, and higher-grade toxicities were 52, 60, and 33%, respectively, in the FLOT group. Febrile neutropenia and thrombocytopenia were the most common toxicities. Another trial[29] concluded that the docetaxel, oxaliplatin, and 5-fluorouracil regimen (docetaxel + FOLFOX 7) provided a high response rate (72%) at the cost of increased toxicity (72% grade ¾).

Stein et al[18] conducted a study which revealed that the TEX regimen resulted in an overall response rate (ORR) of 43%. The study also found that the median PFS was 6.9 months, and the OS was 13 months. The most common higher grade toxicities were diarrhea (30%), nausea/vomiting, and infections.

A study conducted by Tata Memorial Hospital in Mumbai, India, analyzed the TEX regimen in MGGEAC. The ORR was 55.2%, and a clinical benefit rate was 80.8%. The median event-free survival was 6.34 months and the median OS was 15.3 months.[8] The most common higher grade adverse events were hand-foot syndrome (22.5%), neutropenia (19.2%), diarrhea (17.7%), anemia (9.6%), and neuropathy (7.2%).

Van Cutsem et al[14] randomly assigned patients with MGGEAC into three arms—TE, TEF, and TEX. ORR, median PFS, and median OS in the TEX arm were 25.6%, 5.55 months, and 11.30 months respectively. Febrile neutropenia was reported in 9% (TEX) of patients. Other toxicities were similar across the arms.

Our study is prospective, and to the best of our knowledge, it is the largest study to feature the TEX regimen in the region of Kashmir. We reported a higher ORR (63.5%) and better median PFS (9.1 months) in comparison with published literature. Median OS (13 months) was comparable.[8,14,15,18,28,29] Single site of metastases had shown better PFS in our study.

Neutropenia and anemia of grade ¾ were noticed in 36.7 and 20% of patients, respectively. Additionally, only 16.7% of patients had febrile neutropenia. These toxicities are comparable with other studies of FLOT and TEX regimens and much lesser compared with the DCF regimen. Additionally, the incidence of nonhematological toxicities was lower compared with the modified DCF regimen[23,24] and was comparable with other studies of FLOT and TEX regimen.[8,14,15,18,28,29] These findings suggest that the TEX regimen may be associated with a lower risk of certain toxicities, making it a potentially viable treatment option for patients with MGGEAC.

Merits of our study were prospective nature, real-world setting, adequate patient numbers, daycare delivery of chemotherapy, avoidance of peripherally inserted central catheter line and its complications, lesser toxicity, and better response rates. This is the first study from Jammu and Kashmir, supporting the use of the TEX regimen.

The limitations of the study were primarily observational nature, shorter follow-up, and no comparison arm. We did not use trastuzumab in this study because it is not combined with three-drug regimens in other trials.

Conclusion

In MGGEAC, the TEX regimen gives superior response rates and numerically higher PFS. A higher number of sites of metastases is a poor prognostic factor in MGGEAC, which has been seen in our study. The trial needs a longer follow-up for updated results, and we recommend a randomized controlled study comparing CapeOx with TEX to test this regimen further.

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Conflict of Interest
None declared.

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Clinical Benefit and Safety of Palbociclib in Hormone Positive Breast Cancer with Visceral Metastasis: Real-World Experience from a Tertiary Cancer Center

Sandeep K. S.[1,2] Sandhya Appachu[1] Ravi B. Diwaker[1] Sai Vivek[1] Vijai V.S. Simha[1]

[1] Department of Medical Oncology, Sri Shankara Cancer Hospital and Research Centre, Bengaluru, Karnataka, India
[2] Nandadeepa cancer clinic, raichur, Karnataka, India

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Address for correspondence Sandeep K. S., MD, DrNB (Medical Oncology), Sri Shankara Cancer Hospital and Research Centre, Shankara mutt premises Shankar Puram, Basavanagudi, Bengaluru 560004, Karnataka, India (e-mail: sandeepksrt15@gmail.com).

Abstract

Introduction Palbociclib, the first CDK4/6 inhibitor, has shown promising results in phase III clinical studies by enhancing the efficacy of endocrine therapy (ET) in HR+/HER2– advanced breast cancer. However, real-world data on its use in patients with visceral metastatic disease are limited. We aimed to assess the effectiveness and tolerability of palbociclib in this high-risk population across different lines of treatment.

Materials and Methods Patients with hormone-positive metastatic breast cancer who received palbociclib with ET between 2015 and 2021 were grouped into skeletal and visceral metastatic disease. Visceral metastatic diseases were subclassified into lung, liver, and brain metastatic diseases. All subgroups were analyzed for progression-free survival (PFS), toxicity, and prognostic factors. Subgroups were compared using the chi-square test, and survival analyses were done using the Kaplan–Meier test.

Results Among 100 patients who received palbociclib, 70 had progressed on previous ET. The common metastatic site was bone (56%), followed by lung (24%), liver (18%), and brain (2%). With a median follow-up of 37 months, the median PFS of the overall population was 24 months: bone metastasis 27 months, lung 25 months, liver 12 months, and brain 4 months. Weak hormone positivity, ET-resistant metastatic patients, and high grade were associated with poorer responses. The common side effects were neutropenia (40%), anemia (35%), thrombocytopenia (15%), and hepatotoxicity (10%). Three percent of patients discontinued treatment due to toxicity.

Conclusion Palbociclib with ET showed improved PFS and safety in visceral metastatic disease, comparable to randomized controlled trials. However, further studies are required to evaluate its efficacy in extensive visceral metastatic disease and previously heavily treated patients.

Keywords
- CDK4/6 inhibitors
- palbociclib
- visceral metastatic breast cancer
- metastatic hormone-positive breast cancer

Introduction

Breast cancer is the most commonly observed cancer (13.5% of total cases) and the leading cause of cancer death (10.6% of total cases) in India, contributing significantly to the cancer burden.[1] Hormone receptor-positive subtypes are the most common, both in India and worldwide, with an incidence in India ranging from 25 to 60%.[2–4]

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The pathogenesis in the hormone receptor-positive subgroup is driven by estradiol through the estrogen receptor/progesterone receptor (ER/PR) pathway.[5] These subgroups are considered prognostically better; hence, hormonal agents are the treatment of choice in metastatic breast cancer (MBC) unless the patient has a visceral crisis or progressive visceral metastasis.[6,7]

Six years have elapsed since the first cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor was approved for use in ER+ breast cancer. Its effectiveness and safety when paired with endocrine therapy (ET) have been established through numerous randomized trials, making it the preferred first-line treatment for the majority of patients[8]

Palbociclib, a first-in-class, selective inhibitor of CDK4/6, when combined with ET, results in synergistic effects. These findings led to the design of clinical studies in which the addition of palbociclib to ET resulted in significantly improved progression-free survival (PFS) in both previously treated (PALOMA-3)[9] and treatment-naive (PALOMA-1 and -2)[8,10] women with HR +/HER2– advanced breast cancer.

The real-world experience of patients with visceral metastatic disease, prognostic factors, and tolerance of this drug in the first, second, and subsequent lines is limited. It is crucial to consider the potential outcomes and risks for patients with visceral organ metastases, who are at high risk, when exploring new treatment options.

In our study, we analyzed the real-world efficacy and tolerance of palbociclib across different subgroups and treatment lines among HR+ patients with MBC affecting visceral organs.

Materials and Methods

Objectives

Evaluate real-world data for PFS and objective response rate palbociclib in HR + ve MBC with visceral metastatic disease. Tolerance and toxicity of palbociclib in visceral metastatic disease. Compare with the randomized controlled trial (RCT) and other real-world evidence.

Methods

In our present retrospective single-institutional observational study, after obtaining ethical committee approval, we documented clinical, demographic, and tumor-related information, as well as treatment-related toxicity details of patients with hormone-positive HER2 negative MBC who received palbociclib in combination with ET between 2015 and 2021. Patients with a minimum of 2 years of follow-up were analyzed for PFS. Patients were grouped into skeletal and visceral metastatic disease. Visceral metastatic diseases were subclassified into lung, liver, and brain metastatic diseases, while all subgroups were assessed for PFS, toxicity, and prognostic factors.

Primary outcome: Median PFS of HR+ MBC patients treated with palbociclib and ET, stratified by metastatic site (skeletal vs. visceral) and further subclassified into lung, liver, and brain metastases.

Secondary outcomes: Prognostic factors influencing treatment response, including hormone receptor status, ET menopausal status, different lines of palbociclib use, and tumor grade. Evaluation of the safety profile of palbociclib in real-world clinical practice, focusing on the incidence of toxicities, dose reduction, and treatment discontinuation due to toxicity.

Comparison of PFS between different subgroups using the chi-square test and survival analysis with the Kaplan–Meier method.

Assessment of the overall clinical benefit and safety of palbociclib in HR+ MBC with visceral metastasis, including its comparability to results from RCTs.

Inclusion criteria: Hormone receptor-positive MBC patients who have been treated with palbociclib in combination with ET between 2015 and 2021.

Exclusion criteria: Patients with severe comorbidities, those lost to follow-up, individuals who discontinued palbociclib for reasons other than disease progression or intolerance, those with multiple malignancies, and individuals experiencing visceral crisis.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20. All subgroups were analyzed for PFS, toxicity, and prognostic factors. Subgroups were compared using the chi-square test. Survival times and rates were evaluated with the Kaplan–Meier method. Median overall survival (OS) was calculated from the day of starting palbociclib. Factors affecting the treatment results were evaluated using log-rank and Cox regression tests. A *p*-value of less than 0.05 was considered statistically significant.

Ethics

In accordance with the ethical principles outlined in the Declaration of Helsinki, 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.

Institutional Ethical Committee Sri Shankara Cancer Hospital and Research Centre IEC approval no: SSRHRC/IEC16/131; Date of approval: 12-11-2022.

Results

Patient Demographic Details

A total of 100 patients who received palbociclib between 2016 and 2021 were analyzed, with a median follow-up duration of 37 months. The median age of the population was 56 years. Among these patients, 24% were premenopausal, 30% had progressed on previous hormonal therapy, and 70% had metastatic disease without prior hormonal therapy at presentation. Fifty-six percent of the patients had only skeletal metastasis, while 44% had visceral metastasis, with no patients experiencing a visceral crisis. Specifically, 24% had lung metastasis, 18% had liver metastasis, and 2% had brain metastasis (►**Table 1**).

Table 1 Patients' demographic details

CDK4/6 inhibitors	Palbociclib	Percentage
Age group		
> 60	43	43
50–59	33	33
40–49	15	15
< 40	9	9
Menstruation		
Premenopause	24	24
Postmenopause	76	76
Presentation		
ET resistant	30	30
De novo metastasis	70	70
Metastatic sites		
Skeletal	56	56
Visceral metastasis	44	44

Abbreviation: ET, endocrine therapy.

Table 2 Tumor-related factors

CDK4/6 inhibitors	Palbociclib
Histopathology	
Intraductal	86
Lobular	8
Other	6
Grade	
1	8
2	56
3	36
Hormone status	
Strong positive	67
Weak positive	33
HER 2NEU	
Negative	89
Low expression	10
Positive	1
KI-67%	
< 15%	26
15–29%	22
> 30	52

Tumor-Related Factors

The most common histology was intraductal carcinoma (86%), with grade 2 being the most common grade. Sixty-seven percent of patients had strong hormone receptor positivity, and 10% had low HER2 positivity. Based on Ki-67% expression, 52% of patients had > 30% expression, 22% had 15 to 29% expression, and 26% had < 15% expression. One patient had triple-positive disease with HER2 positivity confirmed by fluorescence in situ hybridization testing in a repeat biopsy after progression, but clinically behaved like hormone receptor-positive disease. After discussion in the tumor board, this patient received treatment with palbociclib (►**Table 2**).

Treatment-Related Factors

Fifty-one percent of patients received CDK4/6 inhibitors in the first line, 37% in the second line, and 12% in the third line or subsequent lines. Fifty-eight percent of patients received CDK4/6 inhibitors with aromatase inhibitors, while 42% received them with fulvestrant. Twenty-five percent of patients required a first dose reduction, 8% required a second dose modification, and 3% discontinued CDK4/6 inhibitors due to toxicities. The most common grade 1 and 2 toxicities included neutropenia (40%), followed by anemia (35%). Twenty-two percent of patients experienced non-hematological toxicities such as fatigue, nausea, mucositis, and elevation of liver enzymes (►**Table 3**).

Treatment Outcomes

Among the patients treated with palbociclib, 5% exhibited a complete response, 41% showed a partial response, and 47% experienced disease progression. Additionally, 7 patients died during treatment. The median PFS of palbociclib when used in the first line was 32 months, compared to 23 months in the second line, and 13 months in the third line or subsequent lines. Premenopausal women had a PFS of 21 months compared to 25 months for postmenopausal women.

Weak hormone positivity, ET-resistant metastatic patients, and high grade were identified as poor responders. With a median follow-up of 37 months, the median PFS of the overall population was 24 months. Specifically, bone metastasis had a median PFS of 27 months, lung metastasis 25 months, liver metastasis 12 months, and brain metastasis 4 months (►**Table 4**; (►**Graphs 1** and **2**).

Discussion

The present study examined palbociclib's efficacy and safety in 100 HR-positive MBC patients with visceral metastases, finding a median PFS of 24 months. Bone metastasis had the longest PFS (27 months), followed by lung (25 months), liver (12 months), and brain (4 months). Common side effects included neutropenia (40%), anemia (35%), thrombocytopenia (15%), and hepatotoxicity (10%), with 3% discontinuing treatment due to toxicity. Among these, two patients had prolonged neutropenia, and one patient had persistent liver enzyme elevation as well as generalized weakness due to the drug. Among the patients who progressed on palbociclib and underwent biopsy followed by molecular testing, 12% started

Table 3 Treatment-related factors

Sequence	No. of patients
First line	51
Second line	37
Third and subsequent	12
CDKi + Endo	
CDKi + AI	55
CDKi + Fulvestrant	42
CDKi + Exemestane	3
Toxicities	
No AE	30
Anemia (grade I II)	35
Neutropenia (I II)	40
Thrombocytopenia (grade I II)	15
Nonhematological	22
Hematological (grade III IV)	3
Nonhematological (grade III IV)	2
Dose modification	
No modification	64
First dose	25
Second dose	8
Discontinue	3
Response to treatment	
Complete	5
Partial	41
Progress	47
Death	7

Abbreviations: AE, adverse event; AI, aromatase inhibitor.

Table 4 Treatment outcomes

Median PFS in subgroups	Months	*p*-Value
Sequence of palbociclib		
First line	32	
Second line	23	0.170
Third and more	13	
Menstrual status		
Premenopausal	21	
Postmenopausal	25	0.218
Site of metastasis		
Skeletal	27	
Visceral	15	0.054
Hormonal status		
Strong positive	32	0.127
Weak positive	14	
KI-67		
< 15	40	0.189
15–30	19	
> 30	22	
Presentation		
ET resistant	22	
De novo	40	0.113

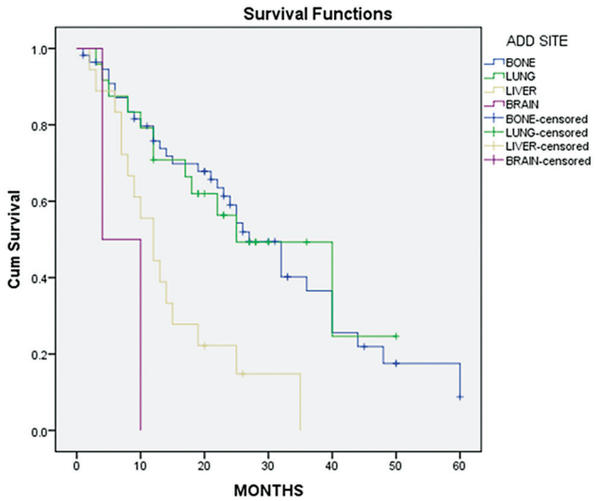
Abbreviations: ET, endocrine therapy; PFS, progression-free survival.

on PiK3 inhibitors (alpelisib), 46% started on everolimus and exemestane, 32% started on chemotherapy, and the remaining patients opted for best supportive care.

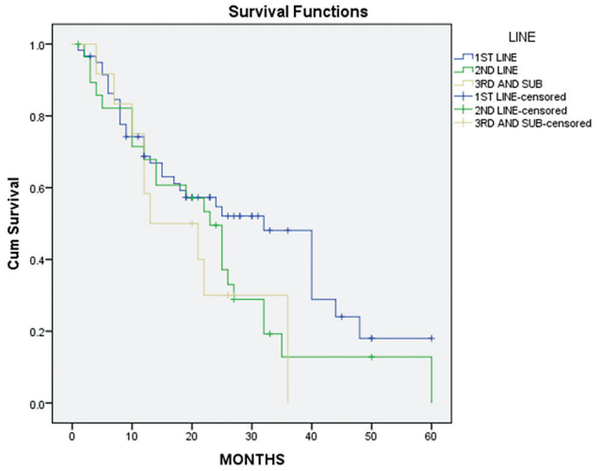
This is the only study evaluating the efficacy of palbociclib in different lines of metastatic hormone receptor-positive breast cancer.

In the landmark PALOMA-2 study,[10] which included 444 metastatic patients treated with palbociclib plus letrozole, the median PFS was 24.8 months, compared to 14.5 months with letrozole alone. Our study, with a median PFS of 24 months, despite 70% of patients having prior ET, showed comparable outcomes. Notably, de novo metastatic disease in our cohort exhibited a median PFS of 40 months, significantly surpassing the PALOMA-2 trial. This divergence may be attributed to the selective use of palbociclib upfront in metastatic disease during the evolving era of CDK inhibitors. Common toxicities in the PALOMA-2 trial included neutropenia (66.4%), leukopenia (24.8%), anemia (5.4%), and fatigue (1.8%), with 1.8% experiencing febrile neutropenia and 9.7% discontinuing treatment, aligning with findings in our study.

In contrast, the initial PALOMA-3 trial[9] evaluated the efficacy of palbociclib plus fulvestrant in MBC patients who had progressed on previous ET, involving 345 patients with a median follow-up of 8.9 months. The median PFS was 9.5 months in those with visceral metastatic disease, whereas in patients with nonvisceral metastases, the median PFS was 16.6 months. In our study, PFS in visceral metastatic disease was 15 months compared to 27 months in skeletal



Graph 1 Progression-free survival (PFS) based on metastatic sites.



Graph 2 Progression-free survival (PFS) based on different lines CDK4/6 used.

metastasis, with acceptable toxicities, the most common being neutropenia, anemia, and thrombocytopenia. This disparity is due to the selection of patients with low visceral metastatic disease in our study during the initial days of CDK4/6i approval.

In the MONARCH 2 phase III RCT,[11] which evaluated abemaciclib plus fulvestrant in subgroup patients having visceral metastasis at presentation, results were more favorable than palbociclib plus ET with an hazard ratio of 0.48.

There are not many studies comparing CDK4/6 inhibitors head-on with chemotherapy drugs, especially in extensive visceral metastasis cases before CDK4/6 inhibitors were available. However, CDK4/6 inhibitors provide a chemotherapy-free regimen for HR-positive MBC without a visceral crisis.

In the RIGHT Choice trial, an open-label phase II study[12] conducted in 13 countries, a head-to-head comparison between a CDK4/6 inhibitor (ribociclib) plus ET and combination chemotherapy was evaluated. The study involved 112 patients receiving ribociclib plus ET, while in our current study, 100 patients received palbociclib plus ET. The percentage of patients with de novo metastatic disease was similar between the two studies (64.4% in RIGHT Choice vs. 70% in our study). However, there were notable differences in the patient populations: 67.6% of patients in the RIGHT Choice trial had visceral metastasis compared to 44% in our study, and 47% of patients in the RIGHT Choice trial had a visceral crisis, while none in our study did. The median PFS in the ribociclib arm of the RIGHT Choice trial was 21.8 months, compared to 12.8 months in the chemotherapy arm. In our study, the median PFS in the palbociclib arm was 24 months. Regarding safety, grade 3 or 4 hematological toxicity occurred in 59.8% of patients in the RIGHT Choice trial, whereas in our study, severe hematological toxicity was only 4%. Severe nonhematological toxicity was 3% in the RIGHT Choice trial compared to 4% in our study. There were five deaths in the ribociclib arm of the RIGHT Choice trial, compared to seven deaths in our study. The trial showed improved PFS, similar response rates, and lower rates of symptomatic adverse events with ribociclib plus ET compared to chemotherapy. In summary, the efficacy and safety results of our study are similar to those observed in the ribociclib arm of the RIGHT Choice trial.

In the FALCON study,[13] which compared fulvestrant with anastrozole, PFS was 22.3 versus 13.8 months in skeletal metastatic disease compared to 40 months in our study, with a comparable toxicity profile.

The KENDO randomized phase II trial[14] is the only study that compared the efficacy and safety of chemotherapy plus ET versus CDK4/6 inhibitors (CDK4/6i) plus ET in hormone receptor-positive (HR+)/HER2-negative MBC. The study found that CDK4/6i plus ET showed clinically meaningful improvements in PFS and OS compared to chemotherapy plus ET, although the difference was not statistically significant. Basal-like tumors under CDK4/6i plus ET had worse PFS and OS compared to other subtypes, while luminal A tumors performed worse with chemotherapy. The PAM50 intrinsic subtypes were found to have prognostic and predictive value, with luminal A associated with the best prognosis and basal-like with the worst prognosis. Genes and pathways involved in breast cancer cell survival and proliferation were associated with worse outcomes, while immune-related genes and signatures showed favorable survival trends, especially in the CDK4/6i arm. Tumor-infiltrating lymphocytes and the presence of tertiary lymphoid structures were associated with better outcomes in the CDK4/6i arm. CD24 was identified as a potential therapeutic target, and messenger ribonucleic acid-based CD19 and CXCL13 were found to be predictors of tertiary lymphoid structure presence. Overall, the results suggest that CDK4/6i plus ET is a viable treatment option for aggressive HR+/HER2-negative MBC instead of chemotherapy, and PAM50 intrinsic subtypes, genomic, and immunological features are promising biomarkers for personalized therapeutic choices.

Our study findings of palbociclib with ET in real-world data suggest that palbociclib plus ET, which is a widely used CDK4/6 inhibitor with ET, showed similar efficacy and safety comparable with RCTs in visceral metastatic disease without visceral crisis. This is the only study that evaluated the efficacy of palbociclib in multiple lines.

Conclusion

Based on real-world evidence, palbociclib demonstrates similar responses and better tolerance in visceral metastatic hormone positive breast cancer. However, further studies are required to identify additional predictive markers and factors related to CDK4/6 inhibitors resistance. Moreover, the efficacy of palbociclib inhibitors should be evaluated, particularly in patients with a high disease burden and extensive visceral metastatic disease.

Patient Consent

Informed patient consent was obtained to conduct this study.

Funding

None.

Conflict of Interest
None declared.

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Spectrum of Somatic Malignancy in Testicular Germ Cell Tumors—A Histopathological Review of 25 Cases with Clinical Outcome

Priyadarsani Subramanian[1] Amandeep Arora[2] Mahendra Pal[2] Gagan Prakash[2] Priyamvada Maitre[3] Vedang Murthy[3] Amit Joshi[4] Swapnil Rane[1] Sangeeta Desai[1] Santosh Menon[1]

[1] Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[2] Department of Urology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[3] Department of Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[4] Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Santosh Menon, MD, Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai 400012, Maharashtra, India (e-mail: mensantosh@gmail.com).

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Abstract

Introduction Germ cell tumors (GCTs) are the commonest testicular malignancy in young males. These tumors are highly chemoresponsive, however become resistant to conventional therapy when a somatic-type malignancy (SM) develops, which happens in ~3 to 6% of the cases.

Materials and Methods We reviewed the histologic profile of all cases of testicular/retroperitoneal GCT with SM, diagnosed over a period of 12 years in our institute. Correlation of histologic profile with clinical outcome was done wherever feasible.

Results A total of 25 cases of testicular/retroperitoneal GCT with SM were identified for review. The histological spectrum of SMs included carcinoma ($n = 9$), sarcoma ($n = 9$), embryonic-type neuroectodermal tumor (ENET) ($n = 4$), and other rare histological types ($n = 3$). SMs were frequently seen at the resected metastatic sites ($n = 13$) and in postchemotherapy setting ($n = 12$); 14 cases had concurrent GCT and SM at the time of diagnosis/initial resection and 9 cases presented as late relapses (more than 2 years after initial presentation). Four patients were treated with metastasectomy and lymph node dissection, six patients were treated with combined resection and chemotherapy, and nine patients were treated with only adjuvant chemotherapy. The patients with SM confined to testis and those treated with multimodality approach had relatively better outcome.

Conclusion GCTs with SM are a highly heterogeneous group of tumors with varying histologic types and management strategies. Strict adherence to histological diagnostic criteria, differentiating these tumors from close mimics such as glandular and sarcomatoid yolk sac tumors, teratomatous overgrowth, and a new second primary somatic tumor are important due to implications in management and prognosis.

Keywords
- germ cell tumors
- somatic malignancy
- embryonic-type neuroectodermal tumors
- rhabdomyosarcoma
- teratomatous overgrowth

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Introduction

Testicular tumors are rare, accounting for 1 to 2% of all tumors in males.[1] Germ cell tumors (GCTs) are the commonest testicular tumors (98%) in young males.[2] Despite being highly malignant tumors, most are amenable to chemotherapy (70–80% cure rate after first-line chemotherapy)[3] and hence, curable (95% 5-year survival rate).[4–6] About 3 to 6% of GCTs develop somatic-type malignancy (SM),[7] which is defined as the occurrence of a distinct component of somatic-type malignant neoplasm, as seen in other organs. The SM component may be epithelial or mesenchymal, and is diagnosed when it measures 5 mm or more with an infiltrative or expansile growth pattern.[8,9] Various histological types of SM have been described—sarcoma (commonly rhabdomyosarcoma [RMS]), adenocarcinoma, peripheral neuroectodermal tumor (PNET) (presently renamed embryonic-type neuroectodermal tumor [ENET] in World Health Organization [WHO] 2022), nephroblastoma, neuroblastoma, and other rare tumor types.[10]

SM occurs frequently in relapses and following chemotherapy but may be present at the time of initial presentation infrequently.[10] It is an important cause of resistance to conventional platinum-based chemotherapeutic regimens.[11] It confers poor prognosis when seen in metastatic sites.[4]

Though studies on therapeutic strategies and clinical outcome of this disease are available, literature on detailed histopathological features is limited to a few case series and multi-institutional studies. Herein, we provide a detailed review of pathological features of 25 cases of GCT with SM diagnosed at our institute.

Materials and Methods

Primary Outcome

To study the clinicopathological features of testicular GCT with SM.

Secondary Outcome

To correlate the histological factors with clinical characteristics of the patients.

Case Selection

The surgical pathology database was retrospectively searched for all cases of primary testicular/retroperitoneal GCTs with SM diagnosed over a period of 12 years (January 2011–June 2023), including in-house and referral cases. The histopathology slides and relevant immunohistochemical stains performed at the time of initial diagnosis were reviewed.

Inclusion Criteria

Only cases confirming to the WHO diagnostic criteria for SM were included in the study (malignant nodules with infiltrative or expansile growth measuring at least 5 mm).

Exclusion Criteria

Cases with teratomatous overgrowth and cases with scattered atypical stromal cells/small atypical epithelial cell clusters were excluded.

Parameters Studied

For cases with unequivocal diagnosis of SM, histological type of SM was assigned as per WHO 2022 terminology. Other histological features such as presence of associated GCT components were noted. The demographic details, clinical presentation, treatment, and outcome details were collected from the institutional electronic medical records database. Histological type of SM, site, and timescale of occurrence (SM occurring concurrently with GCT at initial presentation or presentation as late relapse) were compared with clinical parameters and outcome in patients with adequate available clinical information.

Statistical Analysis

The data collected were entered in MS Excel and the mean, percentage, and statistical analysis were performed by SPSS version 20.1.

Ethical Statement

Institutional Ethics Committee II, Institutional Review Board, Tata Memorial Center, Mumbai. All procedures performed in this study involving human particiapants were in accordance with the ethical standards of the Institutional Ethics Committee II, Institutional Review Board, Tata Memorial Center, Mumbai and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

About 1,650 cases of testicular GCTs were diagnosed in the study period at our institute, of which 25 cases had developed SM (1.52%). A total of 28 cases were initially diagnosed as GCTs with SM; however, on review of histopathological features, only 25 cases met the defined criteria for SM and 3 cases were excluded (teratomatous [glandular and rhabdomyomatous] overgrowth [$n = 2$] and seminoma with anaplastic features [$n = 1$]).

Clinical Parameters

The median age at diagnosis of SM was 31.96 years with an age range of 17 to 48 years. All patients had primary testicular GCT (24/25) except one case of primary retroperitoneal GCT (1/25). SM was detected only in primary site in 11 cases (44%) (testis $n = 10$, retroperitoneum $n = 1$), only in metastatic sites in 12 cases (48%), and in both testis and retroperitoneal lymph nodes (RPLNs) in 2 cases. The metastatic sites were RPLN (10/25), left supraclavicular lymph nodes (1/25), and lung (1/25). The median age of patients with SM in primary site only was 27 and that of patients with SM in metastatic sites was 32.5 years.

About 14 cases (56%) had concurrent GCT and SM at the time of initial presentation and 9 cases (36%) presented as late relapses (at least 2 years after initial presentation). About half of the patients ($n = 12$, 48%) had received prior chemotherapy and/or radiation therapy. The mean time to development of SM in metastatic sites from the time of primary GCT diagnosis was 3.5 years (range 0–22 years).

Pathological Parameters

At initial presentation, 21 cases had nonseminomatous GCT (NSGCT), 2 cases had mixed GCT, 1 case had a burnt-out GCT with germ cell neoplasia in situ (GCNIS); 1 case showed only SM (ENET) in the limited sections available (sections from adjacent testis was not available for review). Concomitant GCT was noted along with SM in 19 cases; teratomatous component was present in 18/19 cases; 1 case had only yolk sac tumor (YST) (1/19); 1 case had only GCNIS. In five cases, no residual GCT component was identified at the time of diagnosis of SM, of which three cases had only core biopsy material for evaluation.

In primary site (testis/retroperitoneum), the histotypes encountered in decreasing order of frequency are sarcoma (6/11; 54.55%), ENET (2/11; 18.18%), mucinous adenocarcinoma (2/11; 18.18%), and Wilms' tumor (1/11; 9.09%). In metastatic sites, the histological types encountered in decreasing order of frequency are carcinoma (7/12; 58.33%), sarcoma (3/12; 25%), ENET (1/12; 8.33%), and desmoplastic small round cell tumor (DSRCT) (1/12; 8.33%). The two cases with presence of SM concurrently in testis and RPLN were carcinosarcoma—with adenocarcinoma and spindle cell sarcoma not otherwise specified (NOS) areas and a case of ENET with scattered SALL4-positive large cells (discussed in detail in the following section).

The histological types of SM observed were carcinoma (9/25; 36%), sarcoma (9/25; 36%), ENET (4/25; 16%), 1 case each of carcinosarcoma (1/25; 4%), Wilms' tumor (1/25; 4%), and DSRCT (1/25; 4%). Sarcoma (RMS) was the most common type of SM in testis and carcinoma (adenocarcinoma) was the most common pathology in metastatic sites. SM which presented as late relapses were adenocarcinoma (7/9), ENET (1/4), sarcoma NOS (1/9), and RMS (1/9).

Among carcinomas, adenocarcinoma was the commonest histotype (7/9); one case had mucinous histology and remaining were adenocarcinoma, NOS (►**Fig. 1**). Two cases in this group had unusual histology—neuroendocrine carcinoma (NEC) and clear cell renal cell carcinoma (CCRCC). The tumor was present only in a small focus in RPLN and measured only 0.5 to 1 cm in both these cases. In the case of NEC, SM was detected 1 year after initial diagnosis of GCT; the tumor showed nested and pseudoglandular patterns with marked nuclear atypia and brisk mitotic activity. It was immunopositive for synaptophysin, CD56, and chromogranin while being negative for EMA, glypican 3, CD30, and cKIT. The patient was given chemotherapy (VIP regimen) and is disease free, 4 years after diagnosis. The case of CCRCC was detected 3 years after the initial diagnosis of GCT; the SM showed classical morphology of CCRCC as seen in kidney with low nuclear grade (►**Fig. 1**). The tumor cells were positive for AE1/AE3, PAX8, and CD10; negative for TFE3 and HMB45. The patient was thoroughly investigated for any occult primary in kidney and no renal mass was found on radiological evaluation. No adjuvant second-line chemotherapy was given and the patient is disease free, 5 years after diagnosis. Both these cases had residual teratomatous elements in the RPLND along with SM.

Among the sarcoma group, seven cases were RMS (7/9) and two cases were high-grade spindle cell sarcoma, NOS (2/9). All RMSs were of embryonal subtype with an appreciable number of rhabdomyoblasts; showed positivity for desmin (focal), myogenin, and/or myoD1.

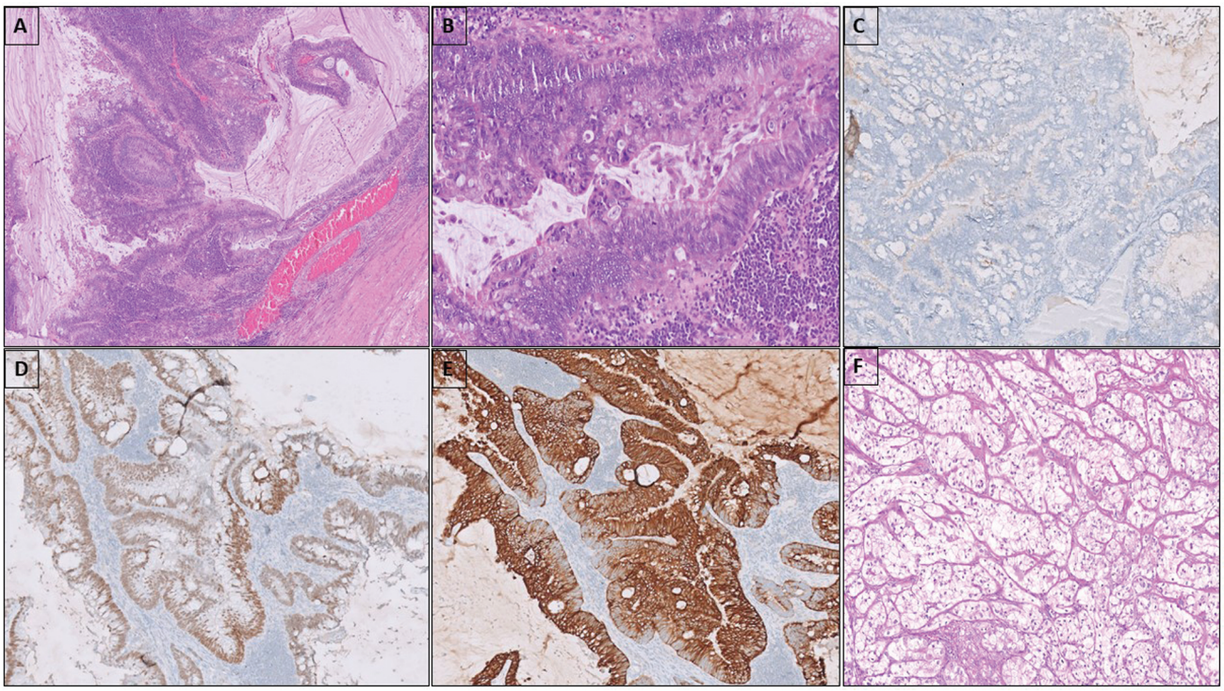

Fig. 1 Adenocarcinoma with mucinous columnar cells in glandular and papillary architecture (A). The cells show nuclear stratification and atypia with frequent mitoses (B). Tumor cells are negative for SALL4 (C), positive for SATB2 (D) and CK20 (E). The case of clear cell renal cell carcinoma composed of nests of clear cells with low nuclear grade (F).

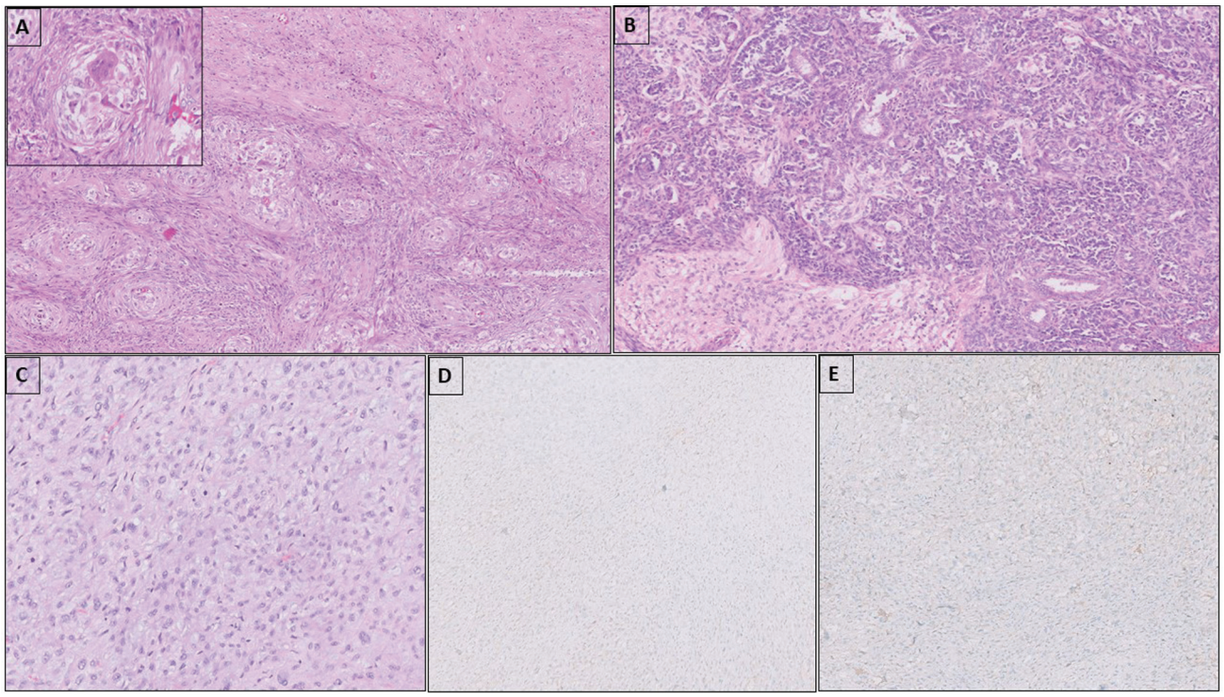

Fig. 2 Carcinosarcoma with nests of clear epithelioid cells and atypical spindle cells around the nests (A). Central blood vessel and multinucleate giant cell can be seen in the center of the epithelioid cell nests (inset). Teratoid Wilms' tumor with nests and sheets of blastemal cells, epithelial tubular elements, and intimately admixed mature glial tissue (B). Sarcoma, NOS with sheets of mitotically active atypical spindle cells (C); the tumor cells are negative for glypican 3 (D) and desmin (E).

The two sarcoma, NOS cases did not show any line of differentiation by immunohistochemistry (smooth muscle, skeletal muscle, and neural lineage markers were negative). The cases showed sheets and vague fascicles of spindle cells with significant nuclear atypia and frequent mitoses (►**Fig. 2**). The tumor was small in one case, measuring 0.8 cm in diameter and was confined to testis; the patient underwent RPLND and no adjuvant chemotherapy was given and patient is disease free 6 months after diagnosis. The other case presented as late relapse in RPLN had disease progression despite second-line chemotherapy.

In the ENET group ($n = 4$), the tumor was confined to testis in two cases; was seen in both testis and RPLN in one case and in the other case, it was seen as a late relapse in RPLN. The tumor cells were positive for SOX11 and negative for SALL4 and YST markers; showed variable immunopositivity for synaptophysin, chromogranin, CD56, and S100. NKX2–2 and GFAP were negative in the cases tested (►**Fig. 3**). EWSR1 break-apart fluorescence in situ hybridization (FISH) was negative in one case tested for. All except one patient responded well to chemotherapy.

Cases with Unusual Histological Features

The case of carcinosarcoma showed intimately admixed epithelial and sarcomatous components, seen in primary site and RPLN. In testis, sarcomatous component was dominant, composed of sheets and vague fascicles of atypical spindle cells with frequent mitosis along with small nests of epithelial cells with clear cytoplasm. At places epithelial cells were seen condensed around thin-walled blood vessels (►**Fig. 2**). In RPLN, epithelial component was prominent and showed features of adenocarcinoma, NOS with infiltrating, irregular angulated atypical glands. Immunostains for SALL4, OCT3/4, desmin, CD34, and inhibin were negative in both epithelial and spindle cell components. The residual GCT component present was a small focus of YST in the RPLN.

In the case of triphasic Wilms' tumor we encountered, there was intimately admixed glial elements, seen along with NSGCT elements, the SM being present at primary site at the time of initial presentation. The tumor showed a predominant blastemal component along with intermingled islands of teratoid/glial elements (mature and immature) in a neuropil-rich matrix (►**Fig. 2**).

The case of DSRCT was detected in RPLNs, 2 years following the occurrence of GCT. The tumor showed malignant round cell morphology with fibrous stroma and a polyphenotypic immunoprofile. The tumor cells were immunopositive for AE1/AE3, desmin, WT1, synaptophysin, MIC-2, and FLI1. Reverse transcriptase polymerase chain reaction for EWSR1-WT1 and EWSR1-FLI1 gene fusions, both were negative.

An intriguing histological finding we observed in a case of ENET was presence of singly scattered large cells with prominent nuclei amidst malignant round blue cells. The smaller cells were positive for synaptophysin, SALL4, and NKX2.2, and negative for desmin, myogenin, calretinin, and D2–40; the scattered large cells were positive for SALL4, D2–40, and OCT3/4. The tumor had mature teratomatous elements and GCNIS was noted in the adjacent testicular parenchyma. There was no seminoma/YST components.

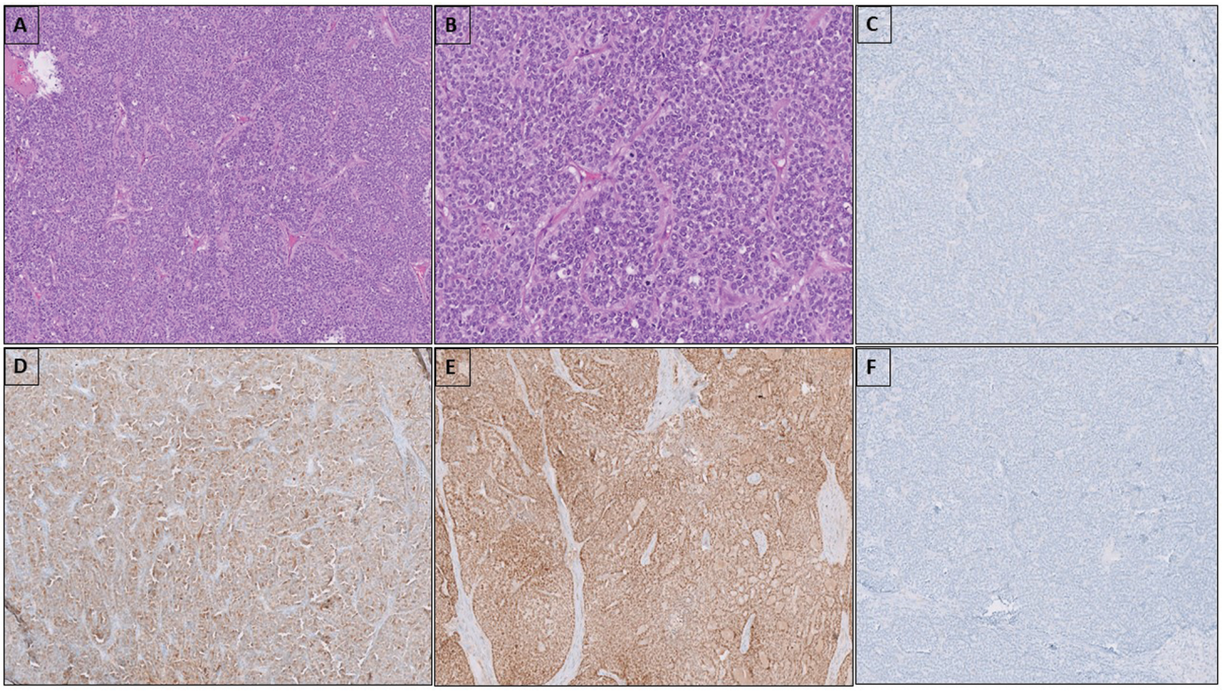

Fig. 3 Embryonic-type neuroectodermal tumor composed of sheets and nests of monomorphic round cells with scant cytoplasm and fine granular chromatin (A, B). Tumor cells are negative for NKX2–2 (C), diffusely positive for S100 (D) and SOX11 (E). Staining for OCT 3/4 is negative (F).

This unusual occurrence of admixed large cells in ENET has not been observed previously, to the best of our knowledge. Considering their immunophenotype we could best regard these cells to be entrapped GCNIS cells.

Outcome Details

Clinical follow-up details were available for 19 patients, 18 patients were alive and 1 was deceased, with mean follow-up duration being 4.88 years (range 0.5–17 years).

Treatment details following the diagnosis of SM were available for 20 patients; 9 patients received only chemotherapy; 5 patients underwent surgical and medical (chemotherapy) management; 4 patients underwent surgical management only; 1 patient was treated with combined chemotherapy and radiotherapy; 1 patient received chemotherapy, radiotherapy, and surgery.

One patient died of surgical complications (post-RPLND) and all other patients were alive for the available follow-up period. Nine patients were disease free and asymptomatic; four patients did not respond well to second-line chemotherapy and had been put on palliative intent management, one patient had stable residual disease after treatment and was being followed up, and four patients had not completed treatment at the time of last follow-up.

Among the patients who had disease progression after second-line therapy (4/19), two were sarcoma (2/4), one DSRCT (1/4), and one ENET (1/4). Other than the testicular ENET, three cases had SM at metastatic sites.

Among the patients treated with surgical resection alone ($n = 4$) or combined surgical resection and chemotherapy/radiotherapy ($n = 7$), most showed good response to treatment (8/11) and were disease free; two patients (DSRCT and RMS; both detected in metastatic sites) developed progressive disease despite multimodality management and one patient (RMS detected in RPLN) died due to surgery-related complications. Among the patients treated only with chemotherapy ($n = 9$), two patients developed progressive disease (sarcoma NOS and ENET with large cells) and one patient had residual disease (adenocarcinoma) after the completion of chemotherapy; three patients are yet to complete the chemotherapy course; two patients were disease free after the completion of treatment; outcome details are not available for a patient.

Discussion

Occurrence of SMs in GCT was described as early as 1946 and included in WHO 2004 under the term "teratoma with somatic-type malignancy"; later renamed "GCTs with somatic type malignancy."[12] SM is believed to arise from pluripotent germ cells or malignant transformation of teratomatous/yolk-sac elements. Some studies have reported occurrence of SM after chemotherapy, which may be due to its DNA damaging effect.[10,13] Pathogenetically, SMs retain the characteristic molecular abnormality, isochromosome 12p seen in postpubertal-type GCTs which can be detected as 12p amplification by FISH.[7]

SMs are most frequently encountered in metastatic sites as primary treatment failure or late disease relapses.[14,15] This finding was reiterated in our study as in nearly 56% of cases SM was seen in metastatic sites and more than half of the patients had received prior chemotherapy. The overall prevalence of SM was less in our cohort than the 3 to 6%

prevalence observed in most other studies. More cases were identified in the past 5 years in our cohort (17/25), probably due to better understanding of this entity and clearer diagnostic criteria. The histological spectrum of SM described in GCT is diverse (sarcomas, carcinomas of various phenotypes, PNET, glial tumors, and nephroblastomas), sarcomas being the commonest in most series (63%).[5] In our series, we observed an equal occurrence of carcinoma and sarcoma with the next frequent being ENET; some rare tumor types such as nephroblastoma, CCRCC, carcinosarcoma, DSRCT, and neuroendocrine carcinoma were also encountered.

We observed carcinomas more frequently in metastatic sites as late relapses, the commonest type being adenocarcinoma, similar to the observation in various studies.[16] The CCRCC and neuroendocrine carcinoma cases we encountered have been not or only sparsely described in literature, respectively. There has been a single report of papillary renal cell carcinoma arising as SM in RPLNs and no other additional renal tumor types have been described previously.[12,17] Both these tumors were present only in a small focus in our cases, measuring <1 cm and did not progress.

The commonest type of sarcoma in our series was embryonal RMS, as reported in studies previously. During the initial screening, we found two cases of rhabdomyomatous overgrowth misdiagnosed as RMS. Rhabdomyomatous overgrowth has been described following chemotherapy and is composed of sheets of maturing skeletal muscle cells without any malignant round cell areas, necrosis, or apoptosis. Hence, detecting immature rhabdomyoblasts or embryonal areas is needed to ascertain a diagnosis of RMS as a SM. In our study, among the RMS group, all except one case showed good response to chemotherapy, with disease-free interval of 1 to 57 months.

The sarcoma, NOS cases did not show any line of differentiation by immunohistochemistry. The closest differential to be considered in such cases is sarcomatoid YST. The sarcomatoid areas in YST can be low or high grade,[18] usually show foci with epithelioid pattern and are immunopositive for SALL4 and glypican 3. Sarcomatoid YST is resistant to platinum-based chemotherapy and has an aggressive clinical course, much like GCT with SM.[14]

The so-called testicular PNETs are distinct from the PNET/Ewings sarcoma of bone and soft tissue. The testicular PNETs are negative for FLI1 and CD99; do not show EWSR1 gene rearrangements, a hallmark of PNET. These tumors are generally confined to testis, frequently contain areas resembling medulloepithelioma, medulloblastoma, and a range of neuroglial tumors.[14,19] Therefore, these tumors are considered to represent "central" rather than peripheral-type neuroectodermal tumors and have been renamed ENET in the WHO fifth edition.[8,20] ENETs when confined to testis are increasingly being recognized to have better outcome. In comparison, metastatic ENET may have a poorer outcome, as seen in one of our cases which progressed despite second-line chemotherapy.

One of our cases was diagnosed as DSRCT based on histological and immunohistochemical features, although molecular findings were not supportive. Occurrence of this tumor as a SM has not been described previously.

Most of the SMs are consistently associated with teratoma, hence the need to carefully distinguish these tumors from immature teratomatous elements, benign teratomatous overgrowth, and teratomas showing nuclear atypia. Teratomatous overgrowth and atypia in stromal cells are well known to occur after chemotherapy. Any form of teratomatous overgrowth can mimic disease progression, presenting with increasing size of the mass clinically; however, it does not behave in a malignant fashion. In our review, two cases initially misdiagnosed as SM were reclassified as teratomatous overgrowth after histological review.

As somatic malignant transformation is common in metastatic sites and can present as late relapses,[16] metastasis from a new primary nongerm cell neoplasm becomes a diagnostic consideration. In such instances, young age of the patient, prior history of GCT, presence of 12p gain, and absence of primary tumor after systematic evaluation points to a diagnosis of SM.[5]

The various histotypes of SM and relevant clinical parameters described in the literature with significant case numbers are summarized in ►**Table 1**. In most studies, poor clinical outcome of GCT with SM was observed only when SM involved metastatic sites.[14] In our series too, most of the patients with SM confined to testis had better outcome with only one patient found to have residual disease posttreatment. Also, some studies have questioned the strict size-based diagnostic criteria for SM, as a case with small focus of ENET (not meeting the 5 mm criteria) presented later with widespread disease.[7] In our series, three cases which had SM occupying less than 1 cm area in slide showed a good outcome, despite the aggressive histological type (neuroendocrine carcinoma, CCRCC, and high-grade sarcoma).

Owing to the rarity of these tumors, the current management strategy is very heterogeneous and the decision is on a case-to-case basis. Most large series suggest combining surgical resection with some form of adjuvant chemotherapy decided based on histotype of SM for a sustained response. With the current ease of availability of molecular testing strategies, SMs are being found to harbor mutations in genes such as TP53, RAS which are not usually seen in GCT. Hence, the role of tumor specific (SM type specific) targeted therapy approaches may be evaluated for a possible clinical benefit in this rare disease entity.[7]

Conclusion

SMs arising in testicular GCT are a rare, heterogenous group of tumors histologically, with varying clinical outcomes. SMs arising in metastatic sites and those presenting as late

Table 1 Comparison of histological and clinical features among the various studies on SM in the literature

	Our study	Magers et al (2014)[5]	Lobo et al (2022)[7]	Hwang et al (2022)[4]	Scheckel et al (2019)[21]	Sharma et al (2019)[10]
Study overview	Morphology, immunophenotype and outcome	Morphology and immunophenotype	Histological spectrum and molecular features	Histological type and clinical outcome	Management and clinical outcome	Management and clinical outcome
Study period	12 y	23 y, single institution	16 y, two institutions	15 y, single institution	35 y, single institution	18 y, single institution
Number of cases	25	124 cases of testicular GCT (excluded PNET and Wilms) 84 histologically confirmed as SM after IHCs	30 (testicular and primary retroperitoneal GCT)	63 (excluded sarcomatoid YST)	24 (testicular, mediastinal and pineal)	30
No. of cases with SM in testis	13	4	14	22	2	–
No. of cases with SM in metastatic sites	14	–	22	41	22	–
Presence of associated GCT	All except two (one showed only GCNIS and other showed only ENET)	Initial diagnosis of GCT known in 50% patients	Initial diagnosis of GCT established in all cases	All except one case of ENET	–	–
Concomitant initial presentation of SM with GCT	14	7 cases	14 (5 were ENET)	–	12	9
H/O chemotherapy and/or radiation therapy before SM	9	83%	15	35		21
Carcinoma	9 (adenocarcinoma, clear cell RCC, neuroendocrine carcinoma)	44 (adenocarcinoma, carcinoma NOS and sarcomatoid carcinoma)	11 (including papillary RCC, neuroendocrine carcinoma)	21 (adenocarcinoma, carcinoma NOS, neuroendocrine carcinoma)	12 (adenocarcinomas)	3
Sarcoma	9 (RMS, sarcoma NOS)	39 cases (RMS, myxofibrosarcoma, sarcoma NOS, UPS, LMS, OGS, gliosarcoma)	6	21 (RMS, angiosarcoma, sarcoma NOS)	12 (RMS and sarcoma, NOS)	16
ENET	4 (one with scattered SALL4-positive large cells)	–	8	15	–	10

Table 1 (*Continued*)

	Our study	Magers et al (2014)[5]	Lobo et al (2022)[7]	Hwang et al (2022)[4]	Scheckel et al (2019)[21]	Sharma et al (2019)[10]
Other rare tumor types	Two cases of carcinosarcoma, one case of DSRCT	High-grade glioma	Neuroblastoma, low-grade glial tumor	Nephroblastoma, mixed RMS, and small cell carcinoma	–	Nephroblastoma
IHC	Relevant markers pertaining to histotype	Reclassification of 37 cases as glandular/sarcomatoid YST	–	NA	–	–
Commonest histological type in metastatic sites	Carcinoma	–	Adenocarcinoma	Carcinoma	–	–
Molecular studies	–	NA	12p FISH, EWSR1 rearrangement in ENET	NA	–	–
Clinical outcome	Carcinoma frequent in late relapses, ENET and sarcoma frequent at initial presentation; SM at metastasis—poor outcome; small SM size (<1 cm) had good outcome; those treated with both surgery and chemotherapy had better outcome	Sarcomatoid SM more aggressive than glandular SM	Late relapse, high-grade sarcomatous SM, ENET, extragonadal primary predictive of poor outcome	Poor survival in metastatic SM group and carcinoma histological type	Carcinomas had better overall survival compared with sarcoma group	Late relapse had poor outcome

Abbreviations: DSRCT, desmoplastic small round cell tumor; ENET, embryonic-type neuroectodermal tumor; FISH, fluorescence in situ hybridization; GCNIS, germ cell neoplasia in situ; GCT, germ cell tumor; H/O, history of; IHC, immunohistochemistry; LMS, leiomyosarcoma; NA, not available; NOS, not otherwise specified; OGS, osteosarcoma; PNET, peripheral neuroectodermal tumor; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SM, somatic-type malignancy; UPS, undifferentiated pleomorphic sarcoma; YST, yolk sac tumor.

relapses show relatively poor outcome. Small tumors (<1 cm) had favorable clinical outcome even without adjuvant chemotherapy. Differentiating GCT with SM from sarcomatoid or glandular YSTs, new independent somatic tumors, teratomatous overgrowth, and reactive stromal atypia postchemotherapy in teratoma has important clinical implications. Though standard therapeutic modalities are not described, multimodal management may have a better outcome.

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Conflict of Interest
None declared.

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Prognostic Discussions in Advanced Cancer: A Qualitative Thematic Analysis of Patients' and Caregivers' Experiences in a Tertiary Cancer Center in India

Avinash Tiwari[1,2] Arunangshu Ghoshal[1,3] Jayita Deodhar[1] MaryAnn Muckaden[1,4]

[1] Department of Palliative Medicine, Tata Memorial Hospital, Mumbai, Maharashtra, India
[2] Department of Palliative Medicine, Sanjeevani Cancer Hospital, Pachpedi Naka, Raipur, Chhattisgarh, India
[3] Department of Palliative Medicine and Supportive Care, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India
[4] Sukoon Nilaya Palliative Care Centre, Anand Niketan, Dr. E Moses Road, Mahalaxmi, Mumbai, Maharashtra, India

Address for correspondence Avinash Tiwari, MD, Department of Palliative Medicine, Sanjeevani Cancer Hospital, Pachpedi Naka, Raipur 492001, Chhattisgarh, India (e-mail: doctoravinashtiwari@gmail.com).

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Abstract

Introduction Advanced cancer poses unique difficulties for patients, caregivers, and health care providers. Prognostic discussions are pivotal in shaping care decisions during this stage. These conversations involve health care professionals conveying disease progression, expected outcomes, and estimated life expectancy. Research consistently underscores the pivotal role of prognostic discussions in advanced cancer care, and most existing research stems from developed countries, necessitating the exploration of experiences within the Indian context.

Objective The aim of this study is to identify the themes and patterns that emerge from the narratives of patients and caregivers surrounding prognostic discussions.

Materials and Methods Using a qualitative methodology, participants were drawn from the palliative care clinic via a purposive sampling in this prospective qualitative study. Semi-structured interviews were conducted, and thematic analysis was employed to understand patient and caregiver experiences. Ethical considerations were adhered to throughout, obtaining informed consent and ensuring anonymity.

Results Findings from 21 participants revealed five themes shaping prognostic discussions: perception and understanding of prognostic information, emotional impact, decision-making and treatment preferences, communication with providers, and cultural and religious influences. Patients struggled to comprehend complex medical terms, while caregivers played essential roles in aiding understanding. Both groups grappled with intense emotions upon learning of limited life expectancy, impacting decision-making. Effective communication and involvement of caregivers in discussions were pivotal, and cultural and religious beliefs shaped the perspectives on death.

Conclusion This study emphasizes the intricate emotional landscape of patients and caregivers during advanced cancer prognostic discussions. It highlights the need for

Keywords
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- palliative care
- prognosis
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- communication
- perception

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health care providers to undergo specialized communication training, prioritize shared decision-making, and respect cultural contexts. However, the study's limitations warrant future research for broader generalizability and long-term impact assessment.

Introduction

Cancer continues to be an important global health challenge, affecting millions of lives worldwide.[1] In India, cancer is one of the leading causes of morbidity and mortality, with a growing burden of advanced-stage cases.[2] Advanced cancer, often characterized by a poor prognosis, presents unique challenges for patients, caregivers, and health care providers. As patients enter the palliative care phase, the focus shifts from curative treatments to relief from symptoms, improving the quality of life, and supporting patients through their end-of-life journey. Prognostic discussions are critical in guiding patient care decisions during this time. These discussions entail health care providers communicating information about a patient's disease progression, expected outcomes, and likely life expectancy. However, these conversations are often complex and emotionally charged, requiring skillful and compassionate communication from health care providers. Additionally, patients and their caregivers bring their fears, hopes, and cultural beliefs to the table, influencing how they perceive and respond to prognostic information.[3]

The literature consistently highlights the critical role of prognostic discussions in guiding patient care decisions during the advanced phase of cancer. By fostering open communication, informed decision-making, and patient-centered care, these discussions have the potential to improve the quality of life for patients and their families, promote realistic treatment choices, and optimize resource allocation in advanced cancer care. However, much of the research is from the developed countries.[4]

Understanding the experiences of patients and caregivers with prognostic discussions is of paramount importance in the Indian health care landscape. This qualitative research delves into the critical aspect of prognostic discussions within the context of advanced cancer, employing a constructionist and interpretive framework to gain valuable insights into the lived experiences of patients and their caregivers. Through qualitative exploration, we seek to identify the recurring themes and patterns that emerge from the narratives of patients and caregivers. We employed thematic analysis to help uncover the underlying complexities and nuances surrounding prognostic discussions.

Materials and Methods

This is a prospective qualitative research study. The participants were selected using purposive sampling to ensure diversity in experiences. Accrual followed till data saturation.

Inclusion and exclusion criteria: All adult patients with advanced cancer (stage III or IV, relapsed, refractory cancer) referred to a palliative care clinic at an Indian tertiary cancer center over the period from April 2019 to June 2021 were included in the study. Patients who were clinically unstable to go through the study procedure were excluded. Only one caregiver per patient was approached to participate in the study. Caregivers who had been providing care for at least 6 months and were $\geq$18 years were included. Incomplete interviews were excluded from the study.

Primary and secondary outcomes: The main outcome centered on patients' and caregivers' understanding and interpretation of the prognostic information shared with them. The secondary outcomes encompassed the unaddressed needs surrounding the sharing of such information, coping mechanisms, as well as the impact of societal, cultural, and religious elements on their choices and preferences regarding treatment.

Patients were assessed at the time of the first contact with the service. Demographic and clinical data were gathered from charts. Semi-structured interviews were engaged to capture comprehensive and intricate insights into their interactions with prognostic discussions. Employing open-ended inquiries, the study aimed to probe emotions, thoughts, and engagements with health care providers during these conversations. The transcripts underwent thorough examination, coding, and categorization to pinpoint recurring themes tied to patient and caregiver experiences with prognostic discussions.[5]

In this study, qualified medical professionals skilled in qualitative research diligently worked to mitigate biases stemming from personal attributes, qualifications, participant relationships, assumptions, and engagement with research participants. Interviews occurred in a distraction-free clinic side room, devoid of time constraints. Notably, researchers took meticulous notes on participant remarks and their reflections during interviews, with all discourse conducted exclusively in Hindi, a language in which the investigators were proficient. This linguistic congruence between investigators and participants played a pivotal role in facilitating effective communication and comprehension (►**Supplementary File S1**, available in the online version only).

To faithfully capture spoken interactions, audio recordings were scrupulously transcribed in Hindi, preserving the subtleties, tones, and nuances inherent in the original spoken language. This step was paramount in upholding the authenticity of conversations and preventing any loss of meaning during transcription. Furthermore, to enable a comprehensive understanding of the amassed data, the transcribed Hindi text underwent a systematic translation into English. This translation process enlisted skilled bilingual translators who employed a rigorous forward–backward translation method. This method initially translated the transcribed Hindi text into English by one group of translators, followed by another group translating the English version back into

Hindi. By comparing this second Hindi version with the original transcription, any disparities or meaning deviations between languages could be identified and rectified. This iterative process ensured a high level of reliability and validity in the translated content.

The analysis employed a thematic approach to scrutinize interview data, uncovering recurrent patterns and themes. The method of constant comparison was applied, aligning new data with existing findings to refine and elaborate emerging themes.[6] Regular assessment ensured that new data either introduced novel insights or fortified previously identified themes, culminating in data saturation.[7]

Statistical Analysis

Statistical analysis were conducted including descriptive statistics (frequency, mean, and median), using Microsoft Excel.

Ethics

All procedures performed in studies involving human participants were per 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. The institutional ethics committee approved this research (IEC/1018/3128/001 dated October 08, 2018).

Results

The study included 21 participants, categorized as follows: 15 caregivers responsible for advanced cancer patients and 3 pairs of patients and caregivers. They were denoted as participant 1 (P1) to participant 21 (P21). Caregivers comprised 3 wives, 3 husbands, 6 sons, 1 son-in-law, 2 daughters, 1 father, and 2 brothers, with 1 interview per category. Patients had a median age of 62 years (range: 40–58 years), while caregivers had a median age of 57 years (range: 35–78 years). In terms of gender, 28.6% were females and 71.4% were males. Marital status indicated that 90.5% were married or living with a partner, with 9.5% being widowed. Regarding education, 28.6% completed junior high school, 52.4% were high school graduates, 9.5% had some college or vocational school education, 4.8% held a college or university degree, and another 4.8% had a graduate degree or professional training. Employment status showed that 42.8% were full-time employed but had lost their jobs, 19% were part-time employed but lost their jobs, 9.5% were homemakers, 23.8% were unemployed, and 4.8% were retired. In terms of household income, 57.1% earned less than INR 10,000, 38.1% earned INR 10,000 to 40,000, and 4.8% earned between INR 40,000 and 75,000. Among patients, 33.3% had breast cancer, and 66.7% had thoracic cancer. All patients (100%) had stage IV cancer diagnoses (►**Table 1**). The study delved into participants' experiences through thematic analysis, uncovering five pivotal themes: (1) perception and comprehension of prognostic information, (2) emotional impact of prognostic discussions, (3) decision-making and treatment preferences, (4) communication with health care providers, and (5) cultural and religious influences.

Table 1 Participant characteristics ($N = 21$)

Characteristic	*n* (%)
Age (y)	
18–39	1 (10.3)
40–49	5 (17.2)
50–59	6 (17.2)
60–69	5 (34.5)
70–79	4 (20.7)
Sex	
Female	6 (28.6)
Male	15 (71.4)
Marital status	
Married and living with a partner	19 (90.5)
Widowed	2 (9.5)
Highest education	
Junior high school	6 (28.6)
High school graduate	11 (52.4)
Some college or vocational school	2 (9.5)
College or university degree	1 (4.8)
Graduate degree or professional training	1 (4.8)
Employment status	
Employed full-time, lost job	9 (42.8)
Employed part-time, lost job	4 (19)
Homemaker	2 (9.5)
Unemployed	5 (23.8)
Retired	1 (4.8)
Household income	
Less than INR 10,000	12 (57.1)
INR 10,000–40,000	8 (38.1)
INR 40,000–75,000	1 (4.8)
Cancer type (patients, $n = 3$)	
Breast	1 (33.3)
Thoracic	2 (66.7)
Cancer stage (patients, $n = 3$)	
Stage IV	3 (100)

Theme 1: Perception and Understanding of Prognostic Information

The first theme explores how patients and caregivers perceive and comprehend prognostic information conveyed by health care providers. Many patients found it challenging to understand medical jargon and prognostic terms, leading

to feelings of confusion and uncertainty. Caregivers often play a crucial role in translating medical information and making it more accessible to patients.

Subtheme 1: Patient's Perspectives

Patients expressed mixed emotions when receiving prognostic information, ranging from shock and denial to acceptance and preparation for the future. Some patients found it empowering to have a realistic understanding of their prognosis, allowing them to make informed decisions about their care.

Patient (P8) said that he is happy with the prognostic discussion: "I am happy you told this to me, I am feeling lighter … doctor used to talk about this drug and that drug, but you told me about my life. I am happy."

Patient (P9): "Yes, I am happy to know. I am thinking whatever life is remaining it should be with smile and happiness … with care they are taking of mine."

Patient (P11) reported fulfillment with their life: "There's nothing left as experience for me … I lived 70 years. Now there is nothing left to experience more …."

Subtheme 2: Caregiver's Perspectives

Caregivers also shared their experiences in supporting patients during prognostic discussions. They expressed the delicate balance between providing hope and maintaining honesty about the patient's condition. Additionally, caregivers discussed their struggle to maintain emotional composure while offering support to their loved ones.

Caregiver (P6): "What to say now? He is in a lot of pain, we don't sleep the whole night, and he is incontinent now."

Caregiver (P7): "I don't feel good about this discussion … you talked about his life expectancy … what to say now? He is in a lot of pain."

Caregiver (P10): "Diagnosis was not made early … she was getting water accumulation repeatedly in the abdomen … we only came to know it after a major surgery."

Theme 2: Emotional Impact of Prognostic Discussions

The second theme delves into the emotional impact of prognostic discussions on both patients and caregivers. Receiving news of a limited life expectancy elicited intense emotional responses, including anxiety, sadness, and fear of the unknown.

Subtheme 1: Patient's Emotions

Patients described feelings of grief and a sense of loss for the life they once had, coupled with a desire to cherish the time they had left with their families. The emotional turmoil often influenced their decision-making process regarding treatment options and end-of-life care preferences.

Patient (P15): "Doctor has told me that my disease is incurable now … and I can sense that my life is limited now … after knowing initially was mentally and physically stressed and in fear. I cried too … I have too many responsibilities of family."

Subtheme 2: Caregiver's Emotions

Caregivers experienced a unique emotional burden, characterized by feelings of helplessness, guilt, and grief. Many caregivers struggled with the responsibility of providing care while dealing with their emotions, which often impacted their mental well-being.

Caregiver (P1): "I am very sad … my heart is very sad … I still feel he will live a long life … I still wish he should live more."

Caregiver (P13): "I just felt that if I would have brought him earlier, he would have received good treatment. We were late …."

Caregiver (P14) reported, "You told me this … you did good … but … I am tensed after knowing this … how I will live without him … (a long silence) … will there be no treatment?"

Theme 3: Decision-Making and Treatment Preferences

This theme explores how prognostic discussions influenced patients' decision-making processes and treatment preferences.

Subtheme 1: Patient's Decision-Making Process

Patients emphasized the importance of being actively involved in decisions related to their care. A comprehensive understanding of their prognosis allowed them to make choices aligned with their values and priorities.

Patient (P4): "Doctor has told me that my disease is incurable now … I have responsibilities to my family … I should start making provisions for them so that they can live when I am gone."

Subtheme 2: Caregiver's Role in Decision-Making

Caregivers described their supportive role in helping patients make informed decisions. They provided emotional and practical support throughout the decision-making process, ensuring the patient's choices were respected and followed.

Caregiver (P13) was happy: "When I was told earlier by the oncologist that my father will live for about 6 months to a year only, I decided not to go for chemotherapy and will work for his comfort now … After knowing his life ahead, I am working in every aspect to fulfill his wishes."

Caregiver (P19): "It's not in our culture to say you're going to die. I don't even want to accept myself still. I know that she is ill, but I'm still thinking you never know. Miracles may happen or something. It's hard, but I will never tell her. She doesn't know now. She doesn't know. I don't think I would like her to know because she'll be scared or something. But in our culture, you never say to the patient."

Theme 4: Communication with Health Care Providers

The fourth theme highlights the significance of effective communication between patients, caregivers, and health care providers during prognostic discussions.

Subtheme 1: Patient–Provider Communication

Patients valued health care providers who communicated with compassion, honesty, and empathy. The quality of the patient–provider relationship notably influenced patients' ability to process and cope with prognostic information.

Patient (P8): Prognostic discussion helped him to look into his future, but at the same time, concern about the future of his family was his main concern: "What will happen to me is in god's hand; it's his wish … it's matter of sadness … I came to this hospital and was not cured … I am prepared for this now … I already stopped thinking about the past now. I am worried about my family …."

Subtheme 2: Caregiver–Provider Communication

Caregivers emphasized the need for health care providers to involve them in the discussions about the patient's prognosis and care plan. Transparent communication with caregivers fostered trust and facilitated coordinated care.

Caregiver (P16): "When I heard this, I was shocked … I am shaken … I was determined I wouldn't give up … now I will give her happiness as much as I can."

Caregiver (P17): "Yes … you told the scenario with her … her cancer is not curable … I was shocked after hearing … (silence … looks a bit frustrated …) … we will give her medicine to relieve her pain."

Caregiver(P2): "Experience is like … I was in follow-up till date … information was like everything is going proper … he is on chemo tablets and health was improving too. Yesterday we had a test and an infection has happened … so we are in a different place today …."

Caregiver (P3): "I felt good about this discussion because no doctor has told this much detail about his life expectancy. You are doing good things by telling such information … many people give many opinions but what you have told me is reality … now I will try to take care of him in the best possible way."

Caregiver (P5): "I feel good about this discussion … if you can tell the life expectancy of the patient in future, it will be good for caregivers … now we know … so we will fulfill her wishes …."

Caregiver (P17): In favor of such a prognostic discussion, as he feels that it will prepare him for the future: "Actually you did right … because if it would have happened suddenly, we might have felt more troubled … whatever we came to know now … we are prepared … Now we know the possibility of scenarios with her … We will face all those problems. Due to this, we will feel less shocked eventually."

Theme 5: Cultural and Religious Influences

The final theme explores how cultural and religious beliefs influenced patients' and caregivers' experiences with prognostic discussions.

One patient and one caregiver reported their feelings about future perspectives during the prognostic discussion.

Subtheme 1: Impact of Culture on Prognostic Discussions

Indian families play a central role in caregiving and decision-making, considering cultural values and familial obligations. Language, metaphors, and reliance on traditional healing practices also shape how patients and caregivers perceive and cope with prognosis.

Example of emphasizing stoicism and acceptance when facing serious illness or death, with the belief in karma and acceptance of fate playing a role: Patient (P12)—"So my cancer is considered very, very dangerous and I shouldn't say my cancer … I believe in God. God says that in everything that comes out of your mouth, you always have to say positive about us. The more we say about negative things, the more that negativity will come to us."

A different example where the participant discussed openly about prognosis, fears, and hopes: Caregiver (P21)—"You're left in a state of uncertainty because no one can give you a definitive answer. You're constantly in fear, if you will get a call from the hospital that he is no more. You cannot share within the family; it's just a waiting game."

Subtheme 2: Religious Coping Mechanisms

Religion provided comfort and hope to many patients and caregivers facing terminal illnesses. Religious beliefs influenced their coping mechanisms and perspectives on life and death.

Caregiver (P18): "I'm a religious person, as in I believe that there is a higher power looking out for my family. God has been helping us throughout this whole illness, and whatever happens will happen for good."

Patient (P20): "Telling 'my God, my God' became more frequent compared with the past. I talked to my God. Now I have more attention toward God, maybe 3 times or maybe 10 times more."

Structured Discussion

Main Findings/Results of the Study

The outcomes of this study illuminate the complex and multifaceted nature of discussions centered around prognosis in advanced cancer. This research underscores that when patients and their caregivers are confronted with the harsh reality of a limited life expectancy, they traverse a diverse spectrum of emotions and obstacles. These intricate dynamics emphasize the crucial role that health care providers play in understanding the subtleties embedded within these discussions, allowing them to deliver care that is both personalized and compassionate. The researchers played a crucial role in approaching the emotionally intense areas with professionalism and sensitivity. They provided support and guidance to both the patients and caregivers, acknowledging the difficult psychological state they were experiencing. The researchers ensured that their interactions were compassionate and that they helped professionally and ethically throughout the study.

What This Study Adds

The emotional landscape experienced by patients and caregivers is profound and intricate.[8–11] The revelation of a limited

life expectancy triggers a cascade of feelings ranging from fear and anxiety to sadness and confusion. Caregivers, often close family members or friends, are equally entwined in this emotional journey, grappling with their emotions while striving to provide the best possible support. This study underscores that the interplay of emotions and challenges in this context is intricate and multifaceted, demanding health care providers be attuned to a wide range of human experiences.

Given the substantial emotional toll borne by both patients and caregivers in this challenging phase, it becomes evident that a critical need exists for integrating comprehensive psychosocial support and counseling services into the framework of palliative care protocols. This inclusion is vital to ensure that the mental and emotional well-being of patients and caregivers is thoughtfully addressed alongside their medical needs. The study highlights that the holistic care approach should encompass not only physical comfort but also emotional solace, thereby improving the overall quality of life during these difficult times.

At the heart of this approach lies the concept of shared decision-making.[12–16] This intricate process serves as a pivotal bridge between patients' treatment preferences and their deeply rooted values and aspirations. The study stresses that health care providers must recognize the significance of involving patients and caregivers in this decision-making process. This integration empowers patients to have a voice in their care, aligning medical choices with their personal beliefs and desires.

For this approach to be successful, health care providers must master the art of effective and empathetic communication during prognostic discussions. The relay of information should be clear, compassionate, and comprehensible to all parties involved. The study underscores the importance of health care providers possessing the skill to convey complex medical information in a way that resonates with patients and caregivers, reducing confusion and facilitating informed decision-making.[17]

Furthermore, the study underscores the importance of acknowledging the influence of cultural and religious factors. Cultural norms and beliefs surrounding death and dying played a role in shaping patients' and caregivers' reactions to prognostic information. Certain Indian cultures emphasize stoicism and acceptance when facing serious illness or death. Families may maintain a calm demeanor, focusing on practical matters and avoiding emotional expression. The belief in karma and acceptance of fate play a role in this approach.[18] Other cultural groups encourage emotional expression. Families openly discuss prognosis, fears, and hopes. Indian families often play a central role in caregiving and decision-making. Collective family discussions consider cultural values, familial obligations, and the desire to protect the patient from distressing information.[19] Religion and spirituality shape end-of-life perspectives. Hinduism, Buddhism, and other spiritual beliefs influence how individuals perceive death, the afterlife, and the acceptance of mortality. Rituals, prayers, and metaphors related to illness and suffering are integral to the cultural context.[20] Patients come from diverse backgrounds, each with their unique perspectives on matters of death and dying. Health care providers must recognize and respect these differences, ensuring that care is tailored to honor patients' individual beliefs and values. This cultural sensitivity enriches the patient–provider relationship, fostering an environment of trust and understanding.[21–26]

Implications and Recommendations

To enhance communication between health care providers and advanced cancer patients, specialized training in delivering sensitive news with empathy is essential. Integrating palliative care education into medical training empowers professionals to offer patient-centered care. Cultural competence training within palliative care equips providers to respect diverse cultural perspectives. Patient-centered care, involving patients and caregivers in decision-making, fosters a more empathetic approach to cancer care.

Significance

This study bridges the gap between the medical community and advanced cancer patients. Insights from patients and caregivers guide health care providers, policymakers, and researchers in understanding the challenges of terminal illness. Exploring emotional and cultural dimensions in prognostic discussions, it informs communication strategies prioritizing the patient's perspective. This enhances empathetic conversations, aiding informed decisions and improving end-of-life care. Additionally, it informs tailored training programs for palliative care professionals, fostering compassion and inclusivity.

Limitations and Future Directions

This study, while insightful, has limitations, including a small sample size and potential recruitment biases, and inadvertent delay due to the coronavirus pandemic. In response to the pandemic, we implemented measures to mitigate its impact on the study like adapting data collection methods to align with safety protocols and extending the data collection period to address any potential influence of the pandemic on the data. Despite that, we encountered reluctance from potential participants and managed to recruit 15 caregivers and 3 pairs of patients and caregivers for our study. The sensitive nature of the topic led to many declining participations. Additionally, contextual constraints in a tertiary cancer center in India (such as time limitations, transportation issues, and emotional stress) influenced willingness to participate. However, data saturation was achieved, allowing us to explore research questions thoroughly. We believe that our focus on qualitative depth compensates for the limited sample size, justifying our approach. However, future studies could explore strategies to enhance recruitment and address these challenges to involve a larger and more diverse participant pool for broader insights. The long-term effects of prognostic discussions on patients and caregivers need in-depth investigation. Furthermore, assessing the effectiveness of communication training for palliative care providers can refine future programs.

Conclusion

In conclusion, understanding the experiences of patients with advanced cancer and their caregivers in prognostic discussions is crucial for delivering patient-centered care in the palliative

care setting. Effective communication, emotional support, and cultural sensitivity are vital in fostering a compassionate and understanding health care environment for patients and caregivers facing terminal illnesses. By addressing the challenges identified in this study, health care providers can notably improve the cancer care experience in India.

Patient's Consent

Informed consent was obtained from all the participants before conducting the interviews, and anonymity and confidentiality were ensured throughout the research process.

Data Availability Statement

Data are available with the corresponding author and can be shared on reasonable request.

Authors' Contributions

Substantial contributions to the conception or design of the work and acquisition, analysis, or interpretation of data for the work were made by A.T., A.G., and M.A.M. Drafting the work and revising it critically for important intellectual content were done by A.T. and A.G. Final approval of the version to be published was given by all the authors. A.T., A.G., and M.A.M. agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

None declared.

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Outcomes with Methotrexate-Free Dyad Chemotherapy in Osteosarcoma Patients: Audit from a Resource-Limited Setting

Nidhi Gupta[1] Kislay Dimri[1] Sudhir Kumar Garg[2] Awadhesh Kumar Pandey[1] Aanchal Arora[3]

[1] Department of Radiation Oncology, Government Medical College and Hospital, Chandigarh, India
[2] Department of Orthopaedics, Government Medical College and Hospital, Chandigarh, India
[3] Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Address for correspondence Nidhi Gupta, MD, DNB, Department of Radiation Oncology, Government Medical College and Hospital, Sector 32, Chandigarh 160030, India (e-mail: nidhiguptaonco@gmail.com).

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Abstract

Introduction Multiagent chemotherapy forms the backbone for the management of osteosarcoma. The globally accepted chemotherapy regimens for osteosarcoma include a combination of Adriamycin, cisplatin, and high-dose methotrexate (HDMTX). However, non-HDMTX regimens are predominantly used in India, secondary to patient profile, toxicity, administration, logistics, and financial constraints. We present our outcomes with a two-drug dyad chemotherapy consisting of Adriamycin and cisplatin in a resource-limited setting.

Objective To determine the disease free and overall survival of osteosarcoma patients and to evaluate the prognostic factors affecting OS for patients with localized disease.

Material and Methods The study was a record-based analysis of all osteosarcoma patients presenting at a tertiary care referral center during the period from 2010 to 2019. A total of 127 patients of osteosarcoma were identified, who were evaluated for their demographic and clinical profile, while treatment details and outcomes were evaluated in 123 patients as disease-free survival (DFS) and overall survival (OS). Univariate and multivariate analysis was done for factors influencing OS.

Results The median age at presentation was 18 years and extremities were the most common site of presentation. Localized disease (LD) was seen in 102 (80%) patients, while 25 (20%) patients had metastatic disease (MD). Overall, 83 (84%) patients with LD underwent surgery, of whom 65 (78%) underwent limb salvage surgery, while 18 (22%) underwent amputation. Only 72 (73%) patients completed the planned six cycles of chemotherapy. At a median follow-up of 50.4 (range: 1–166.3) months, the 5-year OS for patients with LD and the entire cohort was 53 and 43%, respectively. For patients with MD, the 1- and 2-year OS were 41 and 7%, respectively. The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. Primary tumor measuring less than 12 cm ($p = 0.03$) and patients undergoing surgery ($p = 0.003$) were found to be statistically significant for improved OS on univariate analysis but not on multivariate analysis.

Keywords
- osteosarcoma
- pediatric tumor
- resource-limited setting
- chemotherapy
- non-high-dose methotrexate
- survival

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Conclusion The two-drug dyad chemotherapy was well tolerated with manageable toxicity. The outcomes were comparable with Indian studies using non-HDMTX regimens that report a 5-year survival of within 50 to 60%, but were inferior to global outcomes and the dose-dense OGS-12 protocol used in India. Raising awareness for early diagnosis, improving the nutritional status, incorporation of sequential third drug (ifosfamide), use of dose-intensive regimens for selected patients, and increasing compliance to treatment may further help improve the outcomes.

Introduction

Osteosarcoma is a rare bone tumor with an annual incidence of 0.3 per 100,000.[1] Nevertheless, in spite of its rarity, it is the most common primary bone tumor.[1,2] Osteosarcoma mainly affects children and adolescents.[2,3] The majority of osteosarcomas arise in extremities, and the lung is the most common site of metastases, followed by bones.[1,4]

Magnetic resonance imaging (MRI) is considered the investigation of choice for evaluation of primary bone tumor. Computed tomography (CT) scans of the chest and bone are preferred to exclude metastatic disease (MD).[2,4] Standard treatment for osteosarcoma consists of induction chemotherapy, followed by surgery and subsequent completion of adjuvant chemotherapy. Radiotherapy has limited role in view of relative radioresistant nature of the tumor.[4,5]

In developed countries, the overall survival (OS) for patients with localized disease (LD) and MD is around 60 to 75% and 30 to 40%, respectively.[6,7] Standard chemotherapy regimens in osteosarcoma include a dyad of chemotherapy consisting of cisplatin and doxorubicin or the MAP regimen: doxorubicin/cisplatin/high-dose methotrexate (HDMTX).[4–6] While HDMTX is the standard of care for the European and American patients, non-HDMTX regimens are predominantly used in developing countries. The hesitancy to use HDMTX regimens in developing countries is because patients present with poor performance status, costs, and excess toxicity. These patients undergo treatment in medical institutions with limited infrastructure in terms of indoor capacity. They also need constant drug-level monitoring and supportive care.[8,9] Non-HDMTX-based regimens are the most commonly used regimens in the majority of the cancer centers in India for high-grade osteosarcoma.[3,10,11]

Published data on osteosarcoma from India are very limited; hence, the exact magnitude and disease trend are not properly understood. There have been a few Indian studies in recent years, which report the 5-year survival rates as somewhat inferior to the world literature.[2,10,11] We present here the clinicodemographic profile, treatment patterns, and outcomes in terms of DFS and OS for osteosarcoma patients managed with dyad chemotherapy with Adriamycin and cisplatin (AC) in a resource-limited setting where patients generally present late with large tumors and poor performance status.

Materials and Methods

Study Design

This is a retrospective observational study that involves a record-based analysis of all osteosarcoma patients diagnosed and treated at a tertiary care referral center during the period from 2010 to 2019.

Sample Size

A total of 127 histopathologically proven patients of osteosarcoma were identified, who were evaluated for their demographic and clinical profile. One hundred and twenty-three patients who reported for treatment were evaluated for treatment details, recurrence patterns, and survival outcomes.

Inclusion and Exclusion Criteria

All biopsy-proven patients of osteosarcoma who underwent treatment at the tertiary care referral center during the period from 2010 to 2019 were included in the analysis. Patients who did not have a histopathology confirmation from the institutional pathology department or who did not receive treatment at our center were excluded from the analysis.

Primary and Secondary Outcomes

Primary outcomes included the following:

- Evaluation of the disease-free survival (DFS) and OS.
- Evaluation of the demographic and clinical profile of the osteosarcoma patients.

Secondary outcomes included evaluation of the prognostic factors affecting OS for patients with LD.

Study Setting

Data were analyzed for the demographic profile including age at presentation, gender, baseline body mass index (BMI) and hemoglobin levels, rural or urban residence, and any preexisting morbidities or addiction. The clinical profile was evaluated for symptoms at presentation, duration of symptoms before initiating treatment, tumor site, laterality, radiological investigation done for the primary site and MD, maximum size of the primary tumor, and the presence of LD or MD.

Treatment for LD or for patients with curative intent consisted of delivering three to four cycles of neoadjuvant chemotherapy (NACT) followed by surgery, which was followed by

adjuvant consolidation chemotherapy. As per our institutional protocol, three to four cycles of dyad chemotherapy were delivered in the neoadjuvant setting consisting of AC regimen[4] as follows.

Doxorubicin 25 mg/m^2/d IV over 2 hours (days 1–3), cisplatin 100 mg/m^2 IV over 3 hours (day 1), and cycles repeated every 3 weeks. Prophylactic growth factors were not used. The details of NACT and adjuvant chemotherapy delivered in terms of regimen, the number of cycles, toxicity, and timing with respect to local treatment were analyzed. Adjuvant radiotherapy was added for selected patients, predominantly for positive margins. Surgery and radiation details were also evaluated.

Response to NACT was assessed clinically and radiologically and decisions for surgery were taken. Histological evaluation for response to chemotherapy and extent of tumor necrosis was assessed using the Huvos grading system.[12] In the initial years when the Huvos grading was not done universally, many patients did not have the information available in the histopathology reports. Adjuvant chemotherapy was given with the aim to complete a total of six cycles.[4]

Management including chemotherapy protocols for patients with recurrent or MD were selected from the recommended options from standard treatment guidelines.[4] These protocols were individualized based on disease burden, site of metastases, general condition of the patient, and family decision. Recurrence patterns, treatment for recurrence, and MD were also analyzed. Outcomes were evaluated in terms of DFS and OS. OS was calculated from the date of registration in the department to death from any cause, while DFS was calculated from the date of registration to the first event (local recurrence, metastases, or death from any cause). Prognostic factors affecting OS for patients with LD were assessed.

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences version 17 (IBM Inc., Chicago, IL, United States). Descriptive statistics were used for demographic and clinical parameters and treatment modalities, and were reported as median and percentages. OS and progression-free survival were estimated according to the Kaplan–Meier method, stratified by the LD and MD. Univariate and multivariate (Cox proportional hazards regression model) analyses were used to assess the factors influencing OS in patients with LD. Multivariate analysis was performed on the factors that were found to be significant on univariate analysis. A p value of less than 0.05 was considered significant. Age of patient (>21 years), gender, duration of presenting symptoms (>6 months), primary site (lower extremity vs. upper extremity), primary tumor size (<12 cm), number of chemotherapy cycles (≥6), use of surgery as local treatment, and grade of necrosis on histopathology were included as covariates on univariate and multivariate analysis.

Ethics

Waiver was obtained from the institutional ethics committee (reference number GMCH/IEC/2024/1341) as this was a record-based analysis and did not involve any patient interaction or intervention.

Results

A total of 127 patients were evaluated for demographic and clinical profile. Four patients did not report for treatment. The remaining 123 patients were evaluated for treatment details, recurrence pattern, and outcomes.

Demography

In our registry, the median age at presentation was 18 years. The majority of patients had poor nutritional status as reflected by the BMI and baseline hemoglobin. Seventy-seven (61%) patients had a BMI less than 18.5 and 25 (20%) patients had baseline hemoglobin less than 10 g/dL. Details of age and gender distribution, BMI, residence, marital status, comorbidities, and addiction habits are listed in ►**Table 1**.

Table 1 Demographic profile of osteosarcoma patients

Parameter	$n = 127$ (%)
Age (y)	
0–10	4 (3.2)
11–20	83 (65.4)
21–30	27 (21.3)
>30	13 (10.2)
Median age (y)	18 (8–63)
Sex	
Male	86 (67.7)
Female	41 (32.3)
Median hemoglobin (g/dL), *n* (range)	11.8 (6.8–15.6)
Median body mass index (BMI)	17.3 (4.8–31.8)
<18.5	77 (60.6)
18.6–22.9	39 (30.7)
>23	11 (8.7)
Residence	
Urban	44 (34.6)
Rural	83 (65.4)
Marital status	
Single	110 (86.6)
Married	17(13.4)
Morbidity	
Epilepsy	4(3.2)
Tuberculosis	4 (3.2)
CAD	2(1.6)
None	119 (93.7)
Addiction	
Tobacco	6 (4.7)
Alcohol	4 (3.2)
None	119 (93.7)

Abbreviation: CAD, coronary artery disease.

Clinicopathological Profile

Fifty-three (42%) patients presented 3 months after the onset of symptoms and 89 (70%) patients had a primary tumor greater than 8 cm at presentation. The majority of tumors, 113 (89%), arose from the metaphysis. Conventional radiographs were done for all patients at presentation. The most common positive immunohistochemistry markers were SATB2, vimentin, and cytokeratin. Conventional osteosarcoma was the most common histology, followed by chondroblastic osteosarcoma. Details of presenting symptoms, site of presentation, and radiological investigations are listed in ►**Table 2**.

Systemic Treatment

Eighty-nine (89/99; 90%) patients with LD received NACT with a median of three cycles, while the remaining underwent upfront surgery. In the neoadjuvant setting, all patients received the AC regimen. Local therapy was followed by adjuvant chemotherapy with the aim to complete a total of six cycles; however, only 72/99 (73%) patients with LD completed six cycles of chemotherapy. In the adjuvant setting, 65/76 (86%) patients received the AC regimen, while 11/76 (14%) received the ifosfamide/etoposide (IE) regimen (►**Table 3**). During or within 4 weeks after completing adjuvant chemotherapy, 10 (10%) patients already had progressive disease.

Local Treatment

Overall, 83 (84%) of the 99 patients with LD underwent surgery, of whom 65 (78%) underwent limb salvage surgery, while 18 (22%) underwent amputation. Four patients with positive margins received adjuvant radiation after surgery with doses varying from 45 to 54 Gy. The degree of necrosis was assessed by Huvos grade on postoperative specimen. Of the 51 (57%) patients reported, only 12 (24%) patients showed grade 4 necrosis following NACT. Hematological toxicity was the predominant toxicity reported in these patients. The details are presented in ►**Table 3**.

Treatment for Relapse, Progressive, or Metastatic Disease

The most common sites of recurrence and metastases at presentation were the lungs seen in 31/39 (80%) and 24/24 (100%) patients, respectively. This was followed by bones. Chemotherapy was the predominant treatment modality with surgery and radiotherapy received by selected patients. The details of this treatment are reported in ►**Table 4**.

Outcomes

The median follow-up was 50.4 (range: 1–166.3) months. The 5-year OS for patients with LD and the entire cohort was 53 and 43%, respectively, while the 3-year OS for patients with LD and the entire cohort was 63 and 51%, respectively. For patients with MD, the 1- and 2-year OS was 41 and 7%, respectively (►**Fig. 1**). The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. A primary tumor size of less than 12 cm ($p = 0.03$) and patients undergoing surgery ($p = 0.003$), as compared with patients not undergoing surgery, were found to be statistically significant for improved

Table 2 Clinicopathological profile of OS of patients at presentation

Parameter	$n = 127$ (%)
Presenting symptom	
Pain	71 (56)
Swelling	94 (74)
Restricted movement	28 (22)
History of trauma	14 (11)
Pathological fracture at presentation	9 (7.1)
Duration of symptoms before reporting (mo)	
<3	74 (58.3)
3–6	30 (23.6)
6–12	15(11.8)
>12	8(6.3)
Site	
Extremity	122 (96)
Pelvis	2 (1.6)
Face (mandible)	1 (0.8)
Soft tissue/extraskeletal	2 (1.6)
Common extremity subsite	
Femur	59 (46.5)
Tibia	39 (30.7)
Humerus	19 (15)
Fibula	4 (3.2)
Laterality	
Left	72 (56.7)
Right	55 (43.3)
Radiological investigation for primary	
MRI	117 (92.1)
CT scan	10 (7.9)
Radiological size of primary	
<8 cm	38 (30)
8–12 cm	54 (42.5)
>12 cm	35 (27.6)
Radiology consistent with OS	64 (50.4)
Radiological investigation for metastatic disease	
CXR	9 (7)
CT chest	112 (88.2)
PET scan	6 (4.7)
Disease at presentation	
Localized	102 (80.3)
Metastatic	25 (19.7)
Bone marrow positive	10/38 (7.9)

Abbreviations: CT, computed tomography; CXR, chest X-ray; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography.

Table 3 Treatment for localized disease ($n = 99$)

Parameter	*n* (%)
Neoadjuvant chemotherapy	**89 (89.9)**
Median number of cycles	3 (1–6)
AC	89 (100)
Surgery	**83 (83.8)**
Limb salvage surgery	65 (78)
Amputation	18 (22)
Margin positive	4 (4.8)
Adjuvant radiotherapy	**4**
Dose: 45–54 Gy	4
Tumor necrosis	**51**
Grade 1	14 (27.5)
Grade 2	9 (17.6)
Grade 3	8 (15.7)
Grade 4	12 (23.5)
Adjuvant chemotherapy	**76 (76.8)**
Median number of cycles	3 (0–6)
Adriamycin/cisplatin	65 (85.5)
Ifosfamide/etoposide	11 (14.5)
Chemotherapy completed: 6 cycles	
Yes	72 (72.7)
No	27 (27.3)
Toxicity grade 3/4	
Anemia	18 (18.1)
Neutropenia	26 (26.3)
sepsis and shock	2 (2)
Vomiting	4 (4)
Renal failure	1 (1)
PD on 4 wk after adjuvant chemotherapy	10 (10.1)

Abbreviation: AC, Adriamycin and cisplatin; PD, progressive disease.

Table 4 Treatment for relapse/progressive/metastatic disease

Parameter	*n* (%)
Treatment for relapse/progressive disease ($n = 39$)	
Site of recurrence/progression	
Bone	8 (20.5)
Lungs	22 (56.4)
Lungs and bones	6 (15.4)
Lungs and brain	3 (7.7)
Local site	11 (28.2)
Treatment	
Chemotherapy	**28 (71.8)**
Median number of cycles	1 (1–6)
Gemcitabine/docetaxel	3
Adriamycin/cisplatin	3
Ifosfamide/etoposide	15
Gemcitabine/cisplatin	3
Gemcitabine	2
Oral metronomic	2
Surgery	**4 (10.3)**
Amputation	2
Local resection	2
Radiotherapy	**7 (18)**
20–30 Gy	5
56–60 Gy	2
Treatment for metastatic disease at presentation ($n = 24$)	
Sites of metastases	
Lungs	22 (91.7)
Lungs and bones	2 (8.3)
First-line chemotherapy	24 (100)
Median number of cycles	3 (1–6)
Adriamycin/cisplatin	20
Adriamycin/cisplatin/ifosfamide	5
Second-line chemotherapy	7 (29.2)
Median number of cycles	3 (1–6)
Ifosfamide/etoposide	2
Docetaxel/gemcitabine	4
Pazopanib	1
Surgery	13 (54.2)
Amputation	7
Local resection	5
Radiotherapy (20–30 Gy)	3 (12.5)

OS on univariate but not on multivariate analysis in patients with LD. The details of univariate and multivariate analyses are reported in ►**Table 5**.

Discussion

This analysis from a tertiary care center presents the outcomes with a two-drug dyad chemotherapy, delivered in a resource-limited setting, where patients present late with large tumors and poor performance status.

Published literature shows the median age for osteosarcoma patients falls between 15 and 19 years with a male preponderance. This is similar to our study, where the median age was 18 years and the male-to-female ratio was 2:1.[1–3,10]

The most common symptoms (pain and swelling), most common sites of presentation (extremities), and stratification as per LD (80%) and MD (20%) in our analyses are similar to the global and national statistics.[1,2,10,11]

In contrast to the western population where patients present early with small tumor volumes, 53 (42%) of our

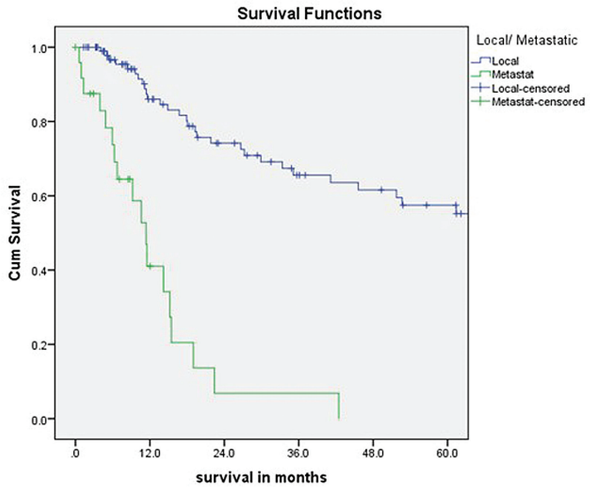

Fig. 1 5-Year Survival for patients with Localized Disease (Local) and Metastatic Disease (Metastat)

patients presented for treatment more than 3 months after the onset of symptoms. This event is similar to the study by Nataraj et al from North India where 43% patients presented more than 4 months after the onset of symptoms.[10] Larger tumor volume is considered to be an adverse prognostic factor. Tumors greater than 12 cm were seen in 35 (28%) of our patients, similar to a study by Bajpai et al from Tata Memorial Hospital India, in which the median tumor size was 11.5 cm.[3]

Financial constraints influence management decisions, with 117 (92%) patients affording MRI for the primary tumor, while positron emission tomography (PET) CT was done in less than 5% patients.[13] Bone marrow biopsy was done for staging in limited patients predominantly with lung metastases or symptomatic for bony pain/raised alkaline phosphatase, who cannot afford to get a PET scan or bone scan. Fertility preservation counselling was done for all patients before the start of chemotherapy, but none consented for the same, in view of the additional costs associated with it.[14]

Multiagent NACT prior to local treatment helps downstage the disease, increase the probability of R0 resection, facilitate limb salvage surgery, and improve survival.[5,6] Response to NACT is considered to be an important prognostic factor with patients showing less than 10% viable tumor on histopathology having a significantly better survival.[12,15]

Osteosarcoma chemotherapy protocols mainly utilize a dyad of cisplatin and doxorubicin, with the addition of a third drug, either ifosfamide or HDMTX, which has been shown to improve the efficacy.[16,17] A recent meta-analysis by Anninga et al has demonstrated the superiority of three-drug regimens to two-drug regimens, and its equivalence to four drugs with lesser toxicity.[18]

Dyad chemotherapy using only two agents, AC, given every 3 weeks is the regimen used in our analysis as per our institutional protocol. Hematological toxicity (grades 3 and 4) with chemotherapy included anemia and neutropenia seen in 18 (18%) and 26 (26%) patients, respectively. Two patients had septic shock secondary to neutropenic sepsis. Patients at our center present with poor performance status and nutritional deficiencies as evident from the fact that 77 (61%) patients had BMI less than 18.5 at presentation. Due to social and financial barriers, these patients were unable to adhere to the support required to manage the toxicities arising from more intensive regimens. In our study, 83 (65%) patients report to tertiary care centers from rural areas, who show a poor compliance to treatment, with only 72 (73%) patients with LD completing the six cycles of chemotherapy and only 83 (84%) patients with LD undergoing surgery. In a study from Northeast India, 32% patients failed to complete preoperative chemotherapy and one-third of the patients did not undergo surgery. Only 23% of patients completed planned postoperative chemotherapy.[19] In an analysis on Ewing's sarcoma, patients from our institute, receiving alternating cycles of Vincristine/adriamycin/cyclophosphamide (VAC) and IE chemotherapy, compliance to treatment was poor. Primary tumor size greater than 8 cm ($p = 0.008$), completion of less than 15 cycles of

Table 5 Overall survival: univariate and multivariate Cox regression analysis for patients with localized disease ($n = 99$)

Variable	Univariate analysis			Multivariate analysis		
	HR	CI	*p* value	HR	CI	*p* value
Age >21 y	0.82	0.39–1.74	0.61			
Gender (male)	1.72	0.77–3.83	0.18			
Duration of presenting symptoms >6 mo	0.88	0.39–1.96	0.75			
Primary site (lower extremity vs. upper extremity)	2.02	0.82–4.95	0.12			
Primary tumor size <12 cm	0.28	0.87–0.9	0.03	2.22	0.79–6.21	0.12
No. of chemotherapy cycles: ≥6	0.54	0.25–1.14	0.10			
Underwent surgery	0.25	0.10–0.65	0.003	0.26	0.06–1.15	0.075
Necrosis grade 4 vs. 1	0.24	0.03–2.04	0.19			
Local vs. metastatic disease	3.87	2.11–7.09	0.001			

Abbreviations: CI, confidence interval; HR, hazard ratio.

chemotherapy ($p = 0.005$), and presence of MD ($p = 0.001$) were associated with inferior survival on multivariate analysis.[20]

Adjuvant chemotherapy is delivered after local surgery. Currently, there is no consensus for changing the chemotherapy regimen after a poor response to NACT due to failure in improving outcomes in patients who respond poorly to the regimen.[21] In one large, randomized trial, muramyl tripeptide added to postoperative chemotherapy was associated with a significant advantage in OS.[22] However, there is no consensus for its use due to the availability of only one randomized study and the lack of a statistical significance for the improvement in event-free survival (EFS). The European and American Osteosarcoma Study (EURAMOS-1) was conducted to test the improvement in outcomes, upon the addition of ifosfamide and etoposide to MAP in the postoperative setting in patients with less than 90% histologic response to preoperative chemotherapy. The study confirmed that more than three drugs were not useful.[23] Change of chemotherapy to IE in the adjuvant setting in our study was done for few patients with very poor histological and/or clinical response and good performance status.

Local treatment is planned in a multidisciplinary meeting after clinical and radiological response assessment. Local treatment may consist of limb salvage surgery or amputation.[24] Quality of life is essential for childhood malignancies where the aim is to provide cure with function preservation.[25] In our study, 65/83 (78%) patients in the surgery arm had undergone limb salvage surgery. Amputation is considered when negative margins cannot be achieved without compromising the functional outcomes. Limb salvage surgery with clear margins helps improve functionality, quality of life, and OS.[26,27]

Radiotherapy in this relatively radioresistant tumor is mainly limited for advanced, unresectable axial tumors where resection is likely to result in residual disease and cause unacceptable morbidity.[28] Postoperative radiotherapy is indicated for positive or close margins (>2 mm). Postoperative radiotherapy (45–54 Gy) at our institute is added for positive margins, and four patients received it following limb salvage surgery.

Recurrent osteosarcoma has poor outcomes, with distant metastases being more common than local recurrences as seen in our study.[29] Chemotherapy is the main modality of management and may include ifosfamide, etoposide, gemcitabine, docetaxel, platinum, pazopanib, etc., used alone or in combination.[4,30] Surgery may be considered for local recurrences and resectable disease. Radiotherapy may be preferred for local treatment of primary or oligometastatic sites.[4,31]

Patients with metastases at diagnosis are treated based on the disease burden, performance status, and with the aim to provide a good quality of life.[2,32] Patients with oligometastases and good response to chemotherapy are treated on lines of LD with chemotherapy followed by local therapy and additional radiotherapy for oligometastases, followed by consolidation systemic therapy.[1,4] In our analysis, patients with MD were predominantly treated with AC chemotherapy, with 13/24 (54%) patients undergoing surgery, predominantly consisting of amputation. The choice of regimen in second-line therapy is quite variable (►**Table 4**) and is based on patient profile and drugs used previously.

At a median follow-up of 50.4 months, the 3-year OS for patients with LD and overall cohort was 63, and 51%, respectively, while the 5-year OS for patients with LD and overall cohort was 53 and 43%, respectively. The 3- and 5-year DFS for patients with LD was 41 and 35%, respectively. For the MD, the 1-year OS was 41%, which dropped to 7% by 2 years.

In a study from TMH, Mumbai, at a median follow-up of 86 months, the 5-year OS with OGS-99 enhanced using a three-drug, non-HDMTX regimen was 60%. The 5-year EFS for OGS-99 and OGS-99 enhanced was 38 and 50%, respectively.[3] In another study from TMH, Mumbai, by Bajpai et al,[33] with the OGS-12 protocol, using a three-drug, non-HDMTX regimen, at a median follow-up of 34.31 (range: 2–60) months, in intention-to-treat (ITT) analysis, the 5-year EFS and OS were 56 and 75%, respectively; the same were 60 and 80% in per-protocol analysis. In a study from South India, using a three-drug non-HDMTX regimen, the 3-year OS was 54.6%.[11] Another study from North India, using a two-drug/-four-drug non-HDMTX regimen, reported a 5-year OS of 50%.[10] In HDMTX-based chemotherapy regimens, outcomes as reported from the west report a 5-year OS and EFS of 64.5 and 48.5%, respectively.[34] Another study from the west with HDMTX- based regimen reported 5-year OS and EFS of 63 and 57%, respectively.[5]

Thus, the majority of Indian studies[3,10,11] with non-HDMTX regimens, using two- or three-drug regimens, report a 5-year survival in the range of 50 to 60% and our study using a two-drug non-HDMTX regimen reports a 5-year survival of 53% for LD. However, one of the largest data on osteosarcoma from India, OGS-12 protocol,[33] sequentially using a three-drug non-HDMTX regimen reported excellent outcomes with 5-year OS of 75%, which is comparable to HDMTX-based regimens used in the west.[5,34] The better outcomes with the OGS-12 protocol[33] were attributed to the use of three active drugs, including ifosfamide with increased dose density and improved supportive care including prophylactic growth factors leading to improved compliance. The incidence of febrile neutropenia was 40%, and grade 3/4 thrombocytopenia and anemia were seen in 36 and 51% patients, respectively.

The poor outcomes in our study arise from various geographical, social, and financial barriers that patients from low- and middle-income countries face. These barriers lead to delayed presentation with advanced disease, a poor performance status, and poor compliance to treatment.[8] To improve outcomes in our patients, the addition of a third chemotherapy agent like ifosfamide, similar to OGS-12, may be considered for intensification of treatment.[3,11] However, patients need to be selected based on the baseline performance status, nutritional status, and social and financial resources of the individual patient for compliance with supportive care and more toxic treatment protocols. Awareness and educative programs for early detection, nutritional buildup, and diet management may further help intensify chemotherapy protocols and improve outcomes.

Various studies have reported old age, female gender, good histological response to chemotherapy (<10% viable tumor), size of primary tumor at presentation, tumor size, site, surgical resectability, and presence of metastases as prognostic factors.[35] In our study, on univariate analysis, the factors that were statistically associated with inferior survival in patients with LD included primary tumor greater than 12 cm ($p = 0.03$) and exclusion of surgery ($p = 0.003$) for the management of the primary tumor. However, on multivariate analysis, none of these factors were found to be statistically significant. The presence of MD ($p = 0.001$) was found to be statistically associated with inferior OS.

The limitations of our study are that it was a single institute–based, retrospective analysis of a small number of patients. Details of toxicity arising from treatment were not precisely available. However, in view of the rarity of osteosarcoma, it is difficult to conduct a prospective randomized trial. Nevertheless, our study adds to the existing knowledge on epidemiology and clinical profile of the patients of osteosarcoma. It reports outcomes with a two-drug dyad chemotherapy in a real-world scenario and reports the challenges faced in a resource-limited setting.

Conclusion

In a resource-limited setting where patients present with large tumors and poor general condition, non-HDMTX-based regimens are easily tolerated with acceptable toxicity. Outcomes in our analysis with dyad chemotherapy were similar to other non-HDMTX-based chemotherapy regimens reported from India but were inferior to the OGS-12 protocol used in India and HDMTX-based regimens used in the west. Creating awareness among patients to seek medical attention early along with intensification of treatment by the inclusion of a third drug like ifosfamide for selected patients may help improve outcomes.

Authors' Contributions

All the authors read and approved the manuscript and contributed to it.

N.G. contributed to the concept, data collection, data analysis, and preparation and finalization of the draft. K.D. contributed to the supervision of data collection and revision of the draft. S.K.G. contributed to the concept and revision of the draft. A.K.P. contributed to the concept and supervision of data collection. A.A. contributed to data collection and data analysis.

Patient Consent

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Conflict of Interest

None declared.

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Cervical Cancer Screening: Comparing PAPs Smear with VIA/VILI in Semiurban Women of Delhi

Vinita Sarbhai[1] Shreshtha Aggarwal[1]

[1] Department of Gynaecology and Obstetrics, Kasturba Hospital, Delhi, India

Address for correspondence Vinita Sarbhai, MD, DNB, G-36, First floor, Pamposh Enclave, New Delhi, India 110048 (e-mail: vinitasarbhai@gmail.com).

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Abstract

Introduction Screening with PAPs smear for screening of cervical cancer has been the gold standard for many years in high-income countries but has still not been successful in low- and middle-income country like India due to unavailability at public ground level. Thus, a simple, effective, and low-cost alternative to cervical cytology for cervical cancer prevention is urgently needed for high-risk, low-resource settings.

Objectives The aim was to compare the efficacy of visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) with the PAP smear for screening precursor intraepithelial lesions and early signs of cervical cancer, and to evaluate their potential as alternative screening methods to the PAP smear in a semiurban population in Delhi.

Materials and Methods A total of 127 married, nonpregnant patients between 18 and 65 years were randomly selected from gynecology outpatient department. Then, PAP smear samples were taken from all patients followed by VIA and VILI. Biopsies were then taken from those who showed positive findings in either of the screening methods. Out of these, 50 PAP and VIA-negative women were included as a control group. The diagnostic accuracy of VIA and VILI was compared with PAP smear, for diagnosis of precancerous lesions.

Results VIA and VILI results were positive in 22 patients out of 127 (17.3%). PAP cytology report showed epithelial cell abnormality in 13 cases (10.2%) with atypical squamous cells of undetermined significance in 1 case, atypical glandular cells of undetermined significance in 4 cases, low-grade squamous intraepithelial lesion in 3 cases, and high-grade squamous intraepithelial lesions in 5 cases. PAP smear had showed better specificity (90.79%) and less sensitivity (85.71%) as compared with VIA and VILI method. Sensitivity of VIA was 100% and specificity was 80.26%. Similar parameters were seen with the VILI method also. The overall *p*-value for all the parameters of either screening method was > 0.05; hence, both methods are comparable for screening.

Conclusion VIA and VILI can be employed as initial screening tools in place of PAP smear, particularly in countries with limited resources or developing regions.

Keywords

- visual inspection by acetic acid (VIA)
- visual inspection by Lugol's iodine (VILI)
- PAP smear
- cancer cervix
- screening
- low- and middle-income countries (LMIC)

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Introduction

Carcinoma cervix is the fourth most common cancer among women worldwide, while in low- and middle-income countries (LMICs) it ranks second in gynecological cancers, with approximately 660,000 new cases and 350,000 deaths globally in 2022.[1] GLOBOCAN also estimated an age-standardized incidence rate of 18 per 100,000 women and a cumulative risk of 2.01%.[2] The cervical cancer occurs as a result of long-term persisting infection with high-risk human papillomavirus (HPV), which is accountable for 90 to 100% of cervical cancer cases. Out of which high-risk type 16 and 18 are the two most common, and constitute for about 70% of carcinoma cervix cases.[3]

High-risk behaviors are poor genital hygiene, early age at marriage, early age at first sexual intercourse, multiple partners, repeated pregnancies, long-term contraceptive use particularly oral contraceptives, smoking, and multiparity, which increase the risk of acquiring HPV in women.[4] Though deadliest, yet it is one cancer which is preventable if an effective treatment is given at an earliest stage, which is easily detectable by routine screening. There are approximately 272.8 million women eligible for screening in India.[5] Numerous efforts are in progress for the prevention of cervical cancer by both the government and nonprofit organizations since long but are yet to make any meaningful impact. The screening methods employed by most advanced countries include PAP smear, HPV deoxyribonucleic acid testing, visual inspection with acetic acid (VIA), or a combination of all these. The United States and other high-income countries have reported a reduction in number of new cases of carcinoma cervix by routine screening with PAP smear in sexually active women.[6] The implementation of PAP smears in low resource settings like India is limited due to inadequate health care infrastructure, restricted health budgets, and a shortage of laboratories and specialized personnel needed for slide preparation and diagnosis. Repeat PAPs smear is needed once every 3 years due to its lower sensitivity. Technical and financial limitations in organizing cytology screenings have prompted the evaluation of visual inspection methods as viable alternatives.

HPV testing is also recommended as an alternative for screening, but it is associated with high costs. Thus, visual inspection methods like VIA and visual inspection with Lugol's iodine (VILI) are the low-cost screening tools that have been proposed as alternatives to PAP smear-based programs, with VIA being the most commonly employed and researched. VIA is simple, cost-effective, and easily scalable for large populations. It requires no laboratory support and can be reliably performed by trained paramedical staff, nurses, and doctors. However, the gold standard for diagnosis of cervical dysplasia is colposcopy-guided biopsy but it is more time-consuming and requires handling by a specialist with good experience.[7] Thus, in this study, it is hypothesized that visual inspection methods have similar screening efficacy as compared with PAPs, and hence they can replace PAPs for mass screening. They have the potential to be utilized as an alternate first screening method and be a pragmatic and effective public health approach for cervical cancer prevention.

Materials and Methods

Study Design

This is a cross-sectional study, carried out at the Department of Obstetrics and Gynecology, Kasturba Hospital, Delhi, India, after due clearance from the institutional ethical committee.

Sample Size

A total of 127 patients were selected from the gynecology outpatient department (OPD) and enrolled for the study after informed consent. The sample size was calculated as per the study by Das et al,[8] using the formula:

$$N = \frac{Z\alpha\text{^}2 \times [P\,(1-P)]}{L\text{^}2}$$

The minimum sample size was around 102.67, nearly $= 103$, taking $Z\alpha$ at a confidence level of 95% as 1.96. L as margin of error $= 5\%$. P is the prevalence of preinvasive lesion of cervical cancer being 7.2%.[9]

Inclusion Criterion

Only married, nonpregnant women between the age group of 18 and 65 years were included.

Exclusion Criterion

Unmarried women, women with confirmed or suspected pregnancy, those having active bleeding per vaginal, previously diagnosed and treated cases of cervical intraepithelial lesion or carcinoma cervix, posthysterectomy patients, and females with major degree of uterine prolapse were excluded from the present study.

Ethics

The institutional ethics committee approved the study, number: D /880/KH/2022 dated August 30, 2022. All participants were explained about the purpose of the study in detail. Consent was taken for participation and all the procedures. Their participation in the study was completely voluntary with the option to withdraw anytime during study. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1964, as revised in 2000.

Most women in this hospital-based study are from semi-urban areas of Delhi, presenting to the gynecological OPD with various complaints such as vaginal discharge, abnormal bleeding, and other related issues. A detailed pro forma was filled including their socioeconomic status and other demographic details, followed by proper clinical examination. PAP smear samples were taken from all patients followed by VIA and VILI.

VIA was performed by applying 3 to 5% acetic acid on to the ectocervix, findings were observed after a gap of

60 seconds. The test results were reported as VIA positive if clearly demarcated, opaque/dense acetowhite lesions with well-defined or raised margins, in the transformation zone or close to the squamocolumnar junction (SCJ), were present. The time taken to appear and disappear was also noted. The location of lesion and area as demarcated by quadrant involvement were also noted. The patients who did not take up white color on acetic acid or showed faint acetowhitening, which disappeared in less than 60 seconds (early to appear, early to disappear), were classified as VIA negative.

VILI was done by Lugol's iodine application to the ectocervix and it was visualized within 30 seconds. The test results were reported as VILI positive if there was presence of bright canary yellow/mustard yellow/saffron yellow areas, without any iodine uptake seen in the transformation zone close to or abutting the SCJ, or when the entire ectocervix seems yellow.

A total 50 VIA/VILI and PAPs negative cases were taken as controls from this group. PAPs smear was reported using the Bethesda System 2014.[10] Biopsy was taken in those who showed positive findings in either of the screening method, and random four-quadrant biopsy was taken from these 50 controls.

Patients were followed up in the OPD for 2 weeks. Further management was done as per the diagnosis established and hospital management protocol. The study outcomes were measured as per the following:

Primary outcome: Diagnostic accuracy of VIA and VILI for screening of preinvasive and early manifestations of carcinoma cervix.

Secondary outcome: Comparison of diagnostic accuracy including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of VIA and VILI with PAPs smear for the detection of intraepithelial lesions, preinvasive, and early manifestations of carcinoma cervix.

Statistical Analysis

The collected data was entered in Microsoft Excel and statistically evaluated using Statistical Package for Social Sciences (SPSS) version 25.0. Sensitivity, specificity, PPV, and NPV of each screening test were calculated. Chi-square test was performed and a *p*-value of less than 0.05 was considered statistically significant.

Results

Majority of the study participants belonged to the age group of 30 to 39 years (40.2%) and lower middle-class category from semiurban areas of Delhi. Note that 50.4% of women in our study group had >2 children. The mean age at coitus was 20.11 ± 3.65 years. Majority of patients presented with pelvic inflammatory symptom (88.9%), and only 8 patients had postcoital bleeding.

Ninety-six patients (75.6%) had negative PAP smear report for intraepithelial lesion or malignancy. Thirteen out of 127 women showed epithelial cell abnormality on PAPs (10.2%), with atypical squamous cells of undetermined significance (ASCUS) in 1 case, atypical glandular cells of undetermined significance (AGUS) in 4 cases, low-grade squamous intraepithelial lesion (LSIL) in 3 cases, and high-grade squamous intraepithelial lesions (HSIL) in 5 cases. All patients with AGUS on PAP report were further evaluated by endocervical curettage and endometrial aspiration biopsy, which came out to be negative in all four cases. These patients were advised for regular follow-up.

Twenty-two women were positive for both VIA and VILI (17.3%). The positive results on VIA and VILI were same in the study participants. Comparing VIA and VILI with PAP, of 105 VIA-negative cases, PAP detected 1 LSIL, 1 ASCUS, and 4 AGUS (►**Table 1**) (►**Fig. 1**).

Cervical biopsies were performed on 78 patients: 28 with positive screening results (either PAP positive or positive on both VIA and VILI) and 50 controls. Histopathology from cervical biopsy was used as the confirmatory test, serving as the gold standard for evaluating the diagnostic efficacy of PAP, VIA, and VILI in detecting preinvasive cervical lesions.

For these 78 patients, sensitivity, specificity, PPV, and NPV were calculated for each diagnostic method (PAP, VIA, and VILI) by constructing 2×2 tables. Groups of subjects were organized according to test results from each method, and outcomes were compared against the histopathology results.

Table 1 Comparison of PAPs and VIA/VILI reports

PAPs	VIA/VILI		
	Negative	Positive	Total
Negative (NILM)	84	12	96
Inflammatory	15	3	18
AGUS	4	0	4
ASCUS	1	0	1
LSIL	1	2	3
HSIL	0	5	5
Total	105	22	127

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

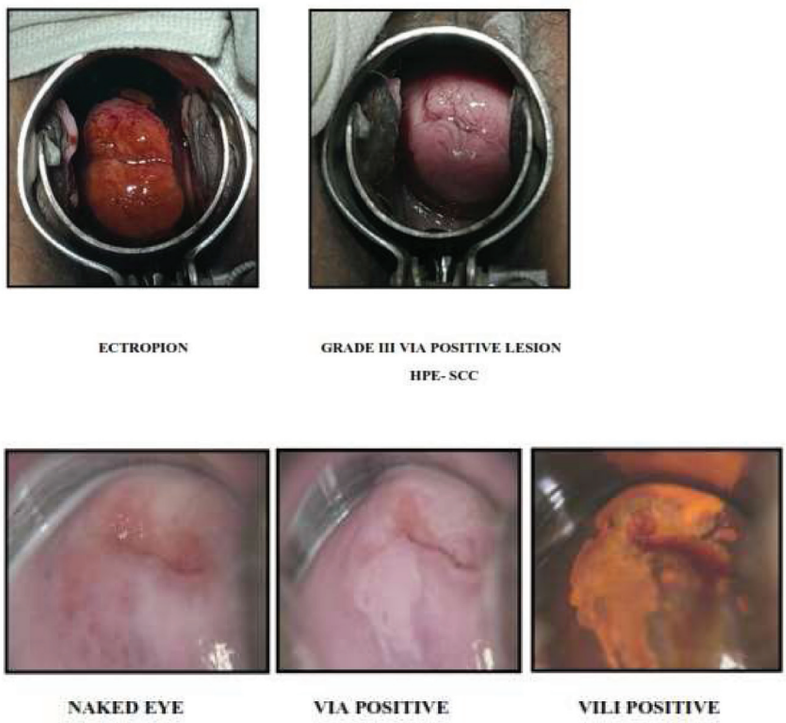

Fig. 1 Visual inspection with acetic acid/visual inspection with Lugol's iodine (VIA/VILI) appearance.

The chi-square test was used to assess diagnostic accuracy, with statistical significance set at a p-value < 0.05.

The data shows that the PAP smear has better specificity (90.79%) as compared with that of VIA (80.26%) and VILI (80.26%), which means PAP has better ability to designate a patient without disease as negative.

Whereas the sensitivity of VIA (100%) and VILI (100%) is much better than that of PAP smear reports (85.71%), that is, they have better ability to designate an individual with disease as positive.

The PPV of PAPs is better (46.15%) than the PPV of VIA (31.82%) and VILI (31.82%), whereas the NPV is better with VIA (100%) and VILI (100%) than that of PAP smear (98.57%).

But the overall p-value of comparisons of diagnostic accuracy of all the three methods, that is, PAPs, VIA, and VILI is > 0.05; hence, the difference is not statistically significant.

Abnormal histopathology was found in seven cases (cervical intraepithelial neoplasia [CIN] grade 1 in two cases and squamous cell carcinoma in five cases), all of which VIA/VILI detected, yielding a 100% NPV. Of 13 PAP-positive cases, only 6 showed abnormal biopsy results. PAP smear showed better specificity (90.79%) but lower sensitivity (85.71%) compared with VIA/VILI, which had 80.26% specificity and 100% sensitivity. The PPV/NPV for PAP were 46.15%/98.57%, and for VIA/VILI, 31.82%/100% (►**Tables 2**–**4**).

After the calculation of p-value for each of the parameter of each screening method, it has been observed that the p-value of every parameter is > 0.05, hence the differences between diagnostic efficacy of VIA or VILI methods with PAPs method are seen statistically insignificant. Therefore, both screening methodologies are to be considered comparable.

Discussion

Carcinoma cervix is the second most common gynecological cancer in Indian women and is considered preventable. The World Health Organization (WHO) recommends VIA and VILI for the detection of precursor cervical cancer lesions in low resource countries as per screen and treat approach.[10,11] These tests are considered affordable, acceptable, and particularly befitting for the screening in developing nations. The results of this test are readily available, thus permitting the same-day screening and treatment strategy.[12,13]

Table 2 Comparison of VIA/VILI with biopsy ($n = 78$)

Biopsy	VIA/VILI findings		
	Negative	Positive	Total
Negative for CIN/malignancy	44	7	51
Infections	10	7	17
Squamous hyperplasia	2	1	3
CIN 1	0	2	2
SCC	0	5	5
Total	56	22	78

Abbreviations: CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

Table 3 Comparison of PAP smear with biopsy ($n = 78$)

Biopsy	PAP smear			
	PAP –ve	PAP inflammatory	PAP +ve	Total
Negative	40	7	4	51
Infections	8	6	3	17
Squamous hyperplasia	3	0	0	3
CIN 1	1	0	1	2
SCC	0	0	5	5
Total	52	13	13	78

Abbreviations: CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma.

This study was conducted to compare the diagnostic efficacy of PAPs smear and visual inspection methods. The PAP smear and visual inspection methods were performed in the same set of patients to compare their results and to evaluate their potential as alternative screening methods to the PAP smear in a semiurban population in Delhi.

It was observed that there were only 18.8% patients who belonged to the age group of > 45 years but showed maximum positivity on PAP smear (29.16%), visual inspection methods (25%), and histopathology report (16.66%), corroborating with the studies done by Bhattacharyya et l[14] and Ami et al[15] who showed maximum positive cases in the age group of > 40 years.

About 17.3% of our screened population showed positive results with VIA and VILI method, which was very much similar with the study done by Das et al[8] who reported 14% VIA positive results and 14% VILI positive results in 200 women. Similarly, the study done by Bhattacharyya et al[14] showed VIA result positivity in 17.3% population but VILI positivity in only 8.6%.

VIA and VILI are cost-effective methods with no extra equipment or laboratory backup requirement. The training and skill for VIA and VILI can be easily imparted to paramedical workers and nurses and hence can be used at a very large scale reaching the remote areas also. They also have the advantage of immediate availability of results, especially if the results are negative; however, a biopsy needs to be performed by a gynecologist if the result is positive. Fokom-Domgue et al[16] also indicated similar results in his meta-analysis for primary screening of cervical cancer in sub-Saharan Africa. VILI was reported to be the most precise substitute to cytology.

There were 13 patients (10.8%) with epithelial cell abnormality on PAP smear in the present study, whereas 14.2% patients had inflammatory report and 96 cases (75.6%) showed no detectable findings. Similar results were reported by Sinha et al[17] where 60.00% showed no major lesions, 31.5% had inflammatory reports, and 8.5% patients showed LSIL or HSIL. Another study by Consul et al[18] reported 72.3% normal smears, 11.00% with inflammatory smears, and 16.27% with positive PAPs smear.

Diagnostic efficacy of PAPs smear was comparable with the one calculated by Consul et al[18] and Bhattacharyya et al[14] as evidenced in a study by Shastri et al.[19] PAPs smear demonstrates moderate sensitivity of 57.4%, while boasting a high specificity of 98.6% in detecting HSIL. Satyanarayana et al[20] observed that the detection rate for CIN I and II by visual inspection methods was more than the PAPs, whereas the detection rate for CIN III was 100% by PAPs smear cytology method. However, sensitivity of PAPs smear (87.5%) for CIN III+ detection was higher than the sensitivity of VIA (50.00%).

However, effective PAP smear screening requires significant infrastructure, including well-trained cytotechnicians, reliable laboratory resources, maintained equipment, logistical arrangements for transport to dependable labs, streamlined communication systems for delivering results, and efficient referral systems for follow-up diagnosis and treatment. Patients often perceive PAP smear as unnecessary and fail to return for follow-up visits to collect cytology reports,

Table 4 Comparison of diagnostic accuracy of screening procedures

	VIA	VILI	PAP smear		–*p*-Value	
				VIA vs. VILI	VIA vs. PAP	VILI vs. PAP
Sensitivity	100%	100%	85.71%	–	1	1
Specificity	80.26%	80.26%	90.79%	–	0.06	0.06
Positive predictive value	31.82%	31.82%	46.15%	–	0.14	0.14
Negative predictive value	100%	100%	98.57%	–	0.98	0.98
Accuracy	81.93%	81.93%	90.36%	–	0.11	0.11

Abbreviations: VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

leading to frequent loss to follow-up. Moreover, the financial burden of cytology charges poses a challenge for many. As reported by Juneja et al,[21] estimates suggest that despite significant efforts to expand cytology services in India, screening even a quarter of the population once in a lifetime may remain unattainable.

The diagnostic efficacy calculated in our study of VIA and VILI were very much similar to the studies done by Blumenthal et al,[8] Sankaranarayanan et al,[22] and Bhattacharyya et al.[14] But certain limitations had been recognized in visual inspection method by different studies. According to a study by Carol et al,[23] women with cervicitis or inflamed cervix were found to be twice as likely to test positive by VIA compared with those without any infection (odds ratio: 2.0, 95% confidence interval: 1.0–3.7). These findings suggest that the cervicitis could be a cause of false positive result by VIA. Also, Ngoma et al[24] showed that VIA positivity is highest immediately after training and retraining, thus indicating that the sensitivity of VIA is dependent on training and skills of the practitioner.

Therefore, the limitation of this procedure is the high number of false-positive cases and lower specificity. However, VIA and VILI can serve as a substitute to PAP smear cytology in a country like India, where resources are limited. There are insufficient cytologists, proper infrastructure, or labs, and where mass screening for early detection of precursor lesions of cervical carcinoma is needed for a large population. While the WHO recommends incorporating HPV testing into screening protocols, its limited availability and high cost in LMICs underscore the need for an affordable and accessible alternative screening method that can be implemented at the peripheral level to reach a wider population.

The introduction of noncytological-based screening methods can bring a paradigm shift in cervical cancer screening.

This study also aimed to raise awareness about the risk factors for cervical carcinoma, promote preventive health-seeking behavior, educate about the signs and symptoms of cervical carcinoma, screen for early precursor lesions, and motivate individuals for regular screening until the age of 65. It targets the disease through primary prevention before its onset and employs secondary prevention through effective screening and treatment.

Limitations

Our research indicates that VIA and VILI tests exhibit sufficient accuracy for cervical cancer screening in India, given proper training and quality assurance measures. However, the high accuracy measures obtained for these tests may be misleading, considering the hospital-based study on small number of subjects and the limitations of the gold standard like colposcopy. Additional large-scale population-based studies are required to evaluate the impact of screening strategies employing these tests on the incidence and mortality rates of cervical cancer in the region.

Conclusion

There has been a rise in cervical carcinoma cases, emphasizing the need for widespread screening, especially in resource-limited countries. Visual inspection methods like VIA and VILI are gaining attention in developing regions like India. Our research shows that VIA and VILI have comparable sensitivity (100% vs. 85.71%) and specificity (80.26% vs. 90.79%) to PAP smears (p-value > 0.05), making them a viable alternative. Despite a higher false-positive rate (PPV 31.82% vs. 46.15%) and lower specificity, their simplicity, low infrastructure demands, and suitability for paramedical staff offer a cost-effective "screen-and-treat" approach with immediate results, reducing follow-up issues. VIA and VILI also aid in determining biopsy sites in areas without colposcopy services.

Noncytological screening methods could shift the approach to detecting cervical cancer precursors, raising awareness, and preparing the ground for HPV-based screening and vaccination programs. Our study highlights the benefits of using visual inspection-based screening, especially in low-resource and rural settings.

Recommendations

The advantages of affordability, straightforward implementation, and a point-of-care diagnosis and treatment protocol should serve as compelling reasons for developing countries like India to adopt visual inspection as a screening method for cervical cancer.

Patient Consent

Informed patient consent was obtained for this study.

Ethics Statement

This article does not contain any studies with human participants or animals performed by any of the authors. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The resources used in the research were totally provided by the hospital and the Municipal Corporation of Delhi. Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

None declared.

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Pralsetinib: A Drug Review

Abha Deshpande[1,2,*] Ryan Varghese[3,*] Jainam Karsiya[4,*] Praveen Jha[4] Padmaj Kulkarni[5]

[1] Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be) University, Pune Maharashtra, India
[2] Department of Clinical Pharmacology, Advanced Centre for Treatment, Research, and Education in Cancer, Tata Memorial Centre, Kharghar, Navi Mumbai, Maharashtra, India
[3] Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, Saint Joseph's University, Philadelphia, Pennsylvania, 19104, USA
[4] RiverRoute Creative Group LLP, Mumbai, Maharashtra, India
[5] Department of Medical Oncollogy, Deenanath Mangeshkar Hospital and Research Center, Pune, Maharashtra, India

Address for correspondence Padmaj Kulkarni, MD, DM, Department of Medical Oncology, Deenanath Mangeshkar Hospital and Research Center, Pune 411004, Maharashtra, India (e-mail: padmaj.kulkarni@gmail.com).

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Abstract

REarranged during Transfection (RET) is a transforming proto-oncogene that codes for the tyrosine kinase receptor. Pralsetinib is an orally bioavailable, selective inhibitor of mutant forms and fusions involving the RET proto-oncogene. Following administration, pralsetinib limits the upregulation or dysregulation of RET gene mutations. This drug review aimed to explore the pharmacokinetics, pharmacodynamics, clinical indications, contraindications, dosing regimen, dose modifications, adverse drug events, and storage and administration of pralsetinib. This review was curated after exhaustive literature screening of all existing documents available on Google Scholar, PubMed, ScienceDirect, Dimensions, and EBSCO Host, as well as by browsing the Web sites of the U.S. Food and Drug Administration (FDA), drug manuals, and conference presentations, using keywords, such as "Pralsetinib," "RET fusion," and "Gavreto." Additional supporting data were obtained from various abstracts and conference proceedings. Presently, pralsetinib has been granted FDA approval for use in non–small cell lung cancer (NSCLC), metastatic RET fusion-positive NSCLC, and metastatic RET-mutant medullary thyroid cancer.

Keywords
- pralsetinib
- Gavreto
- RET fusion
- tyrosine kinase receptor
- thyroid
- cancer

Introduction

REarranged during transfection (RET) is a transforming proto-oncogene that codes for a tyrosine kinase receptor. Tyrosine kinase RET is responsible for various aspects of fetal development; consequently, RET perturbation is a known contributor to several cancers, such as non–small cell lung cancer (NSCLC), medullary thyroid carcinoma (MTC), and papillary thyroid cancer (PTC).[1] RET fusions can be found in 1 to 2% of NSCLCs, ~20% of PTCs, and <1% of many other solid tumors, including ovarian, pancreatic, salivary, and colorectal cancers.[2] Pralsetinib is a novel RET tyrosine kinase inhibitor employed in the treatment of metastatic RET-driven cancers.[3] Previously known as BLU-667, it is an oral anticancer drug capable of selectively targeting RET mutations and displaying potent antitumor activity.[4]

Development and Approval Status

Pralsetinib was granted U.S. Food and Drug Administration (USFDA) approval on September 4, 2020, for the treatment of RET-driven NSCLC. It was approved by the USFDA for the treatment of advanced and metastatic RET-driven MTC and PTC on December 1, 2020. In addition, on November 19, 2021,

* *These authors contributed equally.*

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pralsetinib was approved by the European Commission to treat RET-positive advanced NSCLC.[5] The drug was approved by the Central Drugs Standard Control Organization (CDSCO) on May 26, 2022, for RET-driven NSCLC, MTC, and PTC.[6]

Mechanism of Action

RET activation occurs via chromosomal rearrangements when the 5′ dimerizable domains fuse with the 3′ RET tyrosine kinase portion. This rearrangement leads to autophosphorylation, ultimately resulting in tumor formation and migration. CCDC6-RET is one of the most common sites of perturbed fusion. Pralsetinib is able to selectively target CCDC6-RET sites and prevent their fusion with KIF5B-RET sites. Additionally, it also inhibits other kinases, such as DDR1, TRKC, FLT3, JAK1–2, TRKA, VEGFR2, PDGFRb, and FGFR1. This prevents tumor invasion and proliferation at clinically significant concentrations.

Contraindications

Specific contraindications have not been found.[7]

Dosage

All below doses are to be administered on an empty stomach.[3]

1. MTC, advanced or metastatic, RET mutant—pediatric and adult dosing—400 mg orally once daily until disease progression or unacceptable toxicity.[3]
2. NSCLC metastatic, RET fusion-positive disease—400 mg orally once daily until disease progression or unacceptable toxicity.[3]
3. Thyroid cancer, advanced or metastatic RET fusion-positive disease, in patients who require systemic therapy and who are radioactive iodine refractory—pediatric and adult dosing—400 mg orally once daily until disease progression or unacceptable toxicity.[3]

Dose Modification

1. Pralsetinib administered along with combined permeability glycoprotein (P-gp) and strong CYP3A inhibitors increased the maximum concentration of drug (C_{max}) and area under the curve infinity (AUC_{∞}) by 84 and 251%, respectively.[3] If coadministration is required, pralsetinib dosage should be reduced accordingly as suggested in ►**Table 1**.
2. Pralsetinib 400 mg dose has to be doubled prior to starting treatment if coadministered with strong CYP3A inducers. It was found that rifampin (CYP3A inducer) 600 mg once daily decreased pralsetinib C_{max} and AUC_{∞} by 30 and 68%, respectively.[3]
3. Dose reduction or discontinuation is recommended in patients with hypertension. The daily dose of pralsetinib can be reduced by one level in cases of Grade 3 hypertension. However, Grade 4 persistent hypertension requires permanent discontinuation.[8]

Table 1 Dose modification schedule for pralsetinib upon coadministration

Dose modification of pralsetinib in combination with permeability glycoprotein and strong CYP3A inhibitors	
Regular (conventional) dose	Modified dose
400 mg orally once daily	200 mg orally once daily
300 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily

4. In the case of interstitial lung disease (Grades 1–2), pralsetinib administration should be temporarily halted. Upon disease resolution, treatment can be resumed with reduced dosing. In cases of Grade 3 or higher, the drug should be permanently discontinued.[9]
5. Pralsetinib administration is not recommended in adolescent patients with growth plate abnormalities.[3]
6. Grade 3 or higher hepatoxicity requires dose interruption until the disease is resolved, after which treatment can be continued with dose reduction by one level.[3]
7. If adverse reactions are observed in patients with Grade 3 or 4, pralsetinib treatment is interrupted until symptoms reduce to Grade 2 or less. Treatment can be resumed at a reduced dosage if adverse reactions diminish. However, if no improvement is observed, administration should be permanently discontinued as represented in ►**Table 2**.[3]
8. Comorbidities such as renal and hepatic impairment do not lead to altered pharmacokinetics; thus, no dose modification is required in these cases. Additionally, no dose adjustment is required for geriatric patients.[3]

Administration

Pralsetinib is to be administered orally on an empty stomach. The drug should be administered 1 hour before or 2 hours postmeal. Furthermore, if a dose is vomited, no additional dose is administered, but treatment is continued as indicated. Additionally, if a dose is missed, it should be administered as soon as possible, and treatment should be resumed.[3]

Pharmacokinetics

Absorption

- Time to peak concentration (T_{max}) was found to be 2 to 4 hours for oral route of administration.[3]

Table 2 Dose modification of pralsetinib in an instance of adverse reactions

Dose modifications for adverse reactions	
Dose reduction schedule	Modified dose
First reduction	300 mg orally once daily
Second reduction	200 mg orally once daily
Third reduction	100 mg orally once daily

- Effect of food—C_{max} increased by 104%, AUC_{∞} increased by 122%, and T_{max} decreased by 4.5 hours.[3]

Distribution

- Protein binding of pralsetinib was found to be 97.1%.[3]
- Volume of distribution was found to be 228 L.[3]

Metabolism

Pralsetinib is metabolized in the liver primarily by enzyme CYP3A4, and to a lesser extent by CYP2D6 and CYP1A2. It is also a substrate of P-gp and breast cancer resistance protein (BCRP).[3]

- Pralsetinib induces microsomal enzymes CYP2C8, CYP2C9, CYP3A4, and CYP3A5.[3]
- It inhibits enzymes CYP3A4, CYP3A5, CYP2C8, CYP2C9, and P-gp.[3]
- Further, it also inhibits BCRP, OATP1B1, OATP1B3, OAT1, MATE1, MATE2-K, and BSEP transporters.[3]

Excretion

- Renal excretion was found to be 6%, 4.8% was unchanged.[3]
- Fecal excretion was found to be 73%, 66% was unchanged.[3]
- Rate of total body clearance was found to be 9.1 L/h.[3]

Elimination Half-Life

It was found to be 22.2 hours.[3]

Adverse Drug Effects

1. Common adverse effects[10]
   - Cardiovascular effects—edema (20–29%).
   - Gastrointestinal effects—diarrhea (24–34%) and constipation (35–41%).
   - Hepatic effects—pralsetinib administration displayed increased aspartate aminotransferase (AST) (34%), increased alanine aminotransferase (ALT) (23%).
   - Musculoskeletal pain was also observed (32–42%).
   - Respiratory effects—cough (23–27%) and pneumonia (17%).
   - Other common adverse effects include dry mouth (16%), pyrexia (20%), fatigue (35% for Grades 1–4 and 2.3% for Grades 3–4) and decreased lymphocytes (52 and 20%).
2. Serious adverse effects[10]
   - Cardiovascular—hypertension (28–40%), including 14% with Grade 3.
   - Dermatologic—wound healing impairment.
   - Hematologic—hemorrhage, Grade 3 or higher (2.5%).
   - Hepatic—hepatotoxicity (2.1%) may be observed. Increased AST (69%), including Grade 3 or 4 in 5.4% and increased ALT (46%), including Grades 3 and 4 in 6%.
   - Immunologic—ṣepsis.
   - Respiratory—pneumonitis (10%), including 2.7% incidence with Grades 3 and 4.

Warnings and Precautions

- *Cardiovascular system*: Grade 3 hypertension has been documented and treatment is not recommended for

Table 3 Key clinical trials and their recent results

Name of study	Phase	Condition(s)	Sample size	Overall response rate	Disease control rate	Median duration of response (12 mo)	Clinical benefit rate
ARROW—NSCLC—NCT03037385[4]	Multicohort, open-label, phase 1/2	Previously treated with platinum	$n = 87$	53 (61%; 50–71)	79 (91%; 83–96)	74%; 61–87	69% (58–79)
		No previous systemic treatment	$n = 27$	19 (70%; 50–86)	23 (85%; 66–96)	26%; 0–52	70% (50–86)
ARROW—MTC NCT03037385[2]	Multicohort, open-label, phase 1/2	Previously treated with cabozantinib or vandetanib or both	$n = 55$	33 (60%; 46–73)	51 (93%); (82–98)	92% (82–100)	80% (67–90)
		No previous systemic treatment	$n = 21$	15 (71%; 48–89)	51 (93%); (82–98)	84% (63–100)	100% (84–100)
ARROW—RET fusion-positive thyroid cancer—NCT03037385[11]	Multicohort, open-label, phase 1/2	Previously treated RET fusion-positive thyroid cancer	$n = 9$	8 (89%; 52–100)	9 (100%); (66–100)	86% (60–100)	89% (52–100
ARROW—RET fusion-positive solid tumors—NCT03037385[11]	Multi-cohort, open-label, phase 1/2	RET fusion-positive solid tumors	$n = 23$	13 (57%; 35–77)	19 (83%); (61–95)	11.7 (5.5–19)	70% (47–87)

Abbreviations: MTC, medullary thyroid carcinoma; NSCLC, non–small cell lung cancer; RET, REarranged during transfection.
Note: Data are *n* (%), % (95% confidence interval), or median (interquartile range).

patients with uncontrolled hypertension. Blood pressure levels should be optimized before the commencement of therapy. Furthermore, continuous monitoring followed by dose modification or permanent discontinuation should be implemented as required.[3]

- *Hematological effects*: Trials have reported serious, even fatal, hemorrhagic episodes among patients. In such cases, immediate cessation of therapy is recommended.[3]
- *Hepatic system*: Studies have shown increased AST and ALT levels in patients. In cases of serious hepatic adverse reactions, rigorous monitoring is advised, followed by dose adjustment or discontinuation of therapy if necessary.[3]
- *Reproductive system*: Pralsetinib is contraindicated in pregnancy due to embryo–fetal toxicity (10). Further, females of reproductive potential are advised to use nonhormonal contraception throughout the duration of treatment and for 2 weeks following the final dose.[3]
- *Respiratory system*: Trials have reported life-threatening, fatal pneumonitis/interstitial lung disease in patients. In such cases, rigorous monitoring is advised, followed by dose adjustment or discontinuation of therapy if necessary.[3]
- *Tumor lysis syndrome (TLS)*: TLS was observed in patients with medullary thyroid cancer. Patients with preexisting renal dysfunction, dehydration, rapidly growing tumors, and high tumor burden are at high risk for TLS. In such cases, rigorous monitoring along with prophylactic treatment is recommended.[3]
- *Wound healing*: Pralsetinib administration may impair wound healing by inhibiting the vascular endothelial growth factor signaling pathway. In the case of elective surgeries, treatment is halted for at least 5 days in advance. In the case of major surgeries, drug administration is halted for 2 weeks following surgery or until complete wound healing occurs.[3]

Significant Clinical Studies

The recent significant clinical trials[4] and their studies are tabulated in ►**Table 3**.

Storage

Pralsetinib is to be stored at 20 to 25°C (68–77°F); excursions are permitted from 15 to 30°C (59–86°F). It should be protected from moisture.[10]

Applicability to India

The cost for pralsetinib (Gavreto) in India for 60 capsules of 100 mg is approximated Indian Rupee (INR) 250,000.

Funding
None.

Conflict of Interest
None declared.

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Catch-22 Situation with Unexpected Reports in Acute Lymphoblastic Leukemia

Swetha Palla[1] Parikshaa Gupta[2] Amita Trehan[1]

[1] Pediatric Hematology-Oncology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[2] Department of Cytology and Gynaecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Amita Trehan, MD, Division of Pediatric Hematology-Oncology, Department of Pediatrics, Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: trehanamita@hotmail.com).

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Abstract

Central nervous system (CNS) infections are relatively common among children receiving treatment for acute lymphoblastic leukemia (ALL). However, diagnosing these infections presents challenges. In this report, we present a case of asymptomatic adenoviral meningitis, which presented a diagnostic challenge as it mimicked CNS involvement in a child undergoing treatment for ALL. Our findings underscore the importance of thorough diagnostic evaluation for CNS infections in children undergoing ALL therapy, whether they present with symptoms or exhibit asymptomatic cerebrospinal fluid pleocytosis. Furthermore, distinguishing between infections and CNS leukemia is critical, highlighting the necessity of employing flow cytometry to mitigate the potential misinterpretation of morphological features.

Keywords
- acute lymphoblastic leukemia
- CSF pleocytosis
- CNS infection
- CNS leukemia.

Introduction

A 3-year-old boy presented with fever, and bone pains for the past 3 months. On examination, he had pallor, petechiae, cervical lymphadenopathy, and hepatosplenomegaly. Clinical investigations revealed the following: hemoglobin, 104 g/L; reticulocyte count, 0.28%; platelet count, 11×10^9/L; and white blood cell count, 22.9×10^9/L with 97% blasts. He was diagnosed with pre-B acute lymphoblastic leukemia (PB-ALL) on flow cytometric immunophenotyping. There were no adverse cytogenetics, and he was risk stratified as a standard risk PB-ALL.[1] He was started on induction phase chemotherapy. A diagnostic lumbar puncture done on day 8 of chemotherapy showed a cell count of 12 cells/mm^3 (neutrophils/lymphocytes: 14/86), and the malignant cytology was negative, consistent with central nervous system (CNS) negative disease. Reassessment bone marrow at the end of induction had 3% blasts. However, the minimal residual disease (MRD) was positive (0.05%), necessitating change to the high-risk arm of therapy. The cerebrospinal fluid (CSF) sample sent for malignant cytology at the end of induction (3rd CSF, intrathecal being administered on days 8, 15, and 35 of induction as per protocol) was reported positive. The child had received multiple intrathecal therapies as depicted in ►**Table 1**, among which the third CSF (end of induction) and the sixth CSF (during consolidation) were reported to be infiltrated by leukemic blasts as shown in ►**Fig. 1**.

The CSF samples showed pleocytosis (predominantly had monocytosis and activated lymphocytes—morphologically mimicking ALL blasts). The possibility of infective/chemical meningitis was considered. However, the patient was asymptomatic during the entire period. A detailed molecular investigation of the CSF, which included cell count, Gram stain/culture, flow cytometry, polymerase chain reaction (PCR) for detection of herpes simplex virus (HSV) DNA, cytomegalovirus (CMV) PCR, adenovirus PCR, Japanese encephalitis (JE) PCR, and enterovirus PCR, was performed. The CSF had a

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Table 1 Serial CSF examination findings

Sl. no.	Cell count/cellularity	CSF—malignant cytology	Flow cytometry
1	12 (N/L, %: 14/86)	Negative	–
2	–	Lymphocytic pleocytosis	–
3	–	Positive (end of induction)	–
4	Moderately cellular	Pleocytosis	–
5	30 (N/M, %: 20/80)	Negative	–
6	–	Positive (during consolidation)	–
7	Highly cellular	Inflammation, no malignant cells	15% monocytes, 77% lymphocytes (45% CD4 +, 34% CD8 +), no CD34, CD10, CD19 positive cells
8	Moderately cellular	Lymphocytic pleocytosis	–

Abbreviations: CSF, cerebrospinal fluid; N/L, neutrophils/lymphocytes; N/M, Neutrophils/monocytes.

cell count of 491 cells/mm^3 (predominantly had monocytosis and activated lymphocytes), the sugar/protein levels were normal (normal glucose level is 50–80 mg/dL, normal protein level is 20–45 mg/dL in the CSF), Gram stain negative, and the culture was sterile. Flow cytometry revealed no blasts—CD45+ lymphocytes were negative for CD10, CD19, and CD34. The results for HSV PCR, CMV PCR, JE PCR, and enterovirus PCR were negative. However, the result for adenovirus PCR was found to be positive. Pleocytosis was attributed to adenovirus meningitis, and the child was continued on therapy as a case of CNS-negative ALL. The child completed consolidation and interim maintenance phases of chemotherapy uneventfully.

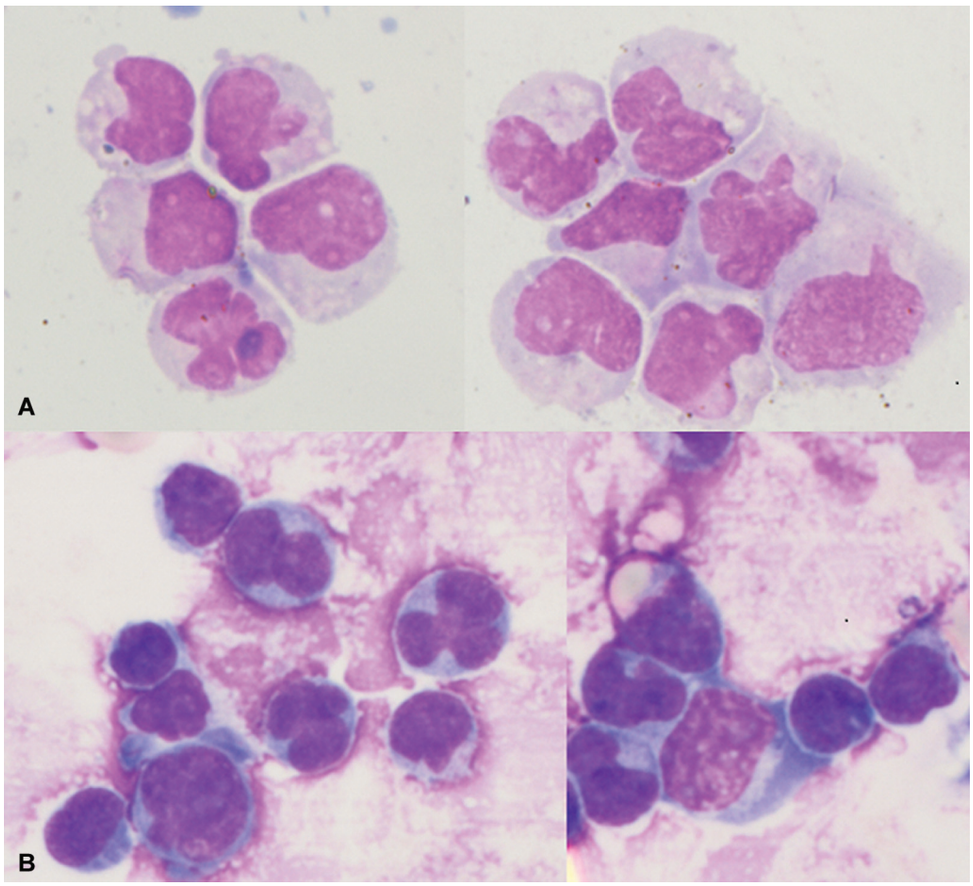

Fig. 1 (A) Cerebrospinal fluid (CSF) cytology shows scattered atypical blasts having high nucleus-to-cytoplasm'' ratio (N:C ratio) with opened-up nuclear chromatin, occasional prominent nucleoli, and scant amount of cytoplasm. (B) CSF cytology shows infiltration by blasts with high N:C ratio, inconspicuous nuclei, and scant amount of pale basophilic granular cytoplasm.

Unfortunately, he developed fever with loose stools following delayed-intensification therapy and succumbed to possible gram-negative sepsis.

Discussion

CNS involvement at diagnosis in childhood ALL ranges from 3 to 5% in B-ALL and 10 to 15% in T-ALL.[2–4] Being a sanctuary site, CNS-directed prophylaxis is given to all children with ALL. Patients who have CNS disease at diagnosis receive intensive CNS-directed therapy, which may include varying combinations of intrathecal chemotherapy, systemic chemotherapy with high-dose methotrexate (HD-MTX), or Capizzi escalating MTX with Peg-asparaginase, often coupled with cranial irradiation to improve survival.[5,6]

CNS-3 leukemia is often asymptomatic at diagnosis, although some patients present with symptoms such as headache, nausea, vomiting, lethargy, irritability, nuchal rigidity, papilledema, and cranial nerve deficits.[7] CNS infections in immunocompromised children can range from asymptomatic presentations (our index case) to severe symptomatic cases.[2]

Distinguishing CNS infection from CNS leukemia is clinically challenging. CSF cell counts are typically elevated in both scenarios, with neutrophilic predominance observed in bacterial infections and lymphocytic predominance in viral infections and CNS leukemia. Cytomorphology alone may be misleading, as activated lymphocytes and monocytes in viral infections can resemble ALL blasts, potentially resulting in false CNS-positive labeling. Hence, comprehensive infectious workup, including cultures and PCR, are essential for identifying infectious etiologies; however, serology may yield false negatives in immunocompromised patients. CSF flow cytometry with timely processing is crucial for confirming the presence of leukemic blasts in CNS-3 leukemia.[8]

In the index case, as there was clinicopathological discorrelation, efforts were made to confirm the CNS status. Eventually, it was confirmed as negative on repeat morphology and flow cytometry. An extensive infectious workup was done to determine the etiology of the pleocytosis wherein adenovirus PCR was positive. Human adenovirus (HAdv) infections are mostly asymptomatic. Meningoencephalitis is a rare complication of HAdv infection, and it is usually seen in immunocompromised patients. Neurological manifestations range from mild aseptic meningitis as seen in our patient to potentially fatal acute necrotizing encephalopathy.[9]

Conclusion

This case highlights the difficulties faced by the cytopathologist and the dilemma of the clinician in the interpretation and management of a discordant CSF cytology report with repeated pleocytosis. Activated lymphocytes mimic ALL blasts leading to false-positive labeling of the acquired CSF sample. In case of doubt/discrepancy, CSF flow cytometry[8] should always be performed along with cytomorphological diagnosis to confirm the findings, as shown for our index patient since infectious cases necessarily require intensive investigation.

Patient Consent

Patient consent is not required in this study.

Author Contributions

S.P. wrote the manuscript, A.T. is the clinician involved in treatment and contributed to betterment of manuscript, P.G. is the Cytopathologist who reported the CSF samples and provided the required images.

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Conflict of Interest

None declared.

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A Rare Case of Acute Hemolytic Anemia in a Patient with Newly Diagnosed Multiple Myeloma: Maintaining a Fine Balance between Occam's Razor and Hickam's Dictum

Jerin Ovett[1] Parathan Karunakaran[1] Jayachandran Perumal Kalaiyarasi[1] Deepa Devi[2] Karthik Bommannan[3] Gopal Gopisetty[4] Nikita Mehra[1,4]

[1] Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[2] Department of Transfusion Medicine, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[3] Department of Onco-Pathology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
[4] Department of Molecular Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence Nikita Mehra, MD, DM, Department of Medical Oncology, Department of Molecular Oncology, Cancer Institute (WIA), Dr. S. Krishnamurthy Campus, 38 Sardar Patel Road, Chennai- 600036, Tamil Nadu, India (e-mail: m.nikita@cancerinstitutewia.org).

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Abstract

Anemia is a common feature in multiple myeloma and is multifactorial. A 52-year-old lady was admitted to our hospital with complaints of fatigue, exertional dyspnea, paresthesia, and a recent-onset confusion state. Fundus examination revealed features of hyperviscosity. The patient received 2 units of packed red blood cell transfusion (PRBC) before the present hospital admission. Laboratory investigations revealed severe anemia and thrombocytopenia. The M-protein was 5.8 g/dL. Bone marrow showed sheets of plasma cells. Immunofixation electrophoresis confirmed the presence of an IgAλ band. FISH was positive for IgH-FGFR3 fusion. The investigations confirmed multiple myeloma R-ISS stage III. The patient was immediately started on CyBorD chemotherapy regimen. The patient had indirect hyperbilirubinemia and symptomatic anemia. Initial testing of the patient's sample showed blood grouping discrepancy with DCT, ICT, and auto control positive. The symptomatic anemia persisted requiring PRC transfusions. Further antibody study revealed the presence of anti-Jka antibody—a warm IgG antibody and cold antibody. Subsequently, the patient received Jka antigen-negative B-positive compatible PRBC transfusions and the hemoglobin normalized. Our patient had transfusion-associated alloimmunization along with hyperviscosity. The timely recognition and early institution of plasmapheresis and myeloma-directed therapy along with transfusion of compatible Jk[a] antigen-negative PRBC lead to rapid improvement.

Keywords
- alloimmunization
- anti-Jk[a]
- cold antibody
- multiple myeloma

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Introduction

Multiple myeloma (MM) is a plasma cell neoplastic disorder characterized by the clonal proliferation of malignant plasma cells.[1] Symptomatic patients present with myeloma-defining events, i.e., CRAB features (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions).[2] Herein, we report a case of IgAλ MM presenting with hyperviscosity and hemolytic anemia.

Case Report

A 52-year-old lady, a resident of Southern India, was admitted to our hospital with complaints of fatigue, exertional dyspnea, and paresthesia involving both her lower limbs for the past month. The patient's past medical history was unremarkable. The patient's son reported that she was confused and had an irrelevant speech for 1 week before the hospital admission. On admission, the patient was conscious, disoriented, and irritable. Her vitals were stable, and she was afebrile. Clinical examination revealed severe pallor, peripheral neuropathy, and skin petechiae over the lower extremities. Fundus examination by ophthalmoscope revealed dilated and tortuous retinal veins, and disc edema bilaterally suggestive of hyperviscosity.[3] The patient did not have acrocyanosis, Raynaud's phenomenon, or skin changes. The patient received 2 units of packed red cell (PRC) transfusion before the current hospital admission. Laboratory investigations revealed hemoglobin 3.5 g/dL (normal range: 12–17), WBC 7000/mm^3 (normal range, 4000–10000), platelet count of 31,000/mm^3 (normal range, 150,000–400,000/mm^3), blood urea 71 mg/dL (normal range, 15–45), serum creatinine 1.4 mg/dL (normal range, 0.7–1.5), and raised serum calcium 12.7 meq/L (normal range, 8.4–10.2). The peripheral smear revealed normocytic normochromic RBCs, reduced RBC density, occasional plasma cells, and reduced platelets. There was no evidence of hemolysis, viz., RBC fragments or spherocytes. CT of the chest revealed extensive skeletal lytic lesions. Further assessment of monoclonal gammopathy revealed total protein: 10.4 g/L (normal range, 6–8), serum albumin: 1.8 g/dL (normal range, 3.5–5), and M-protein of 5.8 g/dL by serum protein electrophoresis (SPEP). Bone marrow showed sheets of plasma cells with suppressed trilineage hematopoiesis (►**Fig. 1**). Flow cytometry revealed 73% clonal plasma cells with lambda light chain restriction. Serum immunoglobulins showed elevated IgA 41 g/L (normal range, 1.03–5.91), IgG 4.91 g/L (normal range, 6.6–16.9), and IgM < 0.19 g/L (normal range, 0.37–2.58). Serum immunofixation (IFE) confirmed the presence of IgAλ band; serum-free light chains (sFLC):λ-35.1 mg/L (normal range, 5.71–26.3), κ-2.20 mg/L (normal range, 3.3–19.4), and κ/λ ratio of 0.063. MALDI-TOF mass spectrometry revealed a λ monoclonal peak (►**Fig. 2**). Fluorescence in situ hybridization was positive for IgH translocation and IgH-FGFR3 fusion, β2 microglobulin was 9.9 mg/L, and serum LDH was 1163 U/L (normal range, 200–400). The investigations confirmed multiple myeloma R-ISS stage III. The nerve conduction study revealed mixed axonal and demyelinating motor-sensory neuropathy of the distal nerves in the lower limb—common peroneal and sural nerves. The patient was immediately started on CyBorD chemotherapy regimen—bortezomib, cyclophosphamide, and dexamethasone. Intravenous dexamethasone was initiated at 40 mg daily for 4 days. The patient had hyperbilirubinemia—6 mg/dL (normal range, 0.2–1.3) with predominant indirect bilirubin elevation of 4.2 mg/dL and normal liver enzymes. Imaging of the liver was within normal limits. Further workup for hemolysis was negative: reticulocyte index 0.45% (normal range, 0.5–2.5) and normal haptoglobin: 40 mg/dL (normal range, 30–200). The indirect Coombs test (ICT) and direct Coombs test (DCT) were strongly positive. The patient had symptomatic anemia for which PRC transfusion was requested. Initial testing of the patient's sample showed blood grouping discrepancy with DCT, ICT, and autocontrol positive. Because the blood bank team could not resolve the blood group, one unit of O-negative best compatible packed red cell unit was issued for emergency use. Subsequently, a B-positive blood group was confirmed; however, the presence of autoantibodies or an alloantibody could not be ruled out. Therefore, two additional units of least incompatible B-positive packed red cell units were transfused, following which the patient had worsening pulmonary congestion and altered sensorium. CSF analysis was not done as the patient had thrombocytopenia with bleeding diathesis–skin petechiae and hematuria. As there was no improvement in the patient's sensorium after initiating anti-myeloma therapy, the patient underwent plasmapheresis. Her clinical status dramatically improved, and she was continued on anti-myeloma therapy. The patient's sensorium, renal dysfunction, hypercalcemia, and thrombocytopenia gradually normalized. However, the symptomatic anemia continued to persist, requiring PRC transfusions. Hence, the patient was worked up for auto- and allo-incompatibility. Further antibody study was performed that revealed the following:

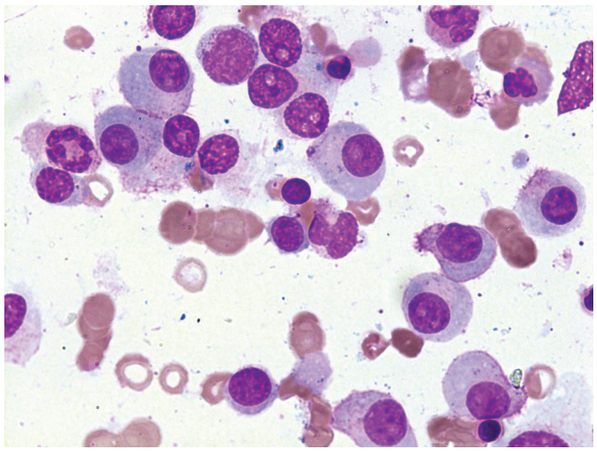

Fig. 1 Leishman stain of bone marrow aspirate at 100x magnification showing atypical plasma cells.

1. Direct antiglobulin test on patient's red cells: weakly positive

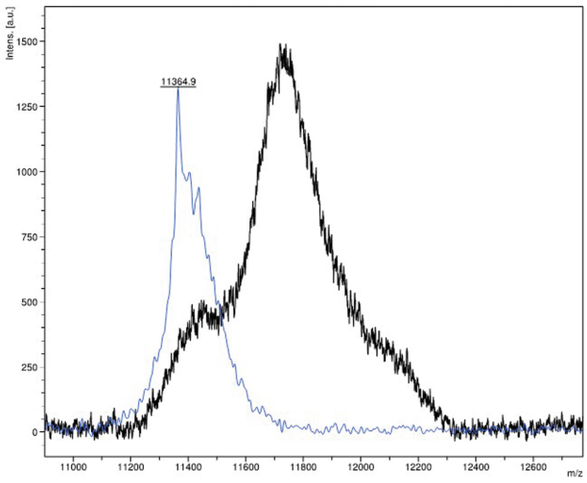

Fig. 2 MALDI-TOF mass spectrometry shows a monoclonal spike in the lambda region (blue) against a normal control (black).

2. Atypical antibody in patient's serum using antibody screening cells:
   - by saline technique (IgM phase): negative
   - indirect antiglobulin technique (IgG phase): positive
3. Patient's serum showed the presence of anti-Jk^a antibody: a warm IgG antibody
4. Presence of cold antibody

Subsequently, the patient received Jk^a antigen-negative B-positive compatible packed red cell unit transfusion. After that, there was no further hemolysis or drop in hemoglobin. Transfusion with compatible blood products and continuation of anti-myeloma therapy gradually normalized the hemoglobin. Cold antibody was detected; however, there were no clinical features to suggest cold agglutinin disease. The patient was subsequently started on bortezomib, lenalidomide, and dexamethasone (VRd regimen). After four cycles, the patient achieved a very good partial response with normalization of hemoglobin (Hb, 12.2 g/dL) and platelet count. The ICT continued to remain positive. The patient underwent high-dose therapy with melphalan (200 mg/m^2) followed by autologous hematopoietic stem cell transplantation (ASCT). The transplant and peritransplant periods were uneventful. On subsequent follow-up, SPEP, serum IFE, sFLC, and bone marrow performed on D + 100 were suggestive of stringent complete response (sCR) and an undetectable MRD at 10^{-6}. The patient was started on bortezomib maintenance.

Discussion

IgA type has an overall poor prognosis partly due to the frequent occurrence of high-risk cytogenetic abnormalities.[4] Anemia is one of the most common presenting features that can significantly impact physical functioning and quality of life variables.[5] Several factors can cause anemia in patients with MM, including abnormal iron utilization, inappropriately low serum erythropoietin levels, a reduction in the bone marrow response to erythropoietin, hemolysis, and bone-marrow involvement.[6] Autoimmune hemolytic anemia and cold agglutination disease are rare presenting manifestations of MM.[7,8] Despite several reports showing the association between autoimmune hemolytic anemia and MM, none have shown conclusive evidence that the myeloma monoclonal protein is responsible, and rarely are they symptomatic due to the same.[9] There was evidence of transfusion-associated alloimmunization in our patient, which was confirmed by the identification of the anti-JK^a antibody. Alloimmunization is usually a major concern among patients receiving transfusions over a prolonged duration, which is quite rare with MM.[10] Females who have received multiple transfusions are at a higher risk.[11] The frequency of hemolytic anemia due to alloimmunization is reported in 2 to 6%, of which anti-Jk^a antibody is the most commonly detected.[12] The reported alloimmunization rate among patients with a hemato-oncological diagnosis was 3.2%. Jk^a antigen belongs to the Kidd antigen blood group system. The incidence of anti-JK^a antibodies in population-based studies varies from 1.3 to 2.5%.[13] In India, routine antibody screening is not done in clinical practice except in a few centers.[14] In patients who have hemolytic anemia due to alloimmunization, screening and antigen matching are recommended to prevent further complications.[15] There are instances of alloimmunization which have occurred in the immediate post-transplant period leading to hemolysis and complicating the management due to the increased transfusion requirement post-ASCT.[16,17] Cold antibody-mediated hemolysis is usually IgM, and RBC hemolysis occurs at 3 to 4°C.[18] Therefore, cold agglutinin disease usually presents with Raynaud's phenomenon and acrocyanosis. The anti-JK^a antibody-associated hemolysis is IgG-mediated. Anti-Jk^a antibodies are usually IgG1 and IgG3; however, some are partly IgG2, IgG4, or IgM.[13,19] They can cause severe acute hemolytic transfusion reactions. However, more commonly, they present with delayed hemolytic transfusion reactions even up to 1 week after blood transfusions. Anti-Jk^a antibody is classically evanescent and difficult to detect because the levels rapidly decline in the plasma.[20,21] Symptomatic hyperviscosity is much more common with Waldenström's macroglobulinemia (10–30%) than it is in MM (2–6%). Symptoms of hyperviscosity include mucosal bleeding, ocular neurological, and cardiovascular manifestations. Hyperviscosity is observed in IgA and IgM type paraproteinemia partly due to their higher molecular weights[22,23]. Immediate treatment is indicated in the presence of hyperviscosity-related symptoms. Plasmapheresis immensely aids in reducing hyperviscosity-related symptoms within 1 to 2 days. Simultaneous anti-myeloma therapy with newer daratumumab-based regimens can hasten the recovery.[24,25] Despite its aggressive disease biology, IgA MM demonstrates a good response to bortezomib-based regimens.[26] The use of anti-CD38 monoclonal antibodies, viz., daratumumab and isatuximab have implications in immunohematology; panagglutination caused by these

anti-CD38 monoclonal antibodies during indirect antiglobulin testing can mask a clinically significant RBC alloantibody.[27,28] In the present era where daratumumab is approved for use in the frontline setting in MM, RBC phenotyping or genotyping before daratumumab is recommended. This may prevent immune hemolysis and therefore ensure appropriate transfusion.[27,28] In our patient, the identification of the anti-JK^a antibody and subsequent transfusion of Jk^a-negative PRCs led to improvement and stabilization of hemoglobin. There was no further drop in hemoglobin, indicating that the presence of cold antibody was a silent bystander,[29] despite requiring multiple transfusions during diagnosis and peri-transplant period.

Conclusion

To our knowledge, there is no literature on patients with multiple myeloma presenting with anti-Jk^a antibody and a cold antibody. This case highlights the value of respecting the fine balance one needs to maintain between Occam's razor and Hickam's dictum, especially in plasma cell dyscrasias and their systemic associations.

Conflict of Interest

"Rapid and Accurate Detection of M-Protein by MALDI-TOF by Reagent-Based Extraction" Gopal Gopisetty, Nikita Mehra, Subramani Jayavelu Indian provisional patent application no: 202041009443, filed on March 5, 2020.

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A Case Report and Review of Literature: Epithelioid Hemangioendothelioma—An Uncommon Challenging Case

Sweta Soni[1] Bharti Devnani[2] Poonam Elhence[3] Kapil Soni[4] Deepak Vedant[3] Palak Gupta[4] Puneet Pareek[2] Rakesh Kumar Vyas[2]

[1] Department of Radiation Oncology, All India Institute of Medical Sciences, Rajkot, Rajkot, Gujarat, India
[2] Department of Radiation Oncology, All India Institute of Medical Sciences, Jodhpur, Jodhpur, Rajasthan, India
[3] Department of Pathology, All India Institute of Medical Sciences, Jodhpur, Jodhpur, Rajasthan, India
[4] Department of ENT, All India Institute of Medical Sciences, Jodhpur, Jodhpur, Rajasthan, India

Address for correspondence Bharti Devnani, MBBS, DNB, Department of Radiation Oncology, All India Institute of Medical Sciences, Basni, Jodhpur 342005, Rajasthan, India (e-mail: bhartidevnani@gmail.com).

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Abstract

Introduction Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of soft tissue and bone that may uncommonly occur in the liver, lung, and head and neck region. EHEs have a higher predilection for recurrence at the local site as well as distant metastasis. Surgical excision is important and is the treatment in localized diseases. A decision to give adjuvant radiotherapy should be subjective and may differ on case-to-case basis. Limited studies are available exploring the role of targeted or systemic therapy.

Case Presentation A 56-year-old lady represented with right-sided submandibular region EHE with bilateral lung metastasis. The patient underwent surgery and radiotherapy followed by targeted therapy tab pazopanib for systemic control. At 2 years of follow-up, positron emission tomography-computed tomography showed local regional control and stable systemic diseases.

Conclusion The uncertainty in choosing the most suitable treatment of EHE patients is high and may result in dissatisfactory outcomes among several patients. The present case study identified a treatment dilemma making management more challenging for rare EHE with mandibular involvement.

Keywords
- hemangioendothelioma
- surgery
- radiotherapy
- pazopanib
- outcomes
- case report

Introduction

Sarcomas are malignant tumors of the skeletal and extra-skeletal connective tissue that can arise from mesenchymal tissue at any body site. Uncommon subtypes of sarcoma together account for 5% of sarcoma tumours.[1] They are especially challenging to diagnose and treat. Epithelioid hemangioendothelioma (EHE) is an uncommon vascular sarcoma that accounts for less than 1% of all vascular tumors.[2] The World Health Organization describes malignant EHE as an intermediate malignant neoplasm.[2] The risk of recurrence at the local site and failures distantly are high with EHEs; however, tumor-specific mortality rates may rely on their anatomic site of origin. There are only limited cases reported of EHE in the face–neck region, with an appearance

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in the oral cavity being extremely rare.[3] The frequently reported oral cavity site for EHE is the tongue, which accounts for 26% of cases. This is followed by the mandibular and maxillary gingiva involvement, contributing to 22 and 19% of cases, respectively.[4,5] The present study describes a rare case of mandibular EHE, its management, and a summary of the literature available.

Case Presentation

A 56-year-old lady, with no comorbidities and no habits presented with right submandibular swelling which gradually increased over 2 years. On clinical examination, the submandibular mass was lobulated and soft in consistency measuring 3×4 cm and not fixed to the overlying skin. There were no signs of inflammation and the swelling was not tender to touch. There was a palpable left level Ib neck node of 1.5×2 cm in size in the contralateral neck. The rest of the head and neck area examination was noncontributory. Computed tomography (CT) imaging (►**Fig. 1A**) done was suggestive of a $28 \times 27 \times 39$ mm sized ill-defined soft tissue lesion seen in the hemimandible along the right lower alveolus which was causing destructive cortical erosion. The adjacent enhancing soft tissue component showed loss of fat planes with the right submandibular gland inferiorly. A peripherally enhancing centrally necrotic left submandibular lymphadenopathy was present measuring 18×17 mm in size. Whole-body positron emission tomography-CT (PET-CT) scan done was suggestive of 3×2.4 cm sized fluorodeoxyglucose (FDG) avid spiculated lesion in the right submandibular region, eroding overlying angle and adjacent posterior body of the right hemimandible and infiltrating the right anterior belly of the digastric and closely abutting platysma. A 1.7×2.2 cm sized FDG avid left cervical level Ib lymph node was also noted. Heterogeneously, FDG avid discrete cervical level Ia and bilateral level II lymph nodes were also present. Mild FDG avid multiple subpleural and parenchymal nodules were noted in bilateral lung fields suggestive of metastasis (►**Fig. 1C**). Biopsy from the right submandibular region was suggestive of EHE. In view of rare disease and asymptomatic suspicious lung metastasis, the case was discussed in a multidisciplinary tumor board following which the patient was taken up for wide local excision with right segmental mandibulectomy with bilateral supraomohyoid neck dissection. Histopathology of the resected specimen was suggestive of EHE involving the right submandibular gland and underlying bone (►**Fig. 2A**) with maximum tumor size of 2.8 cm, medial and lateral soft tissue margins were involved by the tumor, perineural invasion was present (►**Fig. 2B**), and lymphovascular invasion was not seen. Federation Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) grade 4, mitotic rate was $< 1/50$ high-power field (HPF), and necrosis 10% (►**Fig. 2C**). One lymph node in the left level Ib was positive (out of 5), while the right-sided nodes were negative. Tumor cells were immunoreactive for CD34 (►**Fig. 2D**). In view of positive margin and lymph node involvement, the patient was planned for adjuvant radiation to a dose of 60 Gy in 30 fractions to postoperative bed and involved the lymph node region by image-guided external beam radiotherapy (RT) technique. In phase 1, 50 Gy in 25 fractions was delivered to the tumor bed and bilateral neck region, and in phase 2 (boost), 10 Gy in 5 fractions was delivered to the tumor bed and involved the nodal region, Therefore, a total of 60 Gy in 30 fractions, 2 Gy per fraction, one fraction daily, over 6 weeks along with cisplatin chemotherapy (40 mg/m^2) concurrently was given once a week, which she tolerated well with grade 1 dermatitis and grade 2 mucositis. The patient recovered from acute toxicities 2 weeks after completion of RT and was started on targeted therapy tablet pazopanib (dose 400 mg) twice a day to control systemic disease and reduce the risk of locoregional failure. PET-CT scan repeated after 3 months was suggestive of postoperative fibrosis of the right submandibular region with stable pulmonary metastasis. At 2-year follow-up, the patient is asymptomatic and on tablet pazopanib dose reduced to 200 mg twice a day due to oral mucositis. Latest PET-CT showed local-regional control and metabolically inactive pulmonary metastatic diseases.

Discussion

Hemangioendothelioma (HE) is a rare vascular neoplasm with an equivocal biological behavior, intermediate between highly malignant angiosarcoma and completely benign hemangiomas. HE involving the skin and soft tissue includes papillary, retiform, kaposiform, epithelioid, pseudomyogenic, and composite type.[6]

EHE is distinguished by epithelioid or histiocytoid cells with endothelial features, accounting for less than 1% of all vascular tumors. In 1975, HE was reported initially by Dail and Liebow as pulmonary in origin.[7] Earlier, it was described as an bronchoalveolar cell carcinoma with vascular invasion with an aggressive behavior, hence, the name given was an intravascular bronchioloalveolar tumour.[8,9] In 1982, the name EHE was coined by Weiss and Enzinger to define a vascular tumor of soft tissue and bone with characteristic features intermediate between hemangioma and angiosarcoma.[10,11]

EHE has been considered to be the most aggressive among all types of HEs with a high risk of distant metastasis and mortality, accounting for 20 to 30% and 10 to 20% cases, respectively.[12] One of the largest series[6,13] of EHE reported, recurrences at local site in 13% of cases and regional-distant failure in approximately 31% sites such as regional lymph nodes, lungs, liver, and bone. The authors concluded in a study with 49 patients of soft tissue EHE, that the risk of metastasis was greater in lesions > 3 cm and those showing ≥ 3 mitotic figures per 50 HPF.[14]

The etiology of EHE up to this time is unclear. At the molecular front, various angiogenic stimulators may act as promoters of endothelial cell proliferation.[15] A study suggests that for proliferation of EHE, monocyte chemoattractant protein-1 is needed and by stimulation the angiogenic nature of endothelial cell, it might promote lesions to proliferate.[16]

EHE is diagnosed predominately in female population, usually between the age group of 20 and 60 years.[17] The

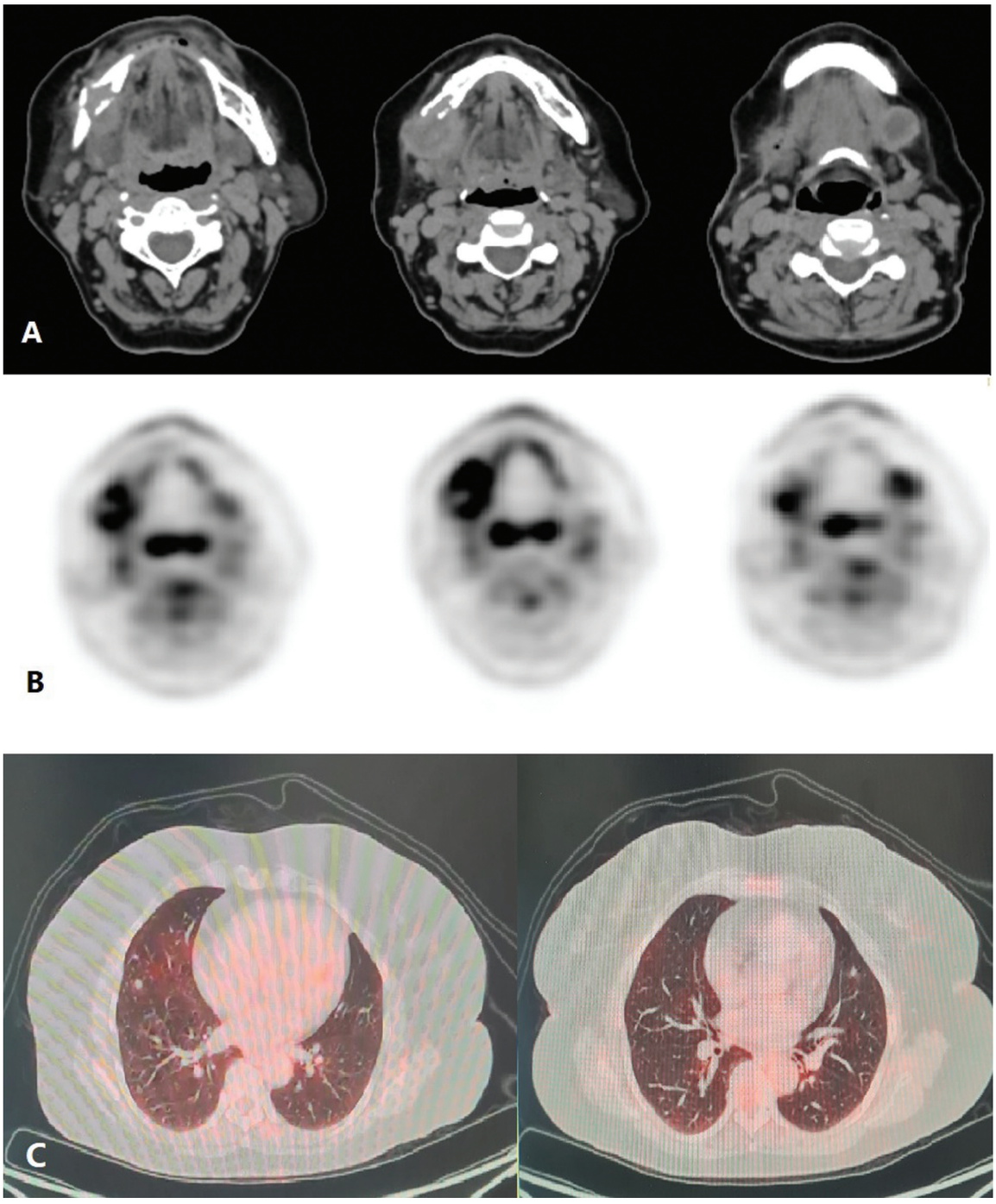

Fig. 1 Contrast-enhanced computed tomography (CT) (**A**) and positron emission tomography (PET) images (**B**) showing soft tissue lesion seen in the right hemimandible causing cortical erosion and involving the submandibular gland inferiorly with an enhancing centrally necrotic left submandibular lymphadenopathy and (**C**) mild fluorodeoxyglucose (FDG) avid multiple parenchymal nodules were noted in bilateral lung fields suggestive of metastasis.

frequently reported symptom is pain. Cutaneous and soft tissue EHE often present as a painful mass and may cause thrombosis or occlusion in the affected vessel. Although in the present case, the mass was painless and nontender on palpation. In the majority of cases, EHE is multifocal or metastatic at diagnosis.

EHE cases show noticeable nuclear atypia with prominent nucleoli, focal and solid growth patterns, necrotic foci, and higher mitotic activity ($>$ 2 mitoses per10 HPF) in approximately 10% of cases. These characteristics are valuable diagnostic hints and also suggestive of the aggressive nature of the disease.[18] EHE has numerous morphological features

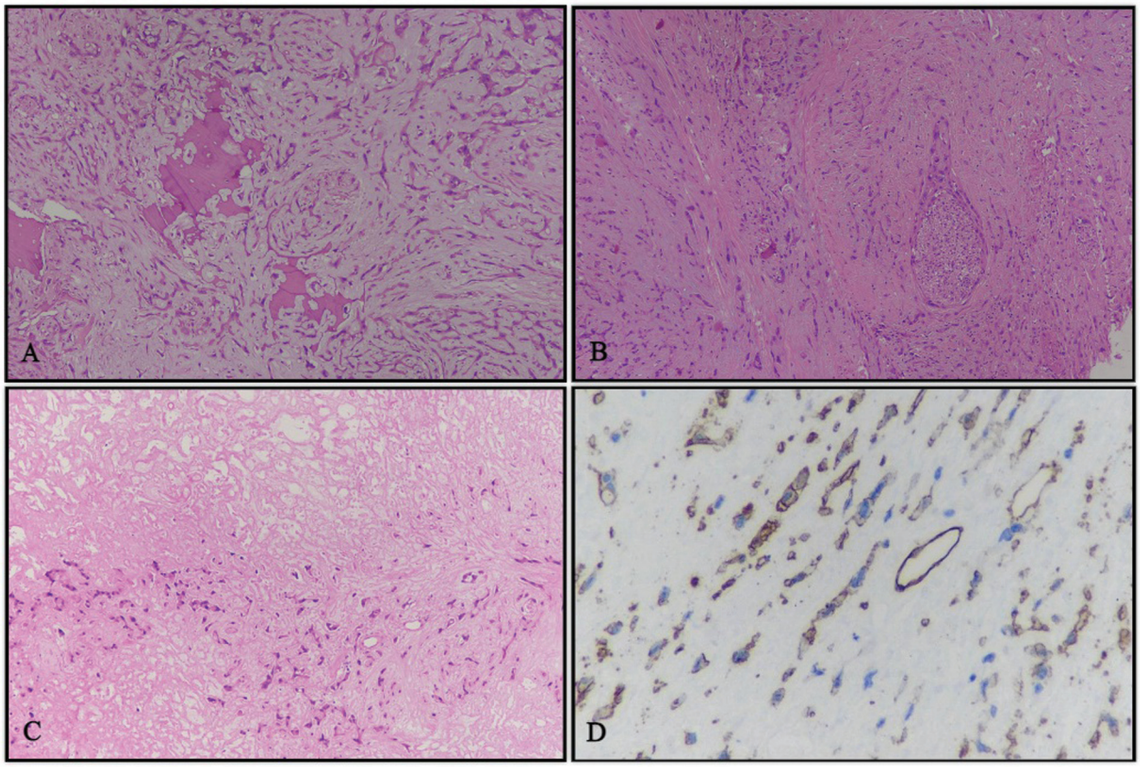

Fig. 2 Histopathological findings. (**A**) Cords of cells infiltrating and destroying bone and embedded in a myxohyaline matrix, hematoxylin and eosin (H&E) stain, 10 ×. (**B**) Perineural invasion, H&E stain, 10 ×. (**C**) Partly viable tumor and partly coagulative necrosis (in the upper half of image), H&E stain, 10 ×. (**D**) Immunohistochemistry for CD34, showing positivity for tumor cells and interspersed vessels within the tumor, DAB-H, 10 ×. H&E, hematoxylin and eosin stain; DAB-H, diaminobenzidine-hematoxylin.

that are indistinguishable from melanomas, carcinomas, and epithelioid sarcomas but the important differential diagnosis is with primary or metastatic carcinomas. CD31, CD34, ERG, and FLI-1 are endothelial differentiation markers frequently expressed in EHE.[19,20] Less than 30% of cases showed focal cytokeratin immunopositivity.[21]

EHE at a molecular level is represented by YAP1-TFE3 (10%) or WWTR1-CAMTA1 (90%) gene fusions.[22–24] The molecular characterization of EHE is highly recommended for diagnostic confirmation and rule out the differential diagnosis, like angiosarcoma and epithelioid hemangioma. Unlike EHE with WWTR1-CAMTA1 fusion, EHE with YAP1-TFE3 consist of epithelioid neoplastic cells with bright copious eosinophilic cytoplasm and focally unequivocal vasoformative features.[23,24] Although, currently molecular study has no predictive or prognostic value, neither can it be utilized for treatment stratification purposes.

Surgical excision with regional nodal resection is the standard treatment for EHE. The main purpose of surgery is to ensure R0 resection, that is, complete resection of the tumor with microscopic negative margins. The expected cure rate in EHE after R0 resection is 70 to 80%.[25]

The risk of recurrence at the local site is approximately 10 to 15% following complete surgical resection.[10] Although EHE is assumed to be a moderately radiosensitive tumor, the role of adjuvant RT is not well established. Indications of adjuvant RT can be extrapolated from the principles and management of soft tissue sarcomas (STS) of the extremity. Adjuvant RT can be considered in cases of close or positive margin to optimize the treatment outcome. Adjuvant RT is advisable to a dose of 60 Gy in patients with positive or close margins or cases where there is a higher risk of local recurrence. Local irradiation after resection of bone EHE up to 60 Gy showed no locoregional failures on 2 years' follow- up.[26] In the present case study, adjuvant RT was planned for the patient as medial and lateral inked margins were positive for tumor cells.

The role of preoperative RT is unclear, as there are no cases published so far for EHE. But for cases where positive or close surgical margins is expected following surgery, preoperative RT to a dose of 50 Gy in 25 fractions may be considered as per standard STS protocols. In cases where the disease is unresectable, definitive RT to a total dose of 60 Gy, 1.8 to 2 Gy/fraction has been recommended. However, depending on the clinical burden, distant metastasis, and symptoms, RT can also be delivered in a palliative setting.[17] Moreover, in neoadjuvant or adjuvant settings, none of the literature supports the use of systemic treatment in patients with resectable EHE.

Cytotoxic chemotherapy and tyrosine kinase inhibitors are the different options for systemic therapy. Although cytotoxic chemotherapy, such as single-agent gemcitabine, can be considered, vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors pazopanib, an

Table 1 Literature review of epithelioid hemangioendotheliomas in the intraoral region and treatment outcomes

No.	Study	Year	No. of cases	Age	Site	Treatment	Follow-up
1.	Wesley et al[29]	1975	1	18	Mandibular gingiva	Surgical excision	NED, 2 years
2.	Mentzel et al[30]	1997	5	30-65	Soft tissue, cheek and neck	Surgical excision	NED, 42–60 months
3.	Ebo et al[31]	1986	1	NA	Gingiva	Surgical excision	NED, 36 months
4.	Ellis and Kratochvil[32]	1986	12	4-67	Neck, gingiva	WLE and surgical excision	LN metastases 2 cases Recurrence: 1 case
5.	Moran et al[33]	1987	1	25	Palate	Surgical excision	NED, 21 months
6.	de Araújo et al[34]	1987	1	4	Gingiva	Surgical excision	NA
7.	Marrogi et al[5]	1991	2	36-45	Tongue, gingiva	Surgical excision	Recurrence: 1 case
8.	Flaitz et al[35]	1995	1	7	Gingiva	WLE	NED, 48 months
9.	Kiryu et al[36]	1996	1	46	Soft tissue, cheek	Surgical excision	NED, 36 months
10.	Orsini et al[37]	2001	1	18	Buccal mucosa	Surgical excision	Recurrence: 9 months
11.	Chi et al[38]	2005	1	28	Gingiva	Surgical excision	NED, 8 months
12.	Rigby et al[39]	2006	1	34	Soft tissue, neck	Surgical excision	NED, 84 months
13.	Yoruk et al[40]	2008	1	44	Submandibular region	Surgical excision	NED, 6 months
14.	Sun et al[41]	2007	9	6-53	Tongue ($n=4$), lip ($n=1$), gingiva and alveoli of the maxilla/mandible ($n=2$), buccal mucosa ($n=1$), FOM ($n=1$).	Surgical excision	NED, 6 months–8 years Recurrence in 3 cases
15.	Mohtasham et al[42]	2008	1	9	Maxillary gingiva	Surgical excision	Recurrence, 1-year
16.	Gordón-Núñez et al[43]	2010	1	17	Mandibular gingiva	Surgical excision	NED, 21 months
17.	Salgarelli et al[3]	2016	1	32	Mandibular gingiva	Surgical excision	Node metastases after 4 years
18.	Ranjit et al[44]	2015	1	25	Submandibular region	Surgical excision	NA
19.	Present case	2021	1	56	Mandible and submandibular region with lung metastasis	Surgical excision → chemoradiation → pazopanib	On follow-up disease free

Abbreviations: FOM, floor of mouth; LN, lymph node; NA, not available; NED, no evidence of disease; WLE, wide local excision.

antiangiogenic drug in phase III trial of STS, showed successful results.[27] Pazopanib resulted in clinical improvement and control of liver and lung metastasis for almost 8 years in a young female with EHE with distant metstatsis.[28] It was well tolerated with no major side effects compared to cytotoxic therapies. Pazopanib therapy was considered postsurgery and radiochemotherapy in the present study to target lung metastasis and reduce the risk of locoregional recurrence.

The efficacy of other targeted agents such as VEGFR inhibitors (bevacizumab, sorafenib), mammalian target of rapamycin (mTOR) inhibitors (sirolimus), and immunomodulatory drugs (lenalidomide) in the treatment of EHE is limited, and further studies are required to determine treatment strategies. However, mTOR inhibitors have been marked with the highest clinical activity, with progression-free survival (PFS) and overall survival of approximately 1 and 2 years, respectively. An even longer PFS has been reported in 10% of patients.[24] The systemic approach is preferred treatment option for advanced, metastatic, and progressive EHE. Owing to the rarity of the disease, no standard treatment protocols for EHE exist. To assess clinical outcomes in EHE, a case-by-case treatment approach and follow-up strategies are needed (►**Table 1**).

Conclusion

EHE is a rare tumor with a borderline behavior between hemangiomas and malignant angiosarcomas. The surgical excision of tumor is the standard approach for localized disease and adjuvant RT use can be extrapolated from the management of STS guidelines. Considering its aggressive behavior and high propensity for distant metastasis and with

no standard treatment guidelines, an individual case-based multimodality approach should be considered to get the best treatment outcomes.

Ethics Approval and Consent to Participate

For submission of a case report, clearance from the Institute Ethics Committee is waived at All India Institute of Medical Sciences, Jodhpur. It is notable that the patient was not subjected to any experimental investigation or treatment at any point of time.

Patient's Consent

Written informed consent was obtained from the patient's guardian for publication of this case report and accompanying images.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

S.S., B.D.: Conception and design of this study, acquisition of data, analysis and interpretation of data, and drafting. All authors read and approved the final manuscript

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Conflict of Interest

None declared.

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An Exasperating and Unusual Presentation of Buschke-Lowenstein Tumor in an Adolescent Girl: Case Report with Review of Literature

Sony Nanda[1] Janmejaya Mohapatra[1] Manoranjan Mahapatra[1] Jita Parija[1] Bhagyalaxmi Nayak[1]

[1] Department of Gynecologic Oncology, Acharya Harihara Institute of Cancer, Cuttack, Odisha, India

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Address for correspondence Sony Nanda, MBBS (hons.), MS (OBS&GYN), DNB (OBS and GYN), MNAMS, MCH Gynecologic Oncology, Department of Gynaecological Oncology, AHPGIC, Cuttack 753007, Odisha, India (e-mail: sony.nanda@gmail.com).

Abstract

Giant condylomata acuminata of Buschke-Löwenstein (GCBL) is a benign condition with a high recurrence rate and a remote possibility of developing into cancer. It is characterized by excessive proliferation of verrucous lesions on the genitalia and/or perianal region, and is frequently linked to human papillomavirus (HPV) subtypes 6 and 11. With the exception of a few case series, case reports make up the majority of the literature. Despite the literature's support for surgical excision, the current evaluation reveals a lack of clarity regarding the disease's diagnosis and best course of action. Better assessment and management of these patients are necessary to prevent any progression/recurrence of disease.

Here, we present a case of a GCBL of the vulva in an 18-year-old girl, who was effectively treated with a simple vulvectomy and split skin graft reconstruction. The reported case is one of the rarest presentations of Buschke-Löwenstein tumor as it is not associated with any of the HPV subtypes and is seen in an 18-year-old girl, one of the youngest patients reported till date. This case report is followed by a brief review of the literature on GCBL, which will add to our understanding of this entity and the most effective therapy to treat the disease.

Keywords

- giant condylomata acuminata
- Buschke-Löwenstein tumor
- human papillomavirus
- adolescent
- verrucous hyperplasia

Introduction

Condyloma acuminatum, often known as venereal warts, is a common sexually transmitted infection that can affect both sexes.[1] Abraham Buschke and Loewenstein Ludwig published the first description of giant vulvar condyloma, often known as the Buschke-Lowenstein tumor (BLT), in 1925.[2] Giant condyloma acuminata (GCA) of Buschke-Löwenstein (GCBL) is a benign condition with a high recurrence rate and a remote possibility of developing into cancer. It is characterized by excessive proliferation of verrucous lesions on the genitalia and is frequently linked to human papillomavirus (HPV) subtypes 6 and 11.[3]

Due to the rarity of this condition, isolated case reports make up the majority of the literature. Data published till date are mere compilation of prior case reports and analysis of the features mentioned in them, which restricts our understanding of this entity and the most effective treatment.[4] Several therapeutic options have been discussed in case reports,[5,6] but there are no strong recommendations or evidence for the optimal treatment of patients with GCBL. The goal of this review was to analyze prior research that outlines this disease's characteristics and provide guidance for treatment. Since GCA is resistant to chemotherapy and radiation therapy, curative treatment typically involves local radical excision. Here, we present a case of a GCBL of the

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vulva who was effectively treated with a simple vulvectomy and split skin graft reconstruction. This is one of the rarest presentations of BLT, as it is not associated with any of the HPV subtypes and is seen in an 18-year-old girl, one of the youngest patients reported till date.

Case Report

An 18-year-old girl presented in the outpatient department with warty growth in her vulval region for 1 year. The growth has been gradually increasing in size over the last 12 months. She was first evaluated in a peripheral hospital, where a biopsy of the mass was done and reported as verrucous hyperplasia in histopathology report. She was from a family with a low socioeconomic background. Upon clinical examination, she was found to be moderately built with a body mass index of 20.8, Eastern Cooperative Oncology Group 0, and mild pallor. Other systems were normal. No signs of any discomfort, mass, or free fluid were present in the abdomen. A large friable growth that involved both of her labia majora and extended anteriorly to the mons pubis and posteriorly to the perianal region was detected during a local examination of her genitalia. (►**Fig. 1A**). On the thighs, perianal region, and labia minora, there were a few satellite lesions (►**Fig. 1B**). The clitoris, urethra, and external anal sphincter were unaffected. The patient's HPV deoxyribonucleic acid (DNA) test, human immunodeficiency virus (HIV), hepatitis B surface antigen, and screening for sexually transmitted diseases (STDs) were negative. She denied any sexual contact in the past. The patient had not been vaccinated for HPV.

Simple vulvectomy with split skin graft reconstruction was planned after consultation with plastic surgeons. Simple vulvectomy was done (►**Fig. 2A**). Vulval reconstruction was performed by harvesting grafts of intermediate thickness

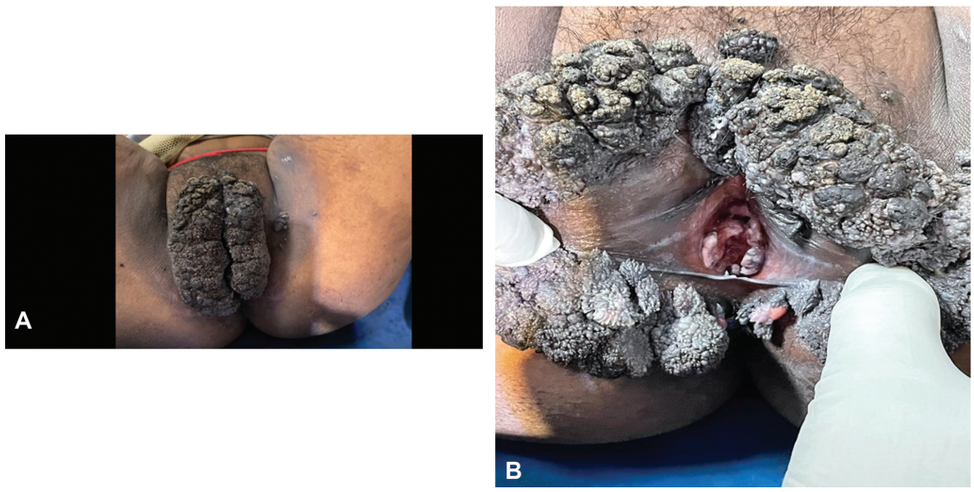

Fig. 1 (A, B) Cauliflower-like growth that involved both of her labia majora and extended anteriorly to the mons pubis and posteriorly to the perianal region.

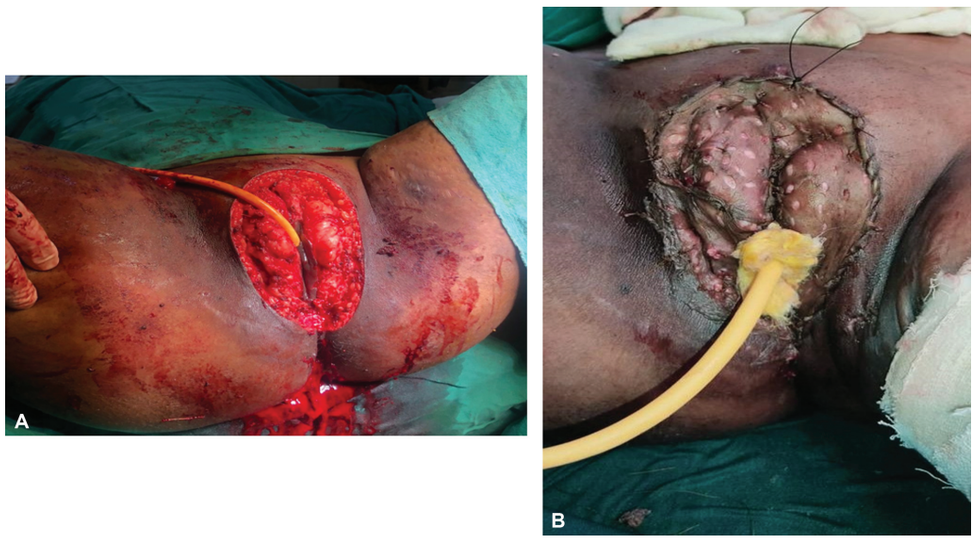

Fig. 2 (A, B) Intraoperative picture. (A) Simple vulvectomy. (B) Split skin grafting done over the defect.

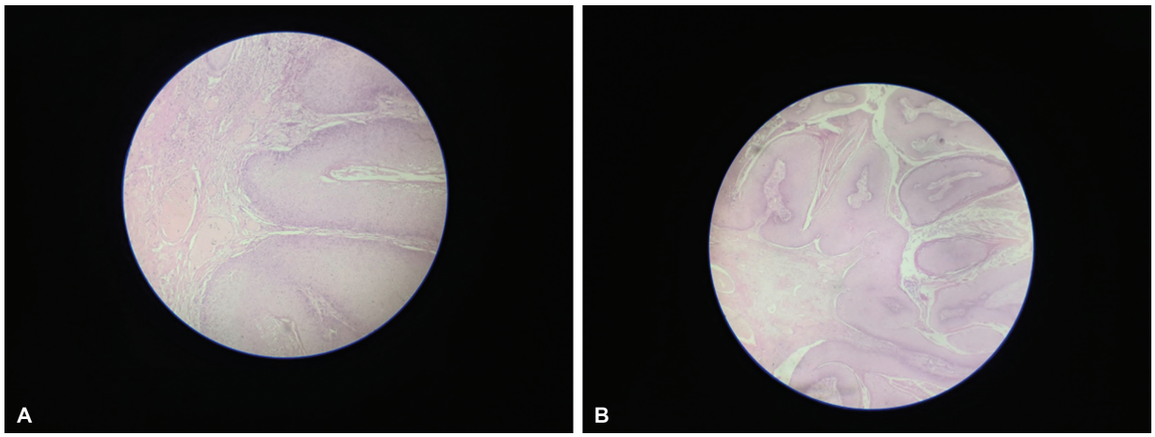

Fig. 3 (A, B) Histopathology image showing papillary proliferation of squamous epithelium with acanthosis and koilocytosis.

from the left thigh and placing them over the excision site (►**Fig. 2B**). The plane of dissection was along the line of cleavage. Gross examination of the excised specimen showed a vulval excised flap of 13*9*4 cm with the skin surface showing wart-like growth. The satellite lesions on the thighs, perianal region, and labia minora were separately excised. Postoperative period was uneventful. The diagnosis of condyloma acuminatum with a moderate degree of dysplasia was confirmed by the final histopathology report (►**Fig. 3**). Immunohistochemically, it was CD ⅝ positive, p63 positive, and p16 negative. Her functional outcome was good and was disease free even after 13 months postsurgery.

Discussion

The results of our analysis demonstrate the low quality of literature published till date. After going through the previous published data, certain trends have become apparent. We attempt to summarize what is currently known regarding these lesions.

Incidence

It is challenging to determine the precise incidence of GCBL due to the lack of standardized diagnostic criteria and the reporting of cases in isolation. However, an estimated prevalence rate of 0.1% of the general population has been reported till date. The most common age group of presentation is 40 to 60 years. However, in our case, the age of presentation was only 18 years, which constitutes one of the youngest patients reported to date.[7]

Terminology

This uncommon tumor has been variously referred to as gigantic condyloma acuminata, condyloma acuminata with malignant transformation, squamous papillomatosis, and well-differentiated squamous cell carcinoma (SCC), suggesting that the terminology used to describe it is unclear.

A GCBL is a condyloma that exhibits destructive growth but not invasion. These lesions exhibit papillomatosis, parakeratosis, hyperkeratosis, acanthosis, and mild koilocytosis histologically. The cells' cytoplasm is vacuolized and they have big nuclei.[7,8] Knoblich and Failing[9] discussed the correlations and contrasts between the clinical and histological aspects of classical condyloma acuminatum and giant condyloma acuminatum. The epithelium's orderly growth, thickening, infrequent appearance of mitotic figures in the spiny and basal layers, and regular maturation from the basal layer to the stratum corneum exhibiting parakeratosis and hyperkeratosis are among the similarities. Additionally, GCA differs from SCC, due to its ability to preserve polarity, an intact basement membrane, lack of lymphatic invasion, and lymph node metastases. Superficial plano-cellular carcinoma has been found as the underlying histology of some cases of gigantic condyloma.

Grading

Davis et al have suggested grading of the GCA.[10] The length of the total lesion (or lesions), as well as the diameter of each lesion's base are assessed for GCA grading. To determine the total size of the lesions, it is frequently helpful to measure each one by quadrant.

Grade

1. 5 to 12 cm in total composite length with a base of < 2 cm or occupying $> 1/3$ the circumference of the penis, vaginal introitus, or anus.
2. > 12 cm in cumulative size or lesions with a base width of 2 to 3 cm.
3. > 12 cm or lesions with a base width greater than 3 cm, or any associated abscess or evidence of systemic infections.
4. Biopsy or excision exhibiting any invasive malignancy.

Risk Factors and Pathogenesis

The primary cause of GCA is HPV, which has been linked to subtypes 6 and 11 in more than 90% of cases in both immunosuppressed patients and individuals with no other concomitant illnesses.[11,12] Numerous subtypes have also been found in the same patient. However, in our case we did not find any association with any of the HPV subtypes. Patients with treatment-resistant genital warts and no discernible immunodeficiency have also been identified. Multiple sexual partners, persistent vaginal infections, bad

hygiene, and immunocompromised conditions have all been linked to the condition.[4,5] Despite the fact that 90% of those infected with HPV will not get genital warts, but individuals who are afflicted can still spread the virus. The majority of HPV infections are successfully repelled by the immune system, which is linked to pronounced local cell-mediated immune responses. However, 10% of people experience persistent infection, which increases their risk of becoming benign proliferative lesions, high-grade precursor lesions, and ultimately invasive cancers.[6]

These lesions are usually multiple and exhibit HPV DNA. But in our case, we did not find any association with HPV. It is important to thoroughly rule out conditions like epitheliomas, SCC, secondary syphilis, verrucous-vegetative tuberculosis, inguinal granuloma, and STDs like hepatitis B, hepatitis C, and HIV.[13] Due to a recurrence rate of 30 to 70% that was discovered 6 months after drug administration, treatments for this STD are currently linked with limited efficacy.

Clinicopathological Presentation

In the vaginal or anorectal region, it manifests as a slowly expanding cauliflower-like tumor that infiltrates deeper tissues gradually.[14] The condyloma acuminatum can enlarge to sizes of more than 10 cm in diameter. It may take 2.8 to 9.6 years or longer from the onset of condyloma symptoms to the development of BLT.[15] Although tumor growth is typically moderate, immunocompromised people may experience faster tumor growth.[16] Although there is a chance of nonsexual transmission by fomites, condyloma acuminata and BLT in minors should always raise the possibility of sexual abuse, for which a thorough medical examination and detailed history is necessary.[16] Rapid growth and unusual clinical manifestations of BLT may indicate malignant transformation. Additionally, condyloma lesions can infrequently grow into substantial exophytic masses that can interfere with vaginal delivery, regular urine, and defecation. Patients also present with complaints of hemorrhoids, constipation, difficulty defecation, dysuria, difficulty urinating, abdominal bloating, and tiredness.[17,18] Areas of benign condyloma may coexist with foci of atypical epithelial cells or well-differentiated SCC in a complicated histological pattern. GCA typically only affects the vaginal area; however, in a small percentage of instances, the tumor may also affect specific anorectal histology zones. Fistulae and abscesses may be seen as a result of the underlying tissue being infiltrated. Reports of extragenital GCA are considerably rare, prefer the folds, and their treatment with resection with disease-free margins is constrained by the potential for developing postsurgical contractures.[17]

Differential Diagnosis

Bowen's disease (dyskeratotic condyloma type), keratotic pseudoepitheliomatous balanitis, and SCC constitute some of its differential diagnosis.[19]

Treatment

Intralesional injection of 5-fluouracil (5-FU), topical chemotherapy (e.g., podophyllin, imiquimod, 5-FU, bleomycin), cryotherapy, interferon, carbon dioxide laser vaporization, curettage, resection alone or with neoadjuvant or adjuvant chemotherapy, radiation therapy, and chemotherapeutic drugs are some of the available treatment options available in the current era.[20,21] These diverse therapeutic strategies, none of which is scientifically proven to be more effective than the other, highlight the disease's poorly established management and high rate of locoregional recurrences. The size, location, and previous unsuccessful treatments are just a few of the many things that need to be taken into account when choosing the best course of action for treatment. Microscopic examination of the genital tissues for subclinical HPV lesions is necessary for the prompt detection of recurrences and for choosing the optimal mode of management.[22]

Prior to surgery, imaging studies (such as computed tomography and magnetic resonance imaging) are necessary to determine the extent of the local and systemic disease and the best course of action. Although healing per secundum is seen as a better strategy since grafting poses a danger for HPV, wide local resections followed by skin grafts are still widely regarded as the mainstay of therapy.[23] After excision of GCBL, the whole affected genital area must be addressed since HPV is a field infection, where large areas of cells in a particular area are affected by the HPV. Currently, surgical intervention with negative margins is the gold standard and must be performed whenever feasible.[24] Although surgery predominates, there are reports of the successful management of BLT with medical therapy as well. Treatment is individual specific and cannot be generalized. Therefore, management of BLT should be left to the clinician's discretion.

Complications

The most frequent side effects of BLT are necrosis, fistulae, or superinfection.[20] Recurrences, soft tissue infiltration, and other complications such as fistulas, abscesses, bleeding from the surgical incision, soft tissue infection, flap failure, urinary infection, urethral obstruction, anal stenosis, and fecal incontinence are linked to the morbidity of GCBL patients.[4] Overall, mortality is 21%, and it is related to disease recurrences and associated morbidities.[18] Histology in cases of GCBL has no specific indicators for malignancy, such as lymphatic invasion, angioinvasion, basement membrane infiltration, or distant metastases. In 30 to 50% of cases infiltration of the tumor base, bleeding, or nodal hypertrophy may raise suspicion of a malignant transition.[21]

Conclusion

The available evidence on Buschke-Lowenstein cancers is inconsistent and raises more issues than it answers. The current evaluation reveals a lack of clarity regarding the disease's diagnosis and best course of action. One step that will enable better analysis of this uncommon disease is the development of a multicentric registry and the establishment of a database to enable a more thorough evaluation, documentation, and study.

Patient's Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity.

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None.

Conflict of Interest

None declared.

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Letter to the Editor Regarding the Article "Spatial Dynamics of TRAIL Death Receptors in Cancer Cells"

Naji Naseef Pathoor[1] Pitchaipillai Sankar Ganesh[1]

[1] Department of Microbiology, Centre for infectious Diseases, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University (Deemed to be University), Chennai, Tamil Nadu, India

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Address for correspondence Pitchaipillai Sankar Ganesh, PhD, MPhil, Department of Microbiology, Centre for Infectious Diseases, Saveetha Dental College and Hospitals, Poonamallee, Saveetha Institute of Medical and Technical Sciences, Saveetha University (Deemed to be University), Chennai 600 077, Tamil Nadu, India (e-mail: p_sankarganesh@hotmail.com).

Dear Editor,

We read with keen interest the review article titled "Spatial Dynamics of TRAIL Death Receptors in Cancer Cells" that was published in Drug Resistance Updates.[1]

The authors clarified the intricate processes controlling the expression and activity of the TRAIL (TNF-related apoptosis-inducing ligand) receptors (DR4 and DR5), especially regarding the resistance of cancer cells to rhTRAIL. The elaborate experimental setup and in-depth data analysis described in this article contribute significantly to our knowledge of the post-translational changes affecting the behavior of the TRAIL receptor and how they may affect treatment approaches. TRAIL is an essential player in the control of apoptosis. When it attaches itself to the death receptors DR4 and DR5, a signaling cascade that causes programmed cell death is started. This process holds particular significance in the field of cancer treatments, as it enables the targeted activation of apoptosis in cancer cells.[2,3] In context with the continuous effort to create more potent cancer treatments, the authors' investigation of TRAIL and its receptors is a relevant and significant contribution to the area. It was very informative to read about the complex glycosylation mechanisms by which the authors altered TRAIL receptors. The article offers critical insights into how these alterations impact cellular sensitivity to TRAIL by describing the functions of certain glycosylation enzymes, such as GALNT14, and the consequences of O- and N-linked glycosylation on receptor stability and function. A substantial amount of knowledge on the regulation of these receptors is added by the discussion of the trafficking pathways of TRAIL receptors to the plasma membrane, including the functions of cargo transport proteins and nuclear localization signals. The authors' finding of endocytosis pathways further highlights the complex nature of receptor modulation and its influence on TRAIL-induced apoptosis, including both clathrin-dependent and -independent processes. Furthermore, the article's analysis of the interaction between oncogenic Ras pathways and TRAIL signaling is a noteworthy addition to the article. The authors successfully illustrate the relationship between H-Ras overexpression and TRAIL resistance in many cancer cell lines by using genome-wide mRNA expression data. This discovery is especially significant since it clarifies the effects of Ras proteins on TRAIL sensitivity that are isoform-specific and creates new opportunities for targeted treatments.[1]

The article is a great addition to the area, but there are a few more things to take into account that can increase its influence even more. It would be very beneficial to provide more precise future study paths and to broaden the conversation on the therapeutic significance of these results. For example, additional specific applications of the findings might be provided by describing possible combination treatments and providing details on how the modification of DR4 and DR5 surface expression can be incorporated into current cancer therapy regimens. It would also give a more defined path for clinical application, which would improve the study's translational component.[4] The article might also be strengthened by addressing the present shortcomings in immunohistochemistry for differentiating membrane-bound receptors from cytosolic fractions. It would deepen the conversation to suggest advanced diagnostic methods for precisely determining receptor location in clinical samples. Investigating these approaches might greatly enhance the process of determining which patient subgroups are most likely to benefit from treatments that target the TRAIL receptor.[5]

Furthermore, even if the in vitro results are strong, the case for clinical translation may be strengthened by adding more

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information or citations to in vivo model validation. In addition to strengthening the overall impact of the study, proving the effectiveness of possible combinational medicines in animal models would provide a more solid basis for upcoming clinical trials. Stressing how crucial multidisciplinary cooperation is to the advancement of this profession could also be helpful. Molecular biologists, clinical oncologists, and bioengineers may collaborate to create novel treatment approaches and diagnostic instruments, which would hasten the use of these discoveries in clinical settings.[6]

A solid basis for further investigation into TRAIL receptor-mediated apoptosis and cancer treatment has been established by the studies reported in this article. By implementing these recommendations, the article might provide an even more thorough and significant addition to the area. It is impressive that researchers were able to clarify the intricate regulation processes of TRAIL receptors, and their discoveries opened up a possible path for the creation of more potent cancer treatments. Finally, we would like to commend the authors for their careful study and important additions to our knowledge of the biology of the TRAIL receptor. Their research has made a substantial contribution to the area and provides information that may influence future treatment approaches. Also, the article will have even more of an effect and further establish its significance in the ongoing effort to overcome cancer resistance to targeted treatments by taking into account the other factors described above.

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