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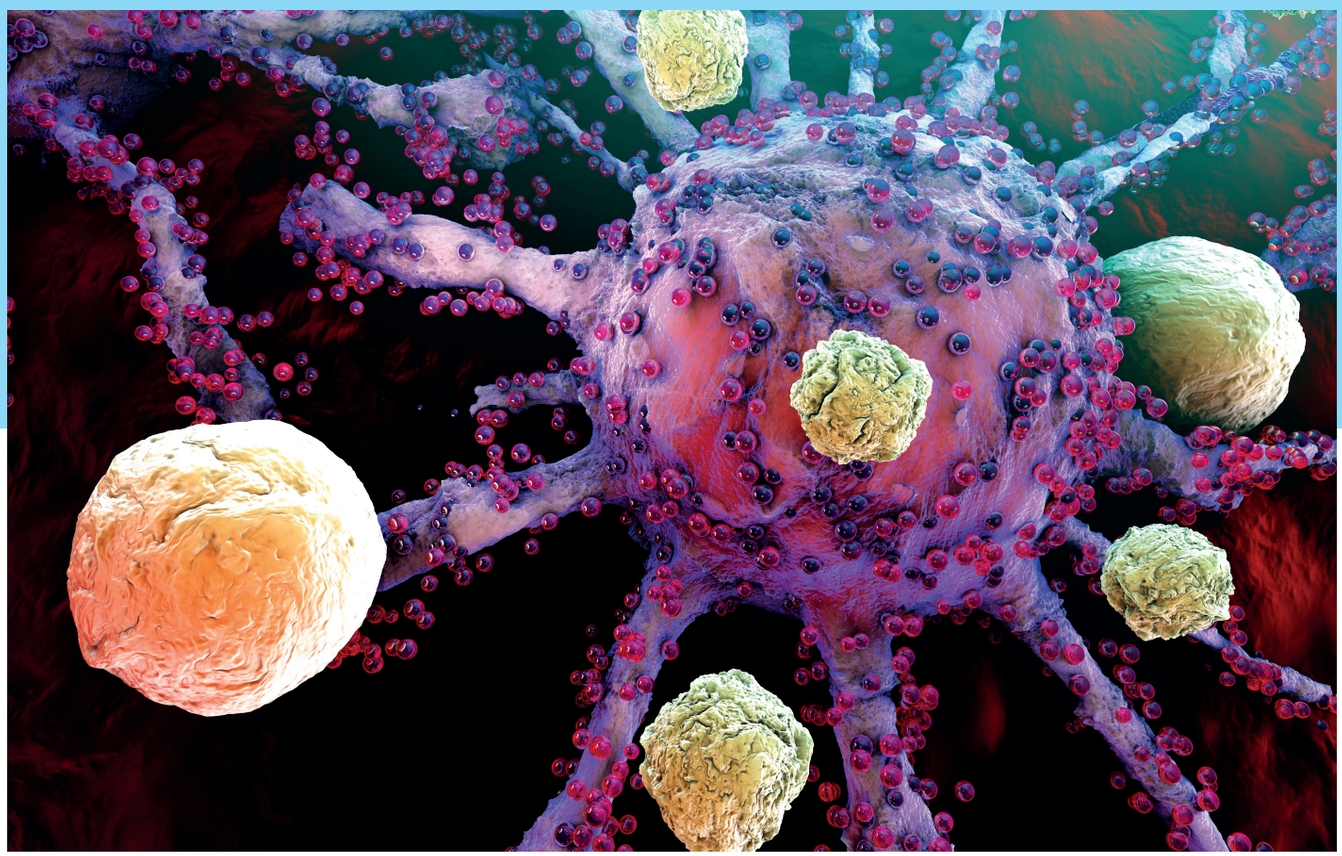

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Localized Rectal Cancer: Indian Consensus and Guidelines

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Abstract

The rising incidence of colorectal cancer (CRC) in India, particularly the prevalence of rectal cancer over colon cancer (0.7:1), has been a growing concern in recent decades; especially notable is the trend of increasing cases among young CRC patients. Given the diverse treatment approaches for rectal cancer globally and the varying economic capacities of patients in low to middle-income countries (LMICs) like India, it is essential to establish consensus guidelines that are specifically tailored to meet the needs of these patients. To achieve this, a panel comprising 30 eminent rectal cancer experts convened to conduct a comprehensive and impartial evaluation of existing practices and recent advancements in the field. Through meticulous scrutiny of published literature and a consensus-building process that involved voting on pertinent questions, the panel formulated management strategies. These recommendations are the result of a rigorous, evidence-based process and encapsulate the collective wisdom and judgment of leading authorities in the field.

Keywords
- Indian consensus and guidelines
- early rectal cancer
- MRI
- MSI

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. According to Globocan data 2020,[1] in India, CRC accounted for 6.7% (89,937) of all cancer cases and 7.7% (65,068) of all deaths, with a cumulative risk of 1.85. The incidence of CRC in India has been increasing over the past few decades, with the National Cancer Registry Programme (NCRP) estimating 70,220 new cases in 2020. Men are more commonly affected than women, with an incidence rate of 10.8 per 100,000 men and 7.5 per 100,000 women. According to a recent study presented in the *Journal of Clinical Oncology* by All India Institute of Medical Sciences, the prevalence and incidence of rectal cancer in India are observed to be higher than colon cancer, with colon to rectal cancer ratio being 0.7:1.[2] Further analysis showed that the mean age at presentation for colon cancer was 51 years, whereas for rectal cancer, it was 45 years. Notably, a considerable proportion of patients qualified as young CRC (diagnosed at or before the age of 40 years), accounting for 34.7% of the total patient cohort. Among this group of young CRC patients, rectal cancer was observed more frequently than colon cancer, with proportions of 41.3 and 25.4%, respectively. In light of different approaches to rectal cancer treatment worldwide, such as variations in the strategies recommended by organizations like the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), and the differing financial situations of patients in India, including some who are covered under government schemes while others face out-of-pocket expenses, it is necessary to develop consensus guidelines that are tailored to the needs of our population. Our initial step toward promoting collaboration involved gathering and scrutinizing the published literature in order to produce an informative guide specifically tailored to rectal cancer patients in low- or middle-income country such as India.

Methodology

Our recommendations for rectal cancer management (►**Tables 1**–**11**; ►**Fig. 1**) were derived from the existing guidelines established by NCCN and ESMO. To ensure a comprehensive and unbiased assessment, we gathered a panel of 30 renowned experts in the field of rectal cancer and requested their participation in voting on relevant questions. (►**Supplementary**) All panel members were urged to vote on every question, with those with potential conflicts of interest advised to abstain from voting on that particular issue. The panel then discussed the recommendations, highlighting areas of substantial disagreement or controversy. After incorporating recent advances and rectifying any inaccuracies, the revised recommendations were circulated to all panel members via email for further review. In accordance with the ESMO guideline methodology, each recommendation is accompanied by a level of evidence and grade of recommendation, which reflect the strength of the available evidence and the degree of agreement among experts, respectively[3] (►**Appendix**). These assessments are further substantiated by a consensus determined by the number of experts who agreed to a given recommendation relative to the total number of experts who voted. These rigorous standards ensure that these recommendations are grounded in a thorough and systematic evaluation of the available evidence, and reflect the collective expertise and judgement of the leading experts.

Screening

Globally, individuals between the ages of 65 and 74 years are the most commonly diagnosed group with CRC.[4] However, it is estimated that approximately 1 in 10 newly diagnosed cases of CRC are observed in individuals who are below 50 years of age.[5] The incidence of CRC, specifically adenocarcinoma, has risen by almost 15% between 2000 to 2002 and

Table 1 Indian consensus and guidelines: screening

Guidelines	LoE	GoR	Consensus
Statement 1[2,7]			
CRC screening may be done for adults (without any family history of cancer) between the age of 40 to 75 years[1,2]	V	A	22/26
Statement 2[7]			
Stool-based tests or direct-visualization tests are acceptable for screening as long as they are performed as per the recommended frequency ◦ Stool-based tests are cheap and freely available. FIT is preferred over gFOBT and should be repeated once every year ◦ Flexible sigmoidoscopy can be performed once every 5 years ◦ Colonoscopy can be performed once every 10 years (if no adenoma or carcinoma detected)	I	A	24/25
Statement 3[8]			
Currently, there is no role of ctDNA based screening for colorectal cancers	Expert opinion	Expert Opinion	26/27

Abbreviations: CRC, colorectal cancer; FIT, fecal immunohistochemical test; gFOBT, guaiac-based fecal occult blood test; GoR, grade of recommendation; LoE, level of evidence.

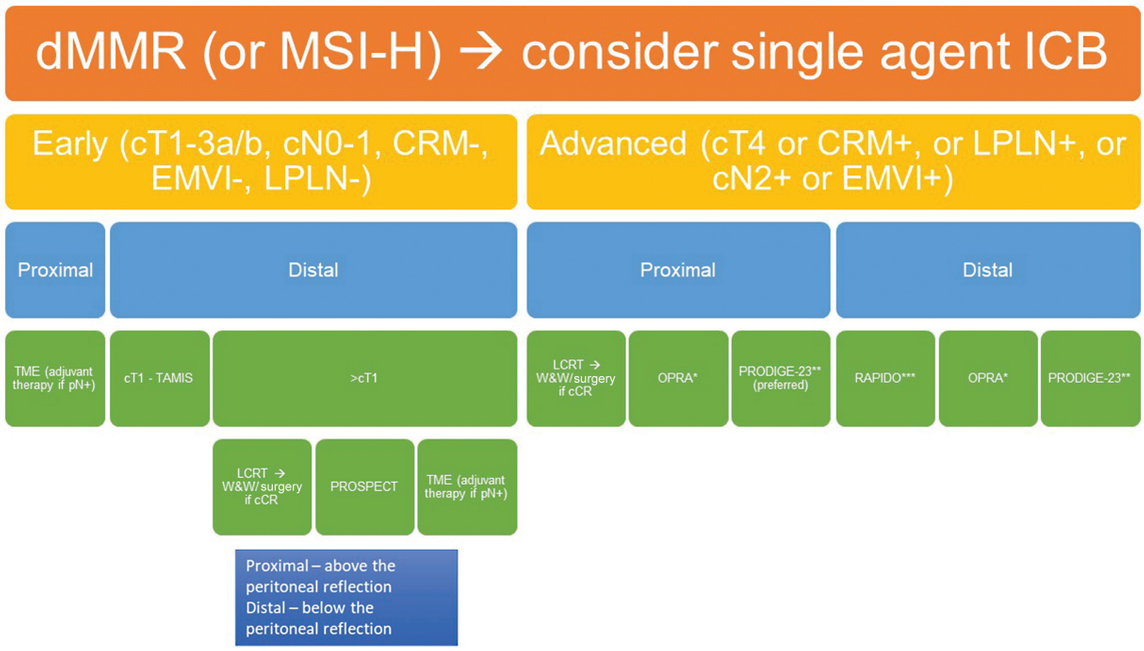

Fig. 1 An algorithm for management of localized rectal cancer. TME – Total mesorectal excision; TAMIS – Transanal minimally invasive surgery; LCRT – 1.8 Gy x 25# radiotherapy with chemotherapy (capecitabine); PROSPECT – perspective FOLFOX and selective RT followed by TME; PRODIGE-23 – Induction mFOLFIRINOX for 2 to 3 months → LCRT → TME or W&W (if cCR); RAPIDO– SCRT→ Consolidation CAPOX or FOLFOX for 3 to 4 months → TME or W&W (if cCR); OPRA – LCRT → Consolidation CAPOX or FOLFOX for 3 to 4 months →TME or W&W (if cCR); cCR – Clinically complete response. *preferred if the goal is to achieve cCR for W&W approach; **preferred if N2 or EMVI where risk of distant failure high. Adjuvant FOLFOX or COPOX after TME. ***may have highter local recurrence compared to LCRT.

2014 to 2016 among adults aged between 40 and 49 years,[6] leading to a renewed focus on young onset CRC.

CRC typically originates from precancerous polyps located in the colon and rectum. Effective screening tests can detect these polyps or identify CRC in its early stages. A panel of experts has reached a consensus with a high level of confidence that screening for CRC in adults aged between 40 and 75 years provides a favorable overall outcome. Additionally, the panel agrees that screening adults aged 76 years or older, who have previously undergone screenings, still offers a modest benefit. Lastly, individuals who have never undergone CRC screening are more likely to experience advantages from the screening process.

These guidelines pertain to individuals aged 40 and above who do not display any symptoms and are considered to have an average risk of developing CRC. Average risk refers to individuals who have not previously been diagnosed with CRC, adenomatous polyps, or inflammatory bowel disease. Furthermore, it includes individuals who do not have a personal or family history of hereditary cancer predisposition syndromes, such as Lynch syndrome or familial adenomatous polyposis, which substantially increase the likelihood of developing CRC.

Consistent with the guidelines provided by the US Preventive Services Task Force,[7] the panel advises the following recommended time intervals for screening using stool-based and direct visualization tests: a yearly administration of the high-sensitivity fecal immunochemical test (FIT), a screening interval of 5 years for flexible sigmoidoscopy, and a screening interval of 10 years for colonoscopy. It should be emphasized that if the results of the FIT-based screening test indicate a positive finding, follow-up with colonoscopy is necessary to fully realize the benefits of screening.

Although circulating tumor DNA (ctDNA)-based tests have shown promise in assessing patient treatment and prognosis, there is currently minimal evidence to support the use of ctDNA-based screening tests in detecting CRC.[8] Therefore, the panel confers opinion that ctDNA-based screening tests for CRC are of limited usefulness at present (►**Table 1**).

Genetic Testing

The panel had a broad consensus that genetic counseling should be advised to every patient with CRC, regardless of age at cancer diagnosis or family history of cancer. However, due to limited availability of genetic testing and counseling services at all tiers in the healthcare system and the cost of testing being a deterrent to the patient, it was noted that provision of genetic counseling for all patients may not be available in certain centers.[9] Nonetheless, efforts should be made to provide pretreatment genetic counseling due to its impact on treatment stratification, prognosis, surgical intervention, and prevention of cancer in other family members.[10]

Lynch syndrome, formerly known as hereditary non polyposis CRC, is the most common hereditary cancer predisposition syndrome that is caused due to variants of the

Table 2 Indian consensus and guidelines: genetic testing

Guidelines	LoE	GoR	Consensus
Statement 4[9,10]			
Genetic counseling could be offered to every patient with colorectal cancer, preferably before the start of treatment. For those who are not ready to consider genetic issues at diagnosis, efforts could be made to offer again at follow-up to address issues of surveillance and other primary tumors	III	C	25/27
Statement 5[11]			
• Genetic testing should be performed according to age, cancer history/ pathology, tumor MSI/ MMR status, and family history. • Germline MMR genes are the most frequently mutated genes; other moderate-to-high-penetrance gene testing are to be considered only when deemed appropriate by a genetic counselor / physician	II	A	29/29

Abbreviations: GoR, grade of recommendation; LoE, level of evidence; MMR, mismatch repair; MSI, microsatellite instability.

mismatch repair (MMR) genes, chiefly—*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Germline testing for these genes individually or as part of a broader sequencing panel may be offered to patients with age of diagnosis less than 50 years, those with first and or secondary relatives with a history of Lynch syndrome-associated cancers, those who have synchronous or metachronous cancer, or those who are deemed high risk based on Amsterdam II or revised Bethesda criteria by genetic counsellor and/or treating clinician.[11]

Practice of genetic counseling and germline testing should be in adherence to the latest national and/or international guidelines. The clinical utility of identification of moderate penetration gene/s in multigene testing is still lacking and this needs to be discussed with patients in both the pre- and post-testing counseling. For those patients who are not ready to undergo genetic testing at diagnosis, access to genetic counseling and testing should be offered again at follow-up to address issues of surveillance, risk of other primary tumors, and risk stratification for the relatives. Patients and their first-degree relatives with a pathogenic or likely pathogenic variant(s) in one of the MMR genes can be offered post-test genetic counseling regarding their risk of cancer by site, age, and affected MMR gene together with approaches to surveillance and cancer prevention interventions in order to reduce risk of cancer[12,13] (►**Table 2**).

Staging

The expert panel recommended that all patients diagnosed with early rectal cancer undergo a comprehensive evaluation, which should include a complete physical examination, blood tests to assess complete blood count, liver function tests (LFTs), renal function tests, and serum carcinoembryonic antigen (CEA) levels. This evaluation should also assess the patient's performance status to determine their operative risk. In addition to a digital rectal examination (DRE), patients should also undergo sigmoidoscopy or full-length colonoscopy to exclude synchronous colonic tumors.

DRE is crucial in determining the location of rectal cancers in relation to the anal margin and for planning primary surgery or a neoadjuvant approach. Abnormal LFTs, particularly elevated levels of alkaline phosphatase, may indicate liver pathology and suggest the possibility of liver metastases. Significantly elevated serum CEA levels should raise suspicion of metastasis, and additional clinical imaging for further staging evaluation should be considered.

The preferred staging system for CRCs is the tumor, node, metastasis (TNM) staging system, developed by the combined American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control.[14] In the 8th edition of the AJCC Cancer Staging Manual, T1 tumors are characterized by involvement of the submucosa, while T2 tumors infiltrate into the muscularis propria. T3 tumors penetrate through the muscularis propria, and T4a tumors directly penetrate to the surface of the visceral peritoneum, while T4b tumors directly invade or are adherent to other organs or structures.

The regional lymph node classification includes N1a, which is characterized by 1 positive lymph node; N1b, characterized by 2-3 positive lymph nodes; N2a, characterized by 4-6 positive nodes; and N2b, characterized by 7 or more positive nodes. Additionally, tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis (i.e., satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage, with N0 being the lowest stage, followed by N1a, N1b, N2a, and N2b.

In rectal cancer, it is noteworthy that the T stage has more prognostic value than the N stage. Some experts have proposed subdividing T3 disease based on the distance of tumor spread from the muscularis propria, although this is a matter of debate. T3 tumors with more than 5 mm of invasion beyond the muscularis propria (i.e., T3c disease) have been found to have an inferior cancer-specific survival rate of approximately 54%, compared to 85% when the depth was 5 mm or less.[15]

The updated guidelines for the treatment of rectal cancer from ESMO incorporate depth of extramural invasion beyond the muscularis propria as a factor in treatment allocation using the T3 subdivision system.[16] However, AJCC and NCCN do not stratify decision making for T3N0 disease according to depth of extramural invasion. The panel recommends that a further subclassification of T3 based on available evidence

may prove valuable in preventing both over-treatment and inadequate treatment. Therefore, the depth of extramural invasion beyond the muscularis propria should be taken into consideration when making treatment decisions for rectal cancer that may improve patient outcomes.

Imaging plays a critical role in preoperative staging for rectal cancer, as it individualizes treatment strategy for each patient. The panel recommends that endoscopic rectal ultrasound (EUS) be used for early T1 tumors[17] that are suitable for transanal endoscopic microsurgery (TEM), as it can determine if a lesion is confined to the mucosa or submucosa. However, for lesions greater than T1, the panel does not mandate the use of EUS as there is no additional benefit. The panel recommends the use of pelvic magnetic resonance imaging (MRI) for accurate locoregional clinical staging.[18] Pelvic MRI has proven to be the best modality so far for assessing the depth of tumor penetration, determining the T substage, detecting extramural vascular invasion (EMVI), estimating the presence of local lymph nodal metastases, predicting the risks of local recurrence and synchronous/metachronous distant metastases, providing accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia, and providing information useful in predicting the circumferential resection margin (CRM) before radical surgery.[19] EMVI, in particular, portends a poor prognosis and serves as a predictor of distant metastasis.[20] The panel's recommendation is supported by the MERCURY trial[21] which confirmed that high-resolution T2 sequence MRI can accurately assess the CRM preoperatively and differentiate patients with low- and high-risk disease. The rectum can be divided into three segments based on their anatomical position on MRI. A low rectal tumor is characterized as a tumor whose inferior margin is positioned at or below the pelvic sidewall's musculus levator origin.[22] The mid-rectum is positioned between the low rectum and the inferior-most point of the anterior peritoneal reflection and the high rectum is located above the mid-rectum and below the sigmoid "take-off".[23] Patients with MRI-clear CRM had higher 5-year overall survival (OS) compared to those with MRI-involved CRM 62.2 versus 42.2%, respectively (hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.27–3.04). Preoperative MRI imaging also predicted disease-free survival (DFS; HR, 1.65; 95% CI, 1.01–2.69; $p < 0.05$) and local recurrence (HR, 3.50; 95% CI, 1.53–8.00; $p < .05$). To ensure a comprehensive report, a standard proforma for MRI and pathology can be followed, and radiology departments can refer to the European Society of Gastrointestinal and Abdominal Radiology consensus guidelines for standardized MRI imaging of rectal cancer.[24]

The panel considers contrast-enhanced computed tomography (CT) scan of the pelvis as an inferior modality to MRI in T and N staging, and for predicting CRM due to its poor sensitivity.[25] Therefore, it is not the preferred choice for local staging of rectal cancer. However, in centers where MRI is unavailable or has limitations such as low field strength (i.e., <1.5T), unavailability of phased-array surface coils, lack of a standardized Rectal MRI protocol or expertise to interpret MRI images, the panel recommends a contrast-enhanced CT scan of the pelvis over an inferior quality MRI or substandard reporting with an understanding that it is a suboptimal modality and every attempt should be made to obtain a standard rectal MRI scan of the patient.

The panel recommends that preoperative imaging should be done in all cases to rule out distant metastases. CT scan of the chest and abdomen is recommended for this purpose. In case CT abdomen is being done, a plain CT scan of the thorax suffices; however, if CT abdomen is being done in the same setting, then CT thorax with contrast along with CT abdomen with contrast is acceptable.

The panel consensus is that positron emission tomography (PET) scan is not recommended for preoperative staging of rectal cancer. However, it may be used to assess an indeterminate finding on a contrast-enhanced CT scan or in patients with a strong contraindication to intravenous contrast and locally extensive disease who require beyond-total mesorectal excision (TME) surgery. In addition, it may be beneficial when used in conjunction with MRI liver in patients at high risk of multiple metastases, and for RT target delineation in radiotherapy planning. Bone scan and brain imaging are not routinely indicated unless patient is symptomatic (►**Table 3**).

Histopathological Examination

The pathologic staging of rectal cancers depends on proper examination of resected surgical specimen. So, a detailed and proper histopathology report of the pathologic evaluation of rectal cancer is needed. A histopathological report (histopathological examination [HPE]) should include (i) gross description of the specimen and tumor, (ii) grade of differentiation of tumor, (iii) depth of penetration and extension of the tumor to the adjacent structures (T), (iv) number of positive regional lymph nodes and number of regional lymph nodes evaluated (N), (v) the presence of distant metastases to other organs including non-regional lymph nodes (M), (vi) the status of proximal, distal, circumferential (radial), and mesenteric margins,[26,27] (vii) neoadjuvant treatment effect,[28] (viii) lymphovascular invasion,[29] (ix) perineural invasion,[30,31] and (x) the number of tumor deposits.[32–35]

Rectal cancer is classified according to the 8th edition of the AJCC TNM staging system. During the grossing of the specimen, it is important to record the distance of the tumor extending outside the muscularis propria into the perirectal tissue, as well as identify the area in which the tumor spreads closest to the CRM. It is necessary to assess at least 12 lymph nodes in patients who have not undergone neoadjuvant treatment.[36–38] It is reported in literature that high-grade tumor budding in pT1 CRC or malignant polyps is associated with an increased risk of lymph node metastasis. The most important resection margin for rectal cancer is the CRM. When reporting involvement of the CRM, it should be noted that it is considered involved if it is located less than or equal to 1 mm from the tumor-free margin. It is important to measure the CRM from the primary tumor and express the measurement in millimeters for accuracy.[36,39] If a positive lymph node or a tumor deposit is closer to the margin, a second CRM measurement should be made and reported.[26,27,40–42] Currently, it is not recommended to

Table 3 Indian consensus and guidelines: staging

Guidelines	LoE	GoR	Consensus
Statement 6[23,28]			
Location and physical characteristics of the primary rectal tumor should be documented by DRE and flexible sigmoidoscopy / colonoscopy. Lower rectum is when the tumor is below 5cm from the anal verge, mid-rectal tumors are situated at 5 to 10 cm from the anal verge and tumors lying above 10 cm from the anal verge are upper rectal tumors. Alternatively, the rectum can be divided into three segments based on their anatomical position on MRI. A low rectal tumor is characterized as a tumor whose inferior margin is positioned at or below the pelvic sidewall's musculus levator origin. The mid-rectum is positioned between the low rectum and the inferior-most point of the anterior peritoneal reflection and the high rectum is located above the mid-rectum and below the sigmoid "take-off"	I	A	28/28
Statement 7[38]			
Full blood count, liver, and renal function tests, serum CEA and CT scan of thorax and abdomen / pelvis (if MRI pelvis could not be done) should be carried out to define functional status and presence of metastases	I	A	30/30
Statement 8[21]			
Pelvic MRI (rectal protocol) is the gold standard test to locally stage the rectal tumor. Also, assessment of CRM and EMVI is most accurate with MRI and predicts high risk of distant metastasis and local recurrence	I	A	31/31
In places with resource constraints and unavailability of MRI, CECT pelvis may be done with the understanding that it is a suboptimal modality and every effort should be made to arrange for MRI	Expert opinion	Expert opinion	
Statement 9[17]			
EUS is appropriate for early T1 tumors where TEM can be performed. It is of no added benefit for advanced tumors	II	A	31/31
Statement 10[38]			
Routine use of PET-CT is not indicated	Expert opinion	Expert opinion	28/31
Statement 11[21,38]			
UICC TNM (8th edition) should be followed and documented accurately before starting any treatment	I	A	27/29
Further classification of cT3 may be helpful in risk stratifying patients for appropriate treatment strategy	II	B	

Abbreviations: CEA, carcinoembryonic antigen; CECT, contrast-enhanced computed tomography; CRM, circumferential resection margin; CT, computed tomography; DRE, digital rectal examination; EMVI, extramural vascular invasion; EUS, endoscopic ultrasound; GoR, grade of recommendation; LoE, level of evidence; MRI, magnetic resonance imaging; PET-CT, positron emission tomography -computed tomography; TEM, transendoscopic microsurgery; UICC TNM, Union for International Cancer Control -Tumour, Node, Metastasis staging system.

routinely report the tumor regression grade after neoadjuvant treatment. However, it is crucial to report pathologic complete response (pCR) to assess the efficacy of the neoadjuvant treatment[28] Tumor budding is defined as the presence of a single cell or a cluster of four or fewer neoplastic cells as detected by routine staining at the advancing edge of an invasive carcinoma.[43] Tumor deposits, also known as satellite nodules, are irregular and discrete tumor deposits that are located in the perirectal fat, but are away from the leading edge of the tumor. These nodules are located within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor as there is no lymph node tissue associated with these nodules. The number of tumor deposits should be mentioned in the pathology report.[32–35,44,45] The presence of perineural invasion is associated with worse prognosis.[30,31,45–48] Immunohistochemistry (IHC) testing for MMR should be performed on all rectal cancers for the discussion of genetic counseling and the role of immunotherapy.[49–53] IHC is not recommended for the routine histopathology reporting; however, if there is a doubt about the morphology, IHC testing can help exclude the possibility of other cancers such as neuroendocrine or melanoma (►**Table 4**).

Risk Adapted Treatment

Every case should be discussed in multidisciplinary tumor boards (MDT) at the time of diagnosis and staging, a multimodality treatment plan should be documented at the beginning based on local institutional policies, resources, and waitlist for locoregional therapy. The MDT should consist of a surgical oncologist, a medical oncologist, a radiation

Table 4 Indian consensus and guidelines: HPE

Guidelines	LoE	GoR	Consensus
Statement 12[26]			
T1 tumors can be subdivided into pedunculated and sessile. Pedunculated tumors must have the grade, presence of LVI and presence of tumor budding documented to predict the risk of lymph node metastasis. PNI if present should be recorded. For sessile tumors, the level of infiltration into the sm and the width of invasion compared with the width of the cancer should be assessed	I	A	28/28
Statement 13[26,28,29]			
For advanced tumors, ◦ The quality and grade of TME specimen should be assessed and preferably photographed ◦ Histologic subtyping should be done as per WHO classification, 5th edition ◦ At least 12 lymph nodes must be assessed (for patients undergoing upfront surgery only) ◦ Tumor deposits (non-nodal, non-neural, non-lymphatic deposits), if present, should be documented ◦ Proper documentation of margins- circumferential resection margin, distal longitudinal and proximal longitudinal, (or additionally any other in extended resections) in mm (millimeters) is required; PNI, LVI, and tumor budding must be reported ◦ If preoperative therapy was administered, TRG using Mandard, Dworak or College of American Pathologist should ideally be documented	I	A	30/30
Statement 14[49,52]			
MMR testing by IHC or MSI-PCR should be performed on all rectal cancers for the purposes of genetic counseling as well as discussion of the use of immunotherapy	II	A	29/30
Statement 15[37]			
◦ IHC is not routinely recommended, however if there is a doubt on morphology, especially in poorly differentiated tumors, mesenchymal or other tumors, (e.g., neuroendocrine, melanoma, lymphoma, and GIST) must be excluded ◦ HER2 testing is not recommended for the purpose of treatment or as a prognostic marker ◦ KRAS / NRAS / BRAF testing is not recommended for the purpose of treatment or as a prognostic marker.	Expert opinion	Expert opinion	30/31

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; HPE, histopathological examination; GoR, grade of recommendation; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; LoE, level of evidence; LVI, lymphovascular invasion; MMR, mismatch repair; MSI, microsatellite instability; NRAS, neuroblastoma ras viral oncogene homolog; PCR, polymerase chain reaction; PNI, perineural invasion; sm, submucosa; TME, total mesorectal excision; TRG, tumor regression grading; WHO, World Health Organization.

oncologist, a radiologist, a pathologist, a psychological counsellor, a geneticist, and a dietician. In case of unavailability of the MDT at the local place, virtual tumor boards (VTB) for difficult and complicated cases should be consulted. Such well-structured VTB facility organized by the National Cancer Grid ensures access to specialized consultations, enhancing the collaborative management of cancer patients.

Risk Adapted Therapy for Very Early and Early Tumors

There are a variety of surgical approaches available for the treatment of primary rectal cancer lesions.[54,55] The selection of the appropriate method depends on several factors such as the location, extent, and stage of the disease. These methods include polypectomy, transanal local excision, and TEM. More invasive procedures that involve transabdominal resection, such as low anterior resection (LAR), proctectomy with TME and coloanal anastomosis, and abdominoperineal resection (APR) are also available.[54,55]

For early rectal cancers, such as cT1N0 without adverse features like grade 3, venous invasion, and LVI+ (lymphovascular invasion), local excisional procedures such as TEM are considered appropriate as a single modality.[56–58]TEM allows for more accurate en bloc, full-thickness local excision of rectal tumors than local excision and can provide similar oncological outcomes as TME in pT1sm1 (clinical cN0) rectal cancers without compromising anorectal function. A meta-analysis in 2015 confirmed that TEM has superior oncologic outcomes compared to transanal local excision in early cancers.[59] During these excision, tumor fragmentation should be avoided and negative deep (>3 mm) and mucosal margins are required.

Local procedures, such as sphincter-sparing procedures, cause minimal morbidity and mortality and result in early postoperative recovery.[60,61] However, they have certain

limitations, such as the absence of pathologic staging of nodal involvement. Endorectal ultrasound is also unable to identify lymph node micrometastases in early rectal lesions.[62] As a result, patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[61,63,64]

Careful patient selection is crucial for local excision of T1, N0 rectal cancer. It is also important to carefully examine the resection specimen, and consider subsequent transabdominal resection for patients found to have T2 disease or high-risk features. In some cases, local radiotherapy such as brachytherapy or contact therapy (Papillon technique) can be considered as an alternative to local surgery,[65] either alone or in combination with chemoradiotherapy.

Patients with rectal cancer who are not suitable for local surgery should undergo transabdominal resection. Whenever possible, sphincter preservation surgeries are preferred, although they may not be feasible in all cases. Tumors such cT2c/T3a/b should be treated by radical TME surgery due to the higher risks of recurrence and mesorectal lymph node involvement.[58] TME is the standard surgery and involves the en bloc removal of the mesorectum, associated lymphatic and vascular structures, fatty tissue, and mesorectal fascia while sparing the autonomic nerves.[55,60,66] In cases of high rectal cancer, a partial mesorectal excision with a distal margin of at least 5 cm of mesorectum may be considered.

When the tumor involves the anal sphincter or the levator muscles or when margin-negative resection would result in loss of anal sphincter function, an APR with TME should be performed, which involves en bloc resection of the rectosigmoid, rectum, anus, surrounding mesentery, mesorectum (TME), and perianal soft tissue, and necessitates creation of a colostomy.[67] Preoperative radiotherapy with or without chemotherapy may be considered for low lying tumors needing an APR to achieve a complete clinical response (CCR) and pursue a "watch-and-wait" (W&W) strategy to avoid a stoma, but it is not a routine recommendation.

The decision of laparoscopic or open surgery should be based on surgeon's experience with the technique, the location and stage of the cancer, and patient related factors such as obesity and previous open abdominal surgery. Robotic-assisted rectal cancer surgery provides some technical advantages for surgeons compared with conventional laparoscopy, but it has not shown to impact survival for the patients. Lateral pelvic lymph node dissection is not routine unless persistently involved on postneoadjuvant therapy imaging. Lateral pelvic nodes are often invaded if multiple mesorectal nodes are involved[68] (►**Table 5**).

Risk Adapted Therapy for Intermediate Risk (IR) Rectal Cancer [cT3a/b (Very Low, Levators Clear, MRF Clear or (cT3a/b in Mid- or High Rectum, cN1-2 (not Extranodal), no EMVI]

Although upfront surgery is still the mainstay of treatment for early rectal cancer, neoadjuvant therapy is becoming increasingly important for downstaging the disease and

Table 5 Indian consensus and guidelines: risk adapted therapy for very early and early tumors

Guidelines	LoE	GoR	Consensus
Statement 16[59,65]			
Very early tumors			26/30
cT1N0 with no additional risk factors (like LVI, G3) may be considered for TEM/local excision	I	A	
EBRT with or without brachytherapy boost can be considered as an alternative to surgery	III	B	
Statement 17[120,121]			
Early rectal tumors not suitable for local excision (cT1–cT2; cT3 if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI)			25/30
TME is the standard treatment option	I	A	
For ultra-low-lying tumors needing an APR and if patient wishes to avoid a stoma, one may consider using preoperative radiotherapy with or without chemotherapy to achieve a CCR and pursue W&W strategy	III	B	
Statement 18[68]			
• In selecting laparoscopic or open surgery, the surgeon should consider his/her experience with the technique, the stage and location of the cancer and patient factors such as obesity and previous open abdominal surgery • Robotic-assisted rectal cancer surgery provides some technical advantages for surgeons compared with conventional laparoscopy but has not shown to impact survival for the patients • Lateral pelvic lymph node dissection is not routine unless persistently involved on postneoadjuvant therapy imaging	Expert opinion	Expert opinion	28/29

Abbreviations: APR, abdominoperineal resection; CCR, complete clinical response; EBRT, external beam radiation therapy; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; MRF, mesorectal fascia; LVI, lymphovascular invasion; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; W&W, watch-and-wait.

reducing the risk of local recurrence.[69] Before the era of total neoadjuvant therapy (TNT), one of the largest meta-analysis involving more than 3000 patients with rectal cancer confirmed increased PCR rates, decreased local recurrences and distant metastasis rates with the use of neoadjuvant long-course chemoradiotherapy (LCRT).[70] However, the criteria for choosing the subset of patients benefitting the most from neoadjuvant therapy are not well defined in the IR group. There are considerable differences of opinion regarding the two approaches. The support for upfront surgery in this subset of patients, where the tumors are proximal and do not threaten the mesorectal fascia, comes from the favorable rates of low local recurrences after TME in the Dutch trial and several other retrospective analyses.[29,71–74] Though there is ample support for neoadjuvant therapy in advanced cT3c/d and cT4 patients with threatened mesorectal fascia, its role in other indications is debatable. Of particular interest here are the patients with radiologically positive nodes.

The advent of improved imaging modalities such as EUS and MRI gives a better picture of CRM. However, their utility in predicting a node's malignant versus reactive nature based on its morphology and size is controversial.[75,76] However, it can be agreed that there is no prognostic importance of involved lymph nodes on preoperative MRI assessment, on the risk of local recurrence. If the surgeon carries out a good quality TME with en-bloc excision of the mesorectum, the chances of local recurrence are low.[77] The updated guidelines for the treatment of rectal cancer from the ESMO suggest that patients with a depth of invasion beyond the muscularis propria, that is, 5 mm or less, are appropriate candidates for upfront surgery rather than neoadjuvant therapy, even if they are node-positive, as long as the levators are not threatened, the mesorectal fascia is clear, and there is no extranodal extension.[16] The American Society of Clinical Oncology (ASCO) Annual Meeting Plenary Session showcased the outcomes of the PROSPECT trial, a randomized phase 3 study, revealing significant findings in the treatment of locally advanced rectal cancer (LARC; cT2N+ or cT3N0/+). The trial demonstrated the noninferiority of neoadjuvant 5-fluorouracil and oxaliplatin (FOLFOX), in combination with selective application of 5-fluorouracil chemoradiotherapy (5-FU CRT), compared to 5-FU CRT alone. Among approximately 1,200 patients enrolled in the study, the 5-year DFS rate was 80.8% in the experimental arm, while it stood at 78.6% in the standard arm. Notably, despite 90% of patients in the experimental arm avoiding radiotherapy, no additional local recurrences were observed.[78] Therefore, we recommend a carefully selected subset of intermediate-risk patients to be considered for upfront surgery where the surgeon is convinced of an adequate TME with complete mesorectal excision. Neoadjuvant therapy can be reserved for the remaining candidates where there is a suspicion that the quality of the surgery will be compromised (►**Table 6**).

Risk Adapted Therapy for Locally Advanced Rectal Cancer [cT3c/d or Very Low Localization, Levators Threatened, MRF Clear, cT3c/d Mid-Rectum, cN1–N2 (extranodal), EMVI +]

LARC are defined as tumors that involve the subserosa or extend into nonperitonealized pericolic or perirectal tissues, or tumors that involve other organs or structures and/or perforate the visceral peritoneum. Additionally, tumors with EMVI on rectal MRI are also classified as LARC. These tumors carry an increased risk of local recurrence and/or synchronous and subsequent metastatic disease.[79] In the case of preop contrast-enhanced MRI showing the features mentioned above, the risk of local recurrence and metastasis is high, and these patients are candidates for neoadjuvant therapy. If such patients undergo upfront surgery, they have a high chance of an R+ resection leading to increased local recurrences. There are two different schedules of preoperative therapy that are standards of care worldwide namely LCRT and short-course RT (SCRT). LCRT with LCRT in the neoadjuvant setting became the standard of care (compared to adjuvant CCRT) after the results of the German trial were first published in 2004, while the role of SCRT was first established in the Swedish trial as early as in 2005.

Choice of Short-Course RT versus Long-Course RT

SCRT with a 25 Gy total dose at 5 Gy/fraction during 1 week is followed by immediate surgery (< 10 days from the first radiation fraction) or delayed surgery. LCRT with a

Table 6 Indian consensus and guidelines: risk adapted therapy for intermediate risk (IR) rectal cancer

Guidelines	LoE	GoR	Consensus
Statement 19[29,71,81,82,91,104–106]			
Intermediate/more locally advanced rectal cancers [cT3 (very low, levators clear, MRF clear) or (cT3 in mid- or high rectum, cN1-2 (not extranodal), no EMVI]			25/31
Upfront surgery for carefully selected subset of intermediate risk patient (early T3, non-bulky)	II	B	
SCRT → TME	II	A	
LCRT → TME	II	A	
SCRT → chemotherapy for 3 to 4 months →TME	II	B	
Perioperative chemotherapy → LCRT / SCRT →TME	II	B	
Perioperative chemotherapy → TME (especially for cT3 mid rectal tumors with N0 or N1)	II	B	

Abbreviations: EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; LCRT, long-course radiotherapy; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TME, total mesorectal excision.

recommended dose of 45 to 50 Gy in 25 to 28 fractions, a boost with 5.4 Gy in 3 fractions, can be considered for preoperative RT if the CRM is threatened, and for postoperative RT routinely with 5.4 to 9.0 Gy in 3 to 5 fractions according to CRM. Several institutes worldwide, including India, have adopted SCRT as their standard of care, especially with newer trials highlighting a higher rate of adverse events in the LCRT arm with no difference in postoperative complications.[80] Further support of SCRT followed by delayed surgery was demonstrated by the Stockholm trial, which was a phase 3, randomized, noninferiority trial[81] and another phase III trial by Bujko et al.[82] The Stockholm III study demonstrated that SCRT with a delayed surgical approach is noninferior when compared to SCRT followed by immediate surgery. Although there was a slightly higher occurrence of acute radiation-related side effects in the former group, the rates of postoperative complications were nearly the same in both groups; hence, SCRT with delayed surgery is an acceptable alternative to SCRT with immediate surgery.[81]

Currently, there are no established guidelines specifying which clinic-radiological substages would benefit the most from SCRT or LCRT in LARC. The decision to use a preoperative approach in LARC is primarily based on the risk of having a positive margin resection at TME surgery. If there is a predicted risk of a positive margin or R+ resection status, chemoradiation therapy (LCRT) may be recommended.[83] For above group patients, LCRT is associated with higher R0 resection rates compared with RT alone.[84] These recommendations are challenged by the findings of a recent trial where even if the predicted margin is at risk (CRM $\leq$ 1 mm or fixed cT3 tumors), similar R0 resection rates and DFS are achieved by both SCRT or LCRT followed by chemotherapy with oxaliplatin/leucovorin/fluorouracil and by surgery.[85]

The management of upper rectal cancer remains debated, with limited studies analyzing the impact of neoadjuvant treatment in this specific population. Current evidence lacks consensus due to the inclusion of different rectal tumor locations in previous trials and the known impact of tumor location on outcomes. While some guidelines (ESMO) suggest treating upper rectal cancers as colon cancer without neoadjuvant treatment, there is disagreement among experts who argue that patients with cT4 tumors of the upper rectum may benefit from neoadjuvant chemoradiation therapy (CRT) or chemotherapy alone. A recent retrospective study in France demonstrated comparable survival outcomes between patients who received radiotherapy and those who did not. Interestingly, the cohort receiving neoadjuvant CRT experienced a higher incidence of postoperative sepsis and other complications.[86]

Choice of Chemotherapy with RT

Continuous intravenous infusion of 5-FU or oral capecitabine during CRT is recommended rather than bolus 5-FU[87,88] Capecitabine is therapeutically equivalent to infusional FU when used during concomitant LCRT, but with a different toxicity profile.[88] However, its oral formulation makes it easier to administer with a higher compliance rate. Though adding oxaliplatin to LCRT may improve the pCR rates and DFS in some patients, several meta-analyses proved it enhances the acute toxicities.[89] Adding a platinum agent increased grade 3 or 4 toxicities, including diarrhea, nausea, neurosensory toxicity, and fatigue. As there is no improvement in survival in several randomized trials testing, this combination precludes oxaliplatin as a radiosensitizer. It is not recommended to be added to fluoropyrimidine-based LCRT outside of a clinical trial.[90,91]

Though some nonrandomized trials suggested the benefit of adding irinotecan to the LCRT regimen, the same could not be shown in an Radiation therapy oncology group (RTOG) trial.[92] Biological molecularly targeted agents have not been successfully integrated into LCRT. There is discord regarding the early reports concerning the benefit of adding cetuximab or panitumumab, two humanized monoclonal antibodies targeting the epidermal growth factor receptor, to conventional FU-based CRT.[93,94] Similarly, the use of bevacizumab (a humanized monoclonal antibody targeting the vascular endothelial growth factor [VEGF] or aflibercept (a recombinant fusion protein that functions as a decoy receptor, preventing VEGFA, VEGFB, and placenta growth factor from binding to their receptors) in addition to conventional FU-based LCRT has had mixed results.[95,96] Thus, their addition to standard LCRT is not recommended due to the paucity of completion of phase III studies.

To summarize, neoadjuvant RT or LCRT is a crucial component of locally advanced mid/low stage II/III rectal cancers, and it reduces the rate of local recurrence without impacting the OS. There is little benefit from adding preoperative SCPRT or LCRT to upper rectal cancers (>12 cm from the anal verge) above the peritoneal reflection, and it should be treated as colon cancer (►**Table 7**).

Risk Adapted Therapy for Very Advanced Tumors [cT3 with any MRF Involved, Any cT4a/b, Lateral Node+]

SCRT has not been perused for the candidates as mentioned above. Involvement of lateral pelvic lymph nodes is an independent poor prognostic feature and addressing it surgically is controversial.[68] Also, any CRM+ (either due to tumor or lymph node) has in general higher risk of local recurrences.[27] It is recommended that such cases be treated with a long course of concurrent chemoradiotherapy and then be considered for surgery followed by adjuvant chemotherapy. (TME and more extended surgery if needed due to tumor overgrowth). However, depending on the treating clinician's discretion, total neoadjuvant therapy (TNT- see below) (TNT) is also feasible for this subset of patients. It is given as a treatment option in the latest NCCN guidelines for unresectable and medically operable tumors (►**Table 7**).

TNT Approach

TNT should be considered for all LARCs, especially clinical T4 disease, local extension to pelvic side walls and sacrum or close or involved CRM, N2 disease, lateral pelvic node involvement, or in presence of EMVI. These tumors are unlikely to undergo curative resection without multivisceral resection; hence, such patients require preoperative treatment to shrink the

Table 7 Indian consensus and guidelines: risk adapted therapy for locally advanced and very advanced rectal cancer

Guidelines	LoE	GoR	Consensus
Statement 20[91,104–106]			
Locally advanced rectal cancers [cT3 or very low localization, levators threatened, MRF clear, cT3 mid-rectum, cN1–N2 (extranodal), EMVI+].			27/27
LCRT → TME	II	A	
SCRT → chemotherapy for 3 to 4 months →TME	II	A	
Perioperative chemotherapy → LCRT / SCRT →TME	II	A	
Statement 21[88,90,93–95]			
Oral capecitabine is preferred over 5-FU-based regimens as a chemotherapy partner for LCRT	II	A	27/28
It is not recommended to add oxaliplatin to fluoropyrimidine during LCRT	Expert opinion	Expert opinion	
Addition of irinotecan or biological agents (like bevacizumab and cetuximab/panitumumab) is not recommended to standard LCRT	Expert opinion	Expert opinion	
Statement 22[86]			
Upper rectal tumors (above the peritoneal reflection) have limited benefit from preoperative radiotherapy and may be considered for upfront surgery	III	C	25/26
Alternatively, if cT4a/b, one may consider neoadjuvant chemoradiotherapy	III	C	
Statement 23[112]			
Very advanced tumors (cT3 with any MRF involved, any cT4a/b, lateral node+)			22/25
TNT approach is preferred in this situation.	II	A	
Preoperative LCRT followed by surgery (TME and more extended surgery if needed due to tumor overgrowth)	II	B	
It is advisable to conduct 8 to 12 weekly imaging evaluation to assess the poor responders to neoadjuvant treatment and consider them for definitive surgery	III	A	

Abbreviations: 5-FU, 5-fluorouracil; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; LCRT, long-course radiotherapy; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

cancer away from the threatened margin, that is, the MRF/CRM. Without preoperative treatment, surgery is likely to lead to either an R1 or an R2 resection.[84] A treatment approach, which includes courses of both chemoradiotherapy (chemoRT) and chemotherapy given as neoadjuvant therapy before definitive surgery, has been the therapy of choice in recent times. This approach, called TNT, was initially tested in small phase II trials and later in larger phase III trials.[97–103]

The TNT approach consists of two approaches: the induction chemotherapy approach and the consolidation approach. The induction chemotherapy approach involves using FOLFOX/CAPOX or FOLFIRINOX for 12 weeks (as per PRODIGE-23),[104] followed by LCRT or SCPRT. A 7-year update of PRODIGE 23 revealed a notable 5.1% increase in DFS through TNT, alongside a significant 5.8% improvement in OS compared to the standard approach of LCRT followed by surgery; both strategies were supplemented by adjuvant FOLFOX chemotherapy.[105] The consolidation approach involves using SCPRT (preferred) or LCRT, followed by FOLFOX (5-FU, leucovorin, oxaliplatin) or CAPOX (capecitabine and oxaliplatin) for 12-16 weeks. The RAPIDO trial enrolled 920 patients who were randomized into two arms: one receiving SCRT followed by chemotherapy (6 x CAPOX or 9 x FOLFOX) and then TME, and the other following the conventional sequence of LCRT followed by TME with optional adjuvant chemotherapy (8 x CAPOX or 12 x FOLFOX). Despite comparable 3-year OS and locoregional failure (LRF) rates, the experimental arm displayed nearly doubled pCR rates and a noteworthy 6.8% reduction in distant metastasis at the 3-year mark.[106,107] However, the 5-year update of the RAPIDO trial revealed an increase in the risk of local relapse in the experimental arm.[106] It is not clear whether it is better to start with chemotherapy, then follow with LCRT, or vice versa when following a TNT approach. In the Organ Preservation of Rectal Adenocarcinoma trial, 324 patients were divided into two arms: one received induction chemotherapy followed by LCRT, while other had received LCRT followed by consolidation chemotherapy. Chemotherapy consisted of 4 months of CAPOX or FOLFOX. The 3-year DFS was similar in both arms and the primary endpoint of the study (DFS between TNT and selective WW versus historical controls) was not met. However, a trend emerged where chemoradiation followed by consolidation chemotherapy correlated with a higher rate of organ preservation (3-year TME-free survival: 41 vs. 53%).[85]

The TNT approach has been shown to offer several benefits, including the potential to prevent or eliminate micrometastases early on, a higher rate of achieving pathologic complete response, longer progression-free survival,[103,108–111] minimizing the duration for need of an ileostomy,[111] facilitating resection, and improved tolerance and completion rates of chemotherapy.[99,103,104,108] In some cases, neoadjuvant

Table 8 Indian consensus and guidelines: TNT

Guidelines	LoE	GoR	Consensus
Statement 24[60,108,110,112]			
Locally advanced rectal tumors with CRM threatened or involved (either due to primary or lymph node) can be considered for TNT approach	II	A	23/25
Statement 25[20]			
Patients with EMVI may benefit from TNT approach as they have more risk for distant metastasis. Treating them with systemic chemotherapy earlier may reduce the risk of recurrence	III	B	21/28
Statement 26[104,105,107]			
Any mid / low lying tumors above cT3/4 or cT1-2 with cN+ may be considered for TNT approach	II	A	25/27
Statement 27[109,111]			
For early ultra-low lying rectal tumors, TNT approach may be acceptable if the goal is to achieve CCR and avoid permanent stoma	III	C	25/28

Abbreviations: CCR, complete clinical response; CRM, circumferential resection margin; EMVI, extramural vascular invasion; GoR, grade of recommendation; LoE, level of evidence; TNT, total neoadjuvant therapy.

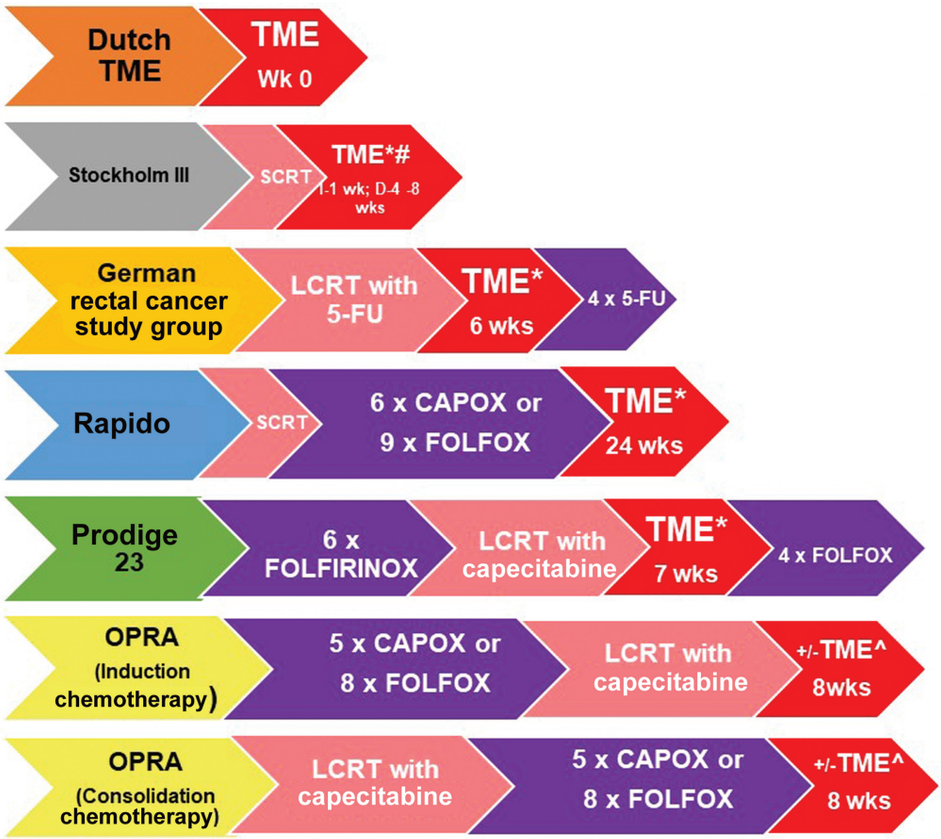

Fig. 2 Timing of total mesorectal excision (TME) in various pivotal trials. TME, Total mesorectal excision; SCRT, Short course radiation therapy – 5 x 5 gy over 5 days; LCRT, Long course chemoradiation; 5-FU, 5-Fluorouracil; FOLFOX, 5-FU, Oxaliplation; FOLFIRINOX, 5-FU, Oxaliplation, Irinotecan; CAPOX, Capecitabine, Oxaliplation; RAPIDO, Radiotherapy and preoperative induction therapy followed by dedicated operation; OPRA, Organ preservation in rectal adenocarcinorma. *Timing from end of RT; #I-immediate – 1 wk; D-delayed – 4 to 8 wks; ^Timing from end of TNT; Wks – Weeks.

therapy may even eliminate the need for surgery if a complete response is achieved. For early ultra-low lying rectal tumors, the TNT approach may be acceptable if the goal is to achieve CCR and avoid a permanent stoma (►**Table 8**).

Timing of Surgery (►Fig. 2)

The optimal timing of surgery after SCRT is debatable, and there is no consensus on the best approach. Most of the

significant trials described above, which compared SCRT followed by surgery versus surgery alone[83]or SCRT versus LCRT before surgery,[82] used an interval to surgery of 7 days after completion of SCRT. On the other hand, the further surgery if needed due to tumor overgrowth, the median interval time for surgery in the Dutch TME trial was 11 days. Some studies have reduced the time to 3 days, citing the cause of treatment-related leukopenia contributing to poor wound healing after delayed surgery.[112,113] Similar to the ESMO guidelines, we recommend that either approach (immediate surgery <10 days after the first RT fraction or delayed surgery four to eight weeks after the end of RT) is acceptable.[16] The optimal interval between completion of neoadjuvant CRT and surgery in rectal adenocarcinoma is also not established. Updated guidelines from the ESMO provide no specific recommendation other than to state that in practice, here is a wide variation in the timing of surgery, with intervals ranging from 4 to 12 weeks. Prolonging this interval may not only enhance the rate of pCR but also provide an opportunity for tumor repopulation. Moreover, delaying surgery can also postpone the administration of postoperative chemotherapy. The benefits of longer intervals must therefore be carefully weighed against the potential risk of subsequent metastases.[16]

Adjuvant Therapy

Postoperative CRT could be considered in patients with adverse histopathological features after upfront surgery—like positive CRM, perforation in the tumor area, incomplete mesorectal resection, nodal deposits with extracapsular spread close to the MRF, or if preoperative RT has not been given in patients with high risk of local recurrence.[114] The rates of local failure with surgery alone range from 15 to 30% with T3N0 stage II disease compared to T1 and T2 disease where it is less than 10%. The failure rate increases up to 65% with node positive status in T3/T4 disease. The suggested chemotherapy partner for treating the patient is infusional 5-FU or capecitabine at a dose of 825 mg/m^2 twice daily, 5 days a week. The bolus 5-FU is not recommended because of the major hematological toxicity associated with it. Moreover, the results of the GITSG and NCCTG trials have shown that RT alone after surgery is an inferior option with a lack of survival benefit when compared to chemoradiotherapy (CRT).[115] Oxaliplatin should not be used concurrently with radiotherapy.

The available randomized controlled trials and meta-analyses have not provided clear evidence on the benefit of adjuvant chemotherapy, as the methods used in these trials for answering this question are not standard. Additionally, there is a lack of data to strongly support the use of adjuvant chemotherapy in patients with rectal cancer who have received neoadjuvant chemoradiotherapy.[114] As such, there are variations in the recommendations for adjuvant therapy between American and European nations. The NCCN recommends the use of adjuvant therapy irrespective of the outcomes of neoadjuvant chemoradiotherapy. On the other hand, the ESMO recommends adjuvant chemotherapy for high-risk patients with pathological stage II and stage III disease. According to a retrospective propensity score matched analysis conducted over a period of 6 years using the National Cancer Database in the USA, there is limited benefit in patients who achieve a complete pathological response after neoadjuvant chemoradiotherapy (CRT).[116] The Indian Society of Medical & Paediatric Oncology recommends the discretion of physicians when deciding whether to observe patients with pCR or to administer adjuvant chemotherapy to all other patients. In the adjuvant setting, the recommended regimen is a combination of 5-FU and oxaliplatin, based on data from the phase II Adjuvant Oxaliplatin in Rectal Cancer (ADORE) trial.[117] Since International Duration Evaluation of Adjuvant therapy study included exclusively colon cancer patients, there is no strong evidence to comment on duration of chemotherapy for the rectal cancer patients. The panel recommends to give a total of 6 months of chemotherapy including the period of chemoradiation[118] (►**Table 9**).

W&W Strategy

De-escalation strategies are being researched in oncology to gain better quality of life without compromising the survival outcomes. Patients with LARC do suffer from significant surgical toxicities like bowel dysfunction, perianal discharge, and LAR syndrome. W&W strategy is being practiced in many institutions wherein patients who have obtained complete clinical response after neoadjuvant concurrent chemoradiotherapy is observed for local recurrence and surgical morbidities are obviated. W&W merits discussion in this important policy document. In the meta-analysis by Dossa et al on published literature primarily on retrospective studies, there was no difference between W&W and surgery in terms of OS in patients who had achieved complete clinical response.[119] However, the risk of local recurrence remains high, with rates as high as 30%, although nearly 85% of these local recurrences can be salvaged.[120] The international registry on W&W database collected data on over 1,000 patients and found that the majority (88%) of recurrences occurred within the first 2 years, and 97% of recurrences were in the rectum wall. Some studies have shown that the OS may be inferior with the W&W strategy.[121]

Considering the morbidity of up to a 90% rate of LAR syndrome, which includes symptoms like tenesmus, perianal discharge, increased stool frequency, pain, and fecal incontinence,[122] many patients would not agree for surgery and or stoma. Newer approaches like total neoadjuvant treatment question the role of universal surgery for all paradigm for LARC. “Wait” is acceptable, but how to “watch” in our setup is a big challenge. The W&W strategy requires intense monitoring or surveillance for local recurrence like DRE, endoscopy, and MRI. These investigations are limited by their sensitivity and specificity. Repeated biopsies are not recommended. The majority of local recurrences in rectal cancer patients who undergo W&W can be successfully treated surgically, as shown by retrospective studies and IWWD data. In absence of strong prospective data and limitations

Table 9 Indian consensus and guidelines: adjuvant therapy

Guidelines	LoE	GoR	Consensus
Statement 28[114]			
Postoperative CRT could be selectively used in patients with unexpected adverse histopathological features after primary surgery—e.g., positive CRM, perforation in the tumor area, incomplete mesorectal resection, extranodal deposits or nodal deposits with extracapsular spread close to the MRF, or in other cases with high risk of local recurrence if preoperative RT has not been given	Expert opinion	Expert opinion	22/23
Statement 29[116,117]			
It is reasonable to consider adjuvant ChT in rectal cancer patients after preoperative CRT/RT with residual disease	II	B	20/24
For patients achieving PCR after preoperative therapy, observation is a reasonable option	II	B	
Statement 30[118]			
If adjuvant chemotherapy is planned, a doublet chemotherapy (CAPOX or FOLFOX) may be preferred; however, single-agent capecitabine is an acceptable alternative	II	B	22/26
Duration of chemotherapy should not be more than 24 weeks (total including preoperative regimen)	II	B	

Abbreviations: CAPOX, capecitabine and oxaliplatin; ChT, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; FOLFOX, 5-fluorouracil and oxaliplatin; GoR, grade of recommendation; LoE, level of evidence; MRF, mesorectal fascia; PCR, pathological complete response; RT, radiation therapy.

of intense follow-up, patient selection remains a key here. Tumors located in the lower and mid-rectum that require TME can be considered for W&W, especially for patients who wish to avoid permanent stoma.

The concept of W&W is applicable to operable cases and can also be extended to medically inoperable cases, where addressing comorbidities like heart disease and diabetes mellitus can be combined with reassurance on the W&W strategy. W&W is a promising nonsurgical option for selected patients, and prospective large sample studies are needed to fill the lacuna in literature to support its universal adoption (►**Table 10**).

Surveillance

The purpose of post-treatment surveillance in rectal cancer is to detect the recurrence of the disease at an early stage, allowing for timely curative interventions. The recommendations for transanal local excision patients include proctoscopy with EUS or contrast-enhanced MRI every 3 to 6 months for the first 2 years, then every half-yearly for a total of 5 years. Colonoscopy at 1 year after surgery with repeat intervals based on status of adenoma and based on expert opinion is recommended for them as well as those with stage I nonLynch rectal cancer.[123]

Stage II and III patients are recommended for intensive postoperative surveillance due to a risk of 5 to 30% recurrence rate. A recent study reported that 95% of CRC recurrences occur within 5 years post-treatment,[124]while data from 20,898 patients in 18 colon cancer trials found that 80% of recurrences occur within the first 3 years.[125] Unfortunately, surveillance strategies such as imaging or CEA screening did not offer a significant survival advantage over a symptom-based approach for these patients.[126] The COLOFOL trial of 2509 patients with stage II or III CRC found no significant difference in 5-year overall or CRC-specific mortality between high-frequency and low-frequency surveillance approaches.[127] A meta-analysis reported a sensitivity of 68% and specificity of 97% for a CEA cutoff of 10 ng/mL; however, it showed limitations in detecting recurrences within the first 2 years post-treatment.[128] Surveillance protocol recommendations for non-Lynch patients with stage II to III rectal cancer include physical examination and CEA screening every 3 to 6 months for 2 years, then every 6 months for 5 years, along with chest/abdominal/pelvic CT every 6 to 12 months for 5 years based on expert opinion.

Lynch syndrome-associated CRCs present at a younger age, are predominantly right-sided, and progress rapidly from adenoma to cancer. Regular colonoscopy is the only effective surveillance protocol, with a decrease in CRC mortality of up to 72%. Guidelines recommend colonoscopy every 2 to 3 yearly starting as early as at age of 25 years for the patients with molecular confirmation of Lynch syndrome. More stringent surveillance may be warranted for MLH1 and MSH2 gene carriers as compared to MSH6 and PMS2.[129] Aspirin, has been found to be associated with reduced CRC risk in Lynch syndrome carriers. We aim to systematically promote this intervention for all Lynch syndrome carriers and recommend low-dose aspirin 100 to 150 mg for at least 2 years.[130]

The application of PET/CT in disease surveillance is not advisable due to potential hazards such as unwarranted medical interventions following false positive results and unjustified radiation exposure.[131,132] While studies have

Table 10 Indian consensus and guidelines: W&W—Indian consensus and guidelines

Guidelines	LoE	GoR	Consensus
Statement 31[119–121]			
A NOM approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient about their risk of recurrence	III	A	23/25
NOM should only be offered to patients achieving CCR as defined by • DRE • Scopy and biopsy if required • MRI	Expert opinion	Expert opinion	
Statement 32[126,128]			
Careful surveillance is essential for those considering a W&W approach to treat tumor regrowth in a timely manner ◦ DRE, flexible sigmoidoscopy, and CEA every 3 to 4 months for the first 2 years, then every 6 months for years 3 to 5 (with photographs); ◦ MRI every 3 to 4 months for the first 2 years, then every 12 months for years 3 to 5; ◦ CT chest/abdomen/pelvis twice a year for 2 years, then once a year for years 3 to 5; ◦ And colonoscopy once at year 1 and again at year 5;	II	A	26/26
Statement 33[53]			
If patient has dMMR or MSI-H, one may consider single agent PD-1/PDl-1 therapy for 6 months	III	A	24/27
Statement 34[119]			
For locally advanced tumors, one may consider brachytherapy boost to augment the chances of cCR in order to pursue W & W strategy. However, it must be done in expert centers only	III	C	23/25

Abbreviations: CCR, clinical complete response; CEA, carcinoembryonic antigen; CT, computed tomography; dMMR, deficient mismatch repair; DRE, digital rectal examination; GoR, grade of recommendation; LoE, level of evidence; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; NOM, nonoperative management; PD-1, programmed cell death protein 1; PDL-1, programmed cell death ligand 1; W&W, wait and watch.

Table 11 Indian consensus and guidelines: surveillance—Indian consensus and guidelines

Guidelines	LoE	GoR	Consensus
Statement 35[123,126]			
For patients with Transanal local excision only ◦ Proctoscopy (with endoscopic ultrasound [EUS] or MRI with contrast) every 3–6 months for the first 2 y, then every 6 months for a total of 5 years ◦ Colonoscopy at 1y after surgery • If advanced adenoma, repeat in 1 year • If no advanced adenoma, repeat in 3 years, then every 5 years	Expert opinion	Expert opinion	25/25
Statement 36[131]			
For patients with stage-I rectal cancer (non-Lynch) ◦ Colonoscopy at 1 year after surgery • If advanced adenoma, repeat in 1 year • If no advanced adenoma, repeat in 3 years, then every 5 years	Expert opinion	Expert opinion	25/25
Statement 37[128,131]			
For patients with stage II to III rectal cancer (non-Lynch) • History and physical examination every 3–6 months for 2 years, then every 6 months for a total of 5 years • CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years • Chest/abdominal/pelvic CT every 6–12 months for a total of 5 years	Expert opinion	Expert opinion	22/27

(*Continued*)

Table 11 (*Continued*)

Guidelines	LoE	GoR	Consensus
Statement 37 (a)[129]			
For patients with/ without prior history of rectal cancer and are known Lynch syndrome carriers (germline pathogenic MMR gene variant carriers)			26/26
MLH1, MSH2, and MSH6 gene carriers: 2-3 yearly colonoscopy surveillance is recommended	III	A	
PMS2 gene carriers: 5-yearly colonoscopy surveillance may be considered, in order reduce colorectal cancer incidence and mortality	III	B	
There is no evidence to support different colonoscopic intervals between men and women	III	A	
MLH1 and MSH2 gene carriers: age of initiation for colonoscopy surveillance is recommended to be 25 years	III	A	
MSH6 and PMS2: age of initiation for colonoscopy surveillance is recommended to be 35 years	III	B	
Statement 38[132]			
PET-CT is not recommended for surveillance.	Expert opinion	Expert opinion	27/28
Statement 39[133]			
Role of ctDNA-based surveillance is promising but cannot be recommended as part of routine clinical practice	Expert opinion	Expert opinion	27/28
Statement 40[130]			
Chemoprevention with low-dose aspirin 100 to 150mg for a minimum duration of 2 years in Lynch syndrome carriers (germline MMR pathogenic variant carriers) with/without prior history of cancer is recommended to reduce risk of cancer	III	B	28/28

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; ctDNA, circulating tumor DNA; MLH1, MutL homolog 1; MMR, mismatch repair; MRI, magnetic resonance imaging; MSH2, MutS homolog 2; MSH6, MutS homolog 6; PET-CT, positron emission tomography/computerized tomography; PMS2, postmeiotic segregation increased 2.

shown that ctDNA detection can predict cancer relapse with high accuracy and earlier than radiologic imaging or CEA, the current evidence for its value in post-treatment surveillance is limited by small sample sizes and lack of validation cohorts. Ongoing trials are aimed at establishing ctDNA-based surveillance strategies and determining if early diagnosis impacts survival[133] (►**Table 11**).

Authors' Contributions

Bhawna Sirohi and Viraj Lavingia were involved in concept and design. All the authors have helped in definition of intellectual content, literature search, manuscript preparation, manuscript editing, and manuscript review.

Patient Consent

No, as in this article, the guidelines presented are derived from a comprehensive literature review and expert consensus.

Conflict of Interest

As mentioned in the individual forms separately by each author.

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Bioethical and Human Right Considerations during COVID-19 Pandemic Period: Reflections of Integrated Oncology Clinical Services from India

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Abstract

Ever since the outbreak of COVID-19, the global health care systems are overwhelmed to cope up with the rapidly evolving disease paradigm through implementation of action plans at societal and medical domains. As per the directives from the World Health Organization and learned professional organizations, the international governments and states have formulated different protocols to prevent disease spread, for diagnosis and treatment of the disease and associated comorbidities, and to educate citizens during this crisis phase. Health care services across the world followed a "prioritizing strategy" for hospital population wherein the non-COVID cases were given less focus. Many hospitals opted for a conscious staff-sparing strategy to minimize exposure and protection of clinically valuable staff. Oncology services across the world reported a decline in the provision of clinical services to patients. There were medical concerns such as missed diagnosis, delayed diagnosis, delayed treatment, stoppage of screening programs, and differed follow-ups during the last 2 years of pandemic. The multidisciplinary oncology teams aim to ensure that cancer patients in the continuum of integrated cancer care pathway get globally accepted standards of optimum care. However, Beauchamp's ethical principles of autonomy, beneficence, nonmaleficence, and distributive justice were arguably compromised during the pandemic period. The

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articles of UNESCO Universal Declaration on Bioethics and Human Rights (UDBHR) declaration were possibly violated in cancer patients as a vulnerable population. This article analyses the bioethical and human right concerns with respect to medical and societal domains in oncology during the COVID-19 pandemic period.

Introduction

Bertrand Russell's quote in History of Western Philosophy (1945) "To teach how to live without certainty, and yet without being paralysed[sic] by hesitation, is perhaps the chief thing that philosophy, in our age, can still do for those who study it" reflects the global uncertainty the humanity is facing for the past 2 years.[1] In December 2019, cases of pneumonia with unknown etiology were discovered in Wuhan City, Hubei Province of China,[2] and this quickly spread across the world to trigger a global pandemic and caused grave misery and deaths worldwide including in India.[3–5]

COVID-19 brought in a plethora of events that impacted health care not only as a disease on its own but also other diseases. Cancer patients were left stranded mid-therapy, thus worsening their prognosis. The COVID-19 pandemic caused significant fatalities and highlighted both the advantages and drawbacks of global health care systems.[6] Even after 3 years since the initial report, the virus continues to mutate, and in spite of global vaccination initiatives, it still infects and spreads, thus challenging the health care providers and health care systems globally.[7–11] This uncertainty about future and unpredictability of this disease have led to multiple medical and ethical dilemmas in oncology [11] reflecting its impact in a clinical service model.

Impact on Oncology

Patients with cancer are obliged to attend health care institutions more frequently than patients with other diseases because of the nature of the disease and its many treatment techniques. Multidisciplinary teams must be fully involved in the treatment of cancer patients at all stages of the disease, from diagnosis through survivorship or end-of-life care.[12,13] In addition to various therapeutic interventions, cancer patients need multiple hospital visits for assessment, diagnosis, staging, or monitoring the effects of treatment. As any unjustified divergence from the well-established norms may result in fragmented and subpar care and affect patient outcomes, these clinical services should operate in harmony and on schedule with strong dedication and compliance from both patients and health care workers.[14]

When compared with the general population, cancer patients are known to be vulnerable and susceptible toward airborne microbial infections and are at increased risk of hospitalizations and mortality due to the ensuing pathogenesis.[15] Regarding COVID-19, research from China has indicated that there was no rise in the prevalence of COVID-19 infection in cancer patients compared with the general population. However, cancer patients showed a higher incidence of serious events such as hospitalization, respiratory complications, and need for care in intensive care units.[16,17] Health services were overburdened during the epidemic principally because COVID-19 care was given priority over other illnesses.[14,18,19] The health care sector was stalled by the fear of COVID-19 transmission in both the public and health care practitioners. In these uncertain times, oncology and health care settings concentrated on four key areas: (1) to protect patients from contracting SARS-CoV-2 and reduce the risk factors for COVID-19-related mortality in the case of infection; (2) to stop COVID-19 from spreading throughout health care facilities and the general public; (3) to reduce the danger of COVID-19 transmission to health care personnel; and (4) to properly distribute resources among all patients during a period of resource shortage.[20]

Global Data from Oncology Service Sector

In the course of the pandemic, the number of cancer patients receiving diagnoses and treatments decreased significantly, according to several cancer centers and societies around the world. According to studies, the pandemic had a significant impact on all facets of cancer care, including screening, diagnosis, treatment, palliative care, and follow-up. For at least a fraction of the individuals who would have received a cancer diagnosis during this time, it is likely that these decreases led to delayed diagnosis and inadequate treatment. Thus, the negative consequences of COVID-19 significantly affected the cancer patients across the globe. To substantiate this, seminal studies by Jazieh et al[14] and Ranganath et al[21] reported that a big majority of cancer patients were exposed to varying degrees of harm in the pandemic, including individual, societal, medical, and ethical problems.[14,21]

Doctor–Patient Paradigm and the Principlist Approach

The unanticipated interruptions in cancer care pathway had detrimental impact on the timely diagnosis and treatment of cancer. The above studies clearly show that cancer care was suboptimal and ethical concerns were evident during this period. In cancer care, a stronger trust and bond form between patients, families, treating physicians, and the support staff because the condition is serious in nature and treatment lasts over longer periods of time. For the patient's physical and mental health, as well as their

compliance with treatment modalities, the development of positive trust and a strong understanding between the oncologist and the patient is crucial, which was affected during the pandemic.[22,23] Unfortunately, the recommendations and measures put forward during the COVID-19 pandemic period failed to take the feelings of cancer patients and their morale into consideration, jeopardizing the desired trust-based physician–patient relationship.[24]

When the situation is analyzed according to Beauchamp and Childress' four ethical principles of beneficence, nonmaleficence, autonomy, and justice, the oncology services during the pandemic faced immense challenges. Deviation from the standard treatment plan, reduced number of treatment sessions, and delayed follow-ups would upset cancer patients, make them feel neglected, and pose risk to their lives.[25] This shows denial of beneficence and imminent harm or maleficence, which was compounded by uncertainty and suboptimal standard of care during the pandemic.[20]

Autonomy of cancer patients during the pandemic was infringed upon as a sequela to this. The decision-making to proceed with cancer treatment was not in the hands of patients or their families although potentially fatal risk is theoretically more associated with cancer than with the pandemic itself. The uncertainty, fear, and anxiety associated with possible SARS-CoV-2 infection influenced the patients' decision regarding their treatment. The situation was worse in people who developed recurrence or metastasis as immediate therapeutic interventions were not easily available. Due to the lockdown, there was acute shortage of anticancer and supportive drugs, and break in supply chain. This shows how nonmedical social contexts that are vital, can interfere with the ethical principles embedded in health care delivery.

Social justice and equity were skewed unfavorably, thus vitiating the fourth principle, which states that all patients should be treated equally.[26] However, an equal treatment does not mean the same treatment for all. The COVID-19 pandemic was an eye opener detailing the imbalance between medical needs and the available resources in health care systems across all nations. This resulted in clinical decisions that affected patient access to necessary care, quality-of-life, or end-of-life situations violating a patient's rights as an individual.[17] In terminally ill cancer patients, the futility of the treatment and choosing less aggressive lifesaving interventions would have been the observed protocol, which is generally substantiated even in non-COVID periods in the past.[27,28] From the clinicians' perspective, dilemma occurred when patients with a high chance of cure and a long life expectancy, like early breast cancer, get neglected due to circumstances, which jeopardized all four ethical principles negatively in clinical oncological services.

Universal Declaration of Bioethics and Human Rights Perspectives

When the pandemic health care services are analyzed within the scope of the Universal Declaration of Bioethics and Human Rights,[29] the national and international guidelines and restrictions imposed on the general population were infringed upon. These aspects said in the articles and guiding principles are described in subsequent paragraphs.

Article 3: Human Dignity and Human Rights

Imposing travel restrictions lead to inconveniences to access of patient care. The right to health care and patient's expectation to be treated in illness in a dignified manner were not always met within global contexts as reflected in studies.

Article 4: Benefit and Harm

This reflects Beauchamp and Childress's [30] principles of beneficence and nonmaleficence. Studies show many clinical trials and research activities faced setbacks[21] delayed treatment. This hampered the expected health benefits and possibly caused harm to patients. These aspects need to be revealed in future studies. The risk-benefit ratio in COVID plays a great role in imparting effective health care despite the lack of evidence was followed Social distancing and other clampdown measures require rethinking based on the benefit and harm principles.

Article 5: Autonomy and Individual Responsibility

For those who have had access to care, oncology services followed this as the standard operating procedures. However, prioritization of care in resource-limited settings affected the autonomy of the patient, as explained earlier. Mandatory vaccination, emergency use, and reuse of drugs should be with the choice of the individual patient and not just for the common good.

Article 6: Consent

Most nations experienced deficits of manpower of health care workers and infrastructure, access to care, and availability of medicines. During the COVID period, the additional comorbidities associated with the pandemic made the situation worse. There were reports wherein the patient's right to consent for a given intervention would have been affected as many were alone at critical stages of the disease and the health care team or the institutional guidelines decided on triage, treatment, and end-of life decisions without respecting this important principle.

Although many clinical trials were halted during the pandemic,[21] there were global efforts in vaccine development and clinical trials. Participants at multinational centers underwent explicit consent protocols in accordance with article 6. Policy decisions notwithstanding, informed consent forms an integral part even in such a dire situation of COVID.

Article 7: Persons without the Capacity to Consent

It is evident that the pandemic caused panic and chaos within the health care sector. There were instances wherein

the general conditions of many cancer patients during their course of treatment suddenly deteriorated, and isolation protocols and a large number of incoming patients burdened the daily functioning of cancer centers. It is expected that in the absence of family members in attendance and in poor general conditions, the provision of special protection available to the cancer patients was suboptimal or compromised.

The pandemic outbreak witnessed many therapeutic interventions that were not evidence based such as post-convalescent plasma infusions, antimalarial drugs, and certain antiviral agents, to name a few. The medical fraternity utilized them without scientific evidence and many patients suffered complications of such research interventions as COVID-19-related complications.

Article 8: Respect for Human Vulnerability and Personal Integrity

Cancer patients are vulnerable and depending upon their stages in continuum of care, the ability to provide consent varies. When there is a shift from Kantian utilitarian principle at early stages of treatment to a patient-centered deontological approach at later stages, the ethical framework changes from a health care provider's perspective. In advanced end-of-life situations, a family-centered approach sets in wherein family takes decisions on behalf of a vulnerable relative. These ethical paradigms in cancer care were affected due to COVID-19 protocols and affected the human rights of such patients as well. Vulnerability is universal in these COVID times, leading to the crossing of barriers that would otherwise not have been reported.

Article 9: Privacy and Confidentiality

In many countries, the initial panic reaction after disease outbreak led to disclosure of patient identities and family whereabouts in the media. In an attempt to "keep safe," many digital platforms were launched and the societal impact of those initiatives is yet to be analyzed with regard to data protection and patient confidentiality. Another issue was how the patent's privacy and confidentiality were protected in crowded hospital wards, hospital corridors, and in do-or-die situations. The nature of the disease and associated comorbidities played a huge role in cancer care settings competing for access to care in compromised infrastructural conditions.

Article 10: Equality, Justice, and Equity

Beauchamp and Childress's [30] principle of social justice echoes here. Duration of cancer treatment is lengthy and requires multiple visits to the health care facility. When the provisions of cancer services were affected due to the pandemic protocols and allocation of resources, patients did not receive the aspect of equality grounded in article 10 as non-COVID patients belonged to a lesser priority category from the service providers' point of view. As they were a medically compromised vulnerable population, priority for vaccination was ensured in the majority of nations for cancer patients. Enforced lockdown, quarantine, and restricted movement of persons across district/state borders could also trespass the lines of justice in access to care.

Article 11: Nondiscrimination and Nonstigmatization

In many communities, stigma still exists for cancer patients; however, cancer awareness programs work in a positive manner to eradicate such fears at the societal level. Unfortunately, during the initial phase of the pandemic, panic and chaos among the general population created unrest and fear in the realm of social psyche. This resulted in inadvertent isolation strategies wherein COVID-positive patients were discriminated and stigmatized in many communities. Denial of access to cancer care resulted as sequelae to this. Declaration of the names of COVID-afflicted patients could lead to positive discrimination. Surprisingly stigmatization did not rally as the infectious period of the disease was short and a multitude of people were affected by the disease in a short period.[27]

Article 12: Respect for Cultural Diversity and Pluralism

The observable trends in general hospital population influenced the paradigm of cancer care services also. Many cancer patients in end-of-life situations were forced to spend their last days in isolation away from family and friends. There was lack of access to perform their religious rituals from a spiritual perspective. Further, many COVID-positive dead bodies were cremated in mass graves in the absence of family members. Due to the fear of spread of the disease, the utilitarian approach enforced by the governments violated article 12 in many instances. Being a pandemic, indigenous traditions were acceptable at times, helpful to some extent, but many required diametrically opposing changes.

Article 13: Solidarity and Cooperation

The pandemic was an example of human beings raising their collective conscience as a species through solidarity and transglobal cooperation. International efforts in preventing the disease, vaccine development, and vaccination drives illustrate this aspect. Although there was a palpable decrease in cancer services across nations, communities of different cancer support groups, NGOs, and professional associations gave advice and support to patients mainly through digital platforms and social media. This pandemic witnessed the coming together of people voluntarily to dispel the afflictions in myriad avenues.

Article 14: Social Responsibility and Health

Under the supervision of WHO and opinions from the international panel of experts, governments worked for the good of all—a utilitarian approach. Professional organizations gave updates on treatment protocols through public health

initiatives. The benefits aimed at the general populations to which cancer patients form an integral part.

The highest attainable standards of care were not achievable in the first year of the pandemic as humanity was not prepared for such a large-scale global catastrophe. The disease affected both developed and developing nations, and different income categories of countries alike. There was shortage of cancer medicines and other lifesaving or supportive care essentials, and supply chain worked hard to keep up with the demands. This was due to logistical hardships in procurement of pharmaceutical agents, infrastructural issues, and suboptimal productivity of drug manufacturers during that time. Loss of jobs and income affected many cancer patients and there were many cases of skipping the treatment due to financial constraints.

The pandemic was a testing time in terms of personal responsibility that fell upon the shoulder of every individual. In addition to maintaining social distancing, quarantine, and other security measures, the spread of false information and news regarding the disease was a challenge to achieve. Isolation for prolonged periods and uncertainty in job prospects coupled with fear and anxiety took a toll on the mental health of a lot of individuals. This was not adequately addressed during the time.

Article 15: Sharing of Benefits

The pandemic witnessed a well-focused and accelerated research program in an attempt to contain, treat, and prevent COVID-19 infection. The changes that led to a paradigm shift in medical developments were shared at international platforms, and efforts to share those benefits were evident transnationally. An example would be vaccine development and provision of its availability in nonmanufacturing countries through sharing of technological assistance and international treaties. This also included capacity building, clinical trials, and training workforce in the fight against the disease. Sustained efforts in this domain halted many routine cancer-related research and screening programs, which could have a detrimental effect in upcoming years. In the wake of the pandemic, the focus of the scientific community and the public was the international sharing of information on a variety of topics regarding the viral genome, mode of transmission, incubation period, vulnerable groups, signs, and symptoms. Information on all these was valuable.

Article 16: Protecting Future Generations

The true biologic impact of the disease on the future generations is still unknown. The virus by virtue of multiple cycles of significant mutations illustrated unpredictability of human disease development and its impact on medical science and social well-being of individuals. Vaccinations could prevent or reduce the seriousness of the disease as of omicron variant of COVID-19. The manner in which vulnerable cancer patients may be affected with subsequent significant mutations of the virus is unknown, which adds to the uncertainty to the future.

Article 17: Protection of the Environment, Biosphere, and Biodiversity

There are debates on the initiation and mode of spread of COVID-19 virus to the first human host. Investigations on the developmental biology of the virus, its viral signature, may shed light on the mystery of whether it was transmitted from across species (putatively from bats) or was artificially created under laboratory conditions. In either case, article 17 details the need for respect while dealing with environment and preserving our biosphere. Adaptive laws and policies are required to integrate new environmental and health knowledge in specific socio-ecosystems. Respecting and nurturing the biodiversity of the planet also means holistic interactions within sociocultural contexts and preserving and protecting animal and human health along with environmental health.

Article 18: Decision-Making and Addressing Bioethical Issues

Promotion of professionalism, honesty, integrity, and transparency in decision-making reflects here. The brunt of the disease bore heavily upon the health care workers during the pandemic. However, the professionalism and true workmanship of many supporting systems were put to test during the pandemic. Intergovernmental and interdepartmental consensus on strategic planning and care delivery resulted in issues on triaging patients, resource allocation, and prioritization. Bioethical and human right issues were identified and addressed in vast majority of situations. But the unprepared and overwhelmed systems were coerced into making decisions on ethically debatable scenarios that violated patients' human rights. The most important example was, waiting for ventilators or oxygen supplements to be made available for the needy. Cancer patients in continuum of care were harmed in these compromising scenarios.

Health professionals engaged globally through open dialogues and debates since the disease was declared internationally. Along with other specialists, professional organizations and researchers in oncology took part in those professional discourses and expert consultations while addressing specialty-wise health concerns. Setting up telemedicine services with inputs from treating centers proved helpful in addressing patient concerns during these times.

Positive Outcomes

Ranganathan et al[21] pointed out some positive outcomes from the COVID-19 pandemic. This includes (1) global realization of the need for a strong public health care system; (2) prioritization of oncology treatments based on value and outcomes, both from a monetary and a patient-benefit viewpoint, emphasizing the importance of value-based care[31]; (3) accessibility of cancer care closer to home that encourages a distributed model of care; (4) adoption of digital platforms such as teleconsultations and video consultations in health care systems, which increases the

efficiency of cancer centers; and (5) research demonstrated that large-scale practice-defining trials can be both pragmatic and reliable, and modification of cancer trial protocols led to more efficient and practical ways of doing clinical research, for example, follow-up evaluations nearer to patients' homes and less frequent imaging in oncological services.[32,33]

What Is Next?

In many countries such as India, patients choose their cancer treatment center based on the personal preference of a named consultant of repute, goodwill, specific skill, or facilities available there. Travel restrictions during these times forced many patients to seek treatment at a nearby facility due to logistical reasons. This trend changed once free travel was possible. In future, telemedicine and video conferencing may be practiced routinely for regular follow-up of distant patients. It is expected that the cessation of different screening programs and reduction in diagnostic services would lead to missed diagnosis, delayed diagnosis, and delay in treatment, which can lead to overall increase in cancer mortality and public health burden in the next 5 years.[21] As Indian yogic teacher Sadhguruji said, "*every uncertainty is a tremendous possibility. What needs to be fixed is not uncertainty, but one's interiority to handle it*." The medical profession will come up with solutions for these anticipated challenges that we face today, and the learned optimism and faith in our fraternity are the way forward for our uncertain future.

Conclusion

Myriad ethical issues plague the oncologists in delivering their integrative clinical services in the pandemic era. Certain issues that came to the forefront were unprecedented. Problems like moral distress and looking on at inevitable grim endings need to be actively countered by willful inclusion of proactive measures. Solidarity, dignified respect, and concern for future generations and the environment are the way forward. The indisputable faith invested in the health care systems should never be compromised, and this will be facilitated by affirming to uphold the principles of UDBHR adopted in 2003 at the UNESCO General Assembly, Paris. COVID has propelled the citizens of the world into unprecedented uncertainty and suspended animation. Despite grappling with the unknown disease entity of SARS COVID2, the health care community needs to use and deliver. The HCW were the need of the hour and yet resisted due to the stigma of infectiousness. The general public need to come to terms with battling the new disease with unfamiliar tactics. The present illness pales in comparison with the potential to be infected with an unknown disease. We further realize the scope and applicability of UDBHR in those global medical emergencies from the bioethical and human rights perspective.

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Optimizing the Outcome of Pediatric Metastatic Neuroblastoma in a Nontransplant Setting in a Developing Country: Retrospective Study from a Tertiary Cancer Center in India

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Abstract

Objective This article estimates the survival of children over 1 year of age diagnosed with metastatic neuroblastoma (NB) and treated in a nontransplant facility and determines the factors affecting survival.

Materials and Method Case records of children aged 1 to 14 years treated for metastatic NB in our center from January 2008 to December 2017 were studied. Patients received conventional chemotherapy followed by surgery, radiotherapy, and metronomic maintenance chemotherapy.

Results Eighty-nine patients with metastatic NB received treatment. Mean age was 3.5 years and male:female ratio was 1.1:1. The most common primary site was suprarenal (55%) and the most common site of metastasis was bone marrow (76%). Forty percent patients had multiple metastatic sites. Mean baseline lactate dehydrogenase (LDH) was 3724 U/L (range 303–16609 U/L) and 65% patients had LDH $>$ 750 U/L. Fifty-three patients (59.6%) had good response to chemotherapy as evidenced by clearance of metastatic disease, but out of them, 43 patients (81%) progressed subsequently. Twenty-six patients underwent surgery and 12 patients received maintenance therapy. Seventy-four patients (86%) developed recurrence and all but one died. Median time to recurrence and death were 9 months (range 0–120 months) and 10 months (range 1–123 months), respectively. At a median follow-up of 72 months (range 15–135 months), 16 patients are alive, with 5-year disease-free survival and overall survival of 17.6 and 18.4%, respectively. Age, baseline LDH, chemotherapy regimen, and response to treatment significantly affected survival.

Conclusion Younger age, lower baseline LDH, and good response to chemotherapy appear to confer survival advantage in pediatric metastatic NB, and may be used for optimization of treatment in the nontransplant setting in developing countries.

Keywords
- pediatric
- metastatic neuroblastoma
- survival
- developing country
- India

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Introduction

Neuroblastoma (NB), the most common pediatric extracranial solid tumor, is one of the most challenging childhood cancers to treat. In the developing countries, majority of children with NB present with high-risk and metastatic disease, with frustratingly low survival even after skillful use of multiple treatment modalities.[1] In the high-income countries, the use of advanced therapeutics like high-dose chemotherapy followed by autologous stem cell transplant (ASCT), surgery, radiotherapy, and immunotherapy is able to yield around 40% survival in high-risk NB.[2] Transplant facilities and anti-GD2 therapy, which form the standard of care in the developed countries, are not available to majority of the needful patients in the low-and-middle-income countries (LMICs). In the nontransplant setting like ours, metastatic NB is treated with conventional chemotherapy combined with local control modalities like surgery and/or radiotherapy.[3] We determined treatment outcome and factors affecting survival of children over 1 year of age with metastatic NB treated at our center with chemotherapy, surgery, and radiotherapy.

Materials and Method

This is a retrospective study of case records of all children aged 1 to 14years with stage 4 NB treated at our center over a 10-year period (January 1, 2008 to December 31, 2017). Disease evaluation was done clinically and by blood investigations including lactate dehydrogenase (LDH) and imaging of the primary site with ultrasound or computed tomography scan. Metastatic workup included skeletal X-rays and bone marrow biopsy. Assessment of bone metastases was dependent on skeletal X-rays, as MIBG (metaiodobenzylguanidine) scintigraphy was not available in our hospital and bone scan could be used only sparsely because of interruptions in availability of reagent. The diagnosis of NB was established by histopathology and immunohistochemistry of bone marrow or primary tumor tissue. N-myc studies were not available in the hospital.

Inclusion and Exclusion Criteria

All patients over 1 year of age diagnosed with metastatic NB and received treatment at our center were included. Patients who received treatment elsewhere and those who expired before starting treatment were excluded.

Chemotherapy

Two chemotherapy schemes were in use for treating pediatric NB in the hospital during this time. Chemo A was a moderately aggressive regimen consisting of vincristine 1.5 mg/m^2, Adriamycin 40 mg/m^2 and cyclophosphamide 1500 mg/m^2 alternating with cisplatin 100 mg/m^2, and etoposide 450 mg/m^2 every 3 weekly for 1 year (maximum cumulative dose of Adriamycin 360 mg/m^2). Chemo B was the less intensive regimen consisting of six 3-weekly cycles of vincristine, Adriamycin 30 mg/m^2, and cyclophosphamide 750 mg/m^2. Patients were assigned to receive the chemotherapy regimen by the treating consultant based on the general condition, extent of metastatic disease, logistic and social factors, and parental decision.

Response to Chemotherapy

Response assessment was done after four cycles of chemotherapy with bone marrow examination and skeletal X-rays. MIBG was not available in the hospital and bone scan was not done universally due to erratic availability of reagent. Disappearance of disease from metastatic sites as evidenced by a normal bone marrow examination and absence of lytic bone lesions on skeletal X-rays was considered as good response. Imaging of the primary site for response assessment was done only for patients who cleared the disease from metastatic sites. Persistent metastatic disease was considered as poor response.

Local Treatment and Maintenance Chemotherapy

Surgery was done if safe resection was feasible, followed by further chemotherapy according to the assigned regimen. Radiotherapy was given for unresectable/residual disease after completion of treatment regimen, followed by oral metronomic chemotherapy with cyclophosphamide 50 mg/m^2 and etoposide 50 mg/m^2 daily for 20 days per month for 6 to 8 months. Patients with disease progression at any time were assigned to palliative care.

Primary and Secondary Outcome Measures

The primary outcome measure was to estimate the survival of children over 1 year of age treated for metastatic NB. The secondary outcome was to determine any clinical or biological factors affecting survival of these patients in the nontransplant setting.

Statistical Methods

The descriptive analysis included the absolute and relative frequency for categorical variables. Comparison between groups was carried out using the chi-square test or Fisher's exact test. Variables for the survival analysis were age, primary site, metastatic site, baseline LDH, chemotherapy regimen, response to chemotherapy, and surgery. The survival curve was estimated for each variable using the Kaplan–Meier method. The comparison between curves was obtained by the log-rank test. The Cox regression model was used to assess the effect of the variables on survival (multivariate analysis to calculate hazard ratios), which included variables with the following characteristics according to the Kaplan–Meier analysis with a significant difference ($p < 0.05$). The level of significance established for all analyses was 5%. All analyses were performed using the software SPSS 20.0 for Windows (Statistical Package for Social Sciences, IBM, United States).

Ethics

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. The study was carried out according to the regulations established by the Institutional Clinical Research Review Board and approved by Human Ethics Committee, Regional Cancer Centre Trivandrum (No. 02/2018/13, dated 22/02/2018, 2 p.m.). Consent for treatment and use of medical record data for scientific studies were routinely obtained for all patients.

Results

Patient Demographics

There were 119 children > 1 year of age with metastatic NB, forming 50.2% of the total noninfant NB patients. Mean age of the patients was 3.5 years (range 1–14 years) and male: female ratio was 1.1:1. Eighty-nine patients consented for treatment and are included in the analysis. Out of these, 24 patients were aged < 18 months and 65 patients were older.

Disease Characteristics

The most common site of primary tumor was suprarenal ($n = 66$, 55.5%), followed by retroperitoneal ($n = 25$, 21%), thoracic/mediastinal ($n = 7$, 5.9%), cervical ($n = 8$, 6.7%), and multifocal ($n = 3$, 2.5%). Primary tumor was undetected in 6 patients (5%). The most common site of metastasis was bone marrow ($n = 68$, 76.3%), followed by bone ($n = 14$, 15.9%), lymph nodes ($n = 6$, 6.2%), and liver ($n = 1$, 1%). Thirty-six patients (40.4%) had multiple metastatic sites. Baseline LDH values were available for 79 patients, with mean value of

Table 1 Prognostic variables on univariate analysis

Prognostic variable	DFS probability	*p*-Value	OS probability	*p*-Value	Hazard ratio	*p*-Value
Age						
< 2 y	19.8	0.96	23.3	0.92	1.02	0.927
> 2 y	15.3		15.2			
Primary site						
Adrenal	14.7	0.178	17.6	0.07	1.00	0.99
Cervical	30.0		30.0			
Posterior mediastinal	50.0		100.0			
Paraspinal	13.3		13.3			
Abdominal/retroperitoneal	33.3		33.3			
Multifocal	25.0		25.0			
Metastatic site						
Bone marrow	18.0	0.865	20.7	0.87	1.3	0.861
Bones	9.1		9.1			
Lymph nodes	25.0		25.0			
Multiple sites	16.3		15.9			
LDH						
< 750 U/L	50.0	0.028	46.9	0.032	2.29	0.013
> 750 U/L	18.6		16.2			
Chemotherapy						
Chemo A + Metronomic	55.6		55.6			
Chemo A	23.6	0.001	27.2	0.001	6.03	0.001
Chemo B	8.3		8.1			
Response						
Good	27.8	0.001	29.7	0.001	6.96	0.001
Poor	3.3		3.3			
Surgery						
No surgery	5.7	0.001	7.5	0.001	1.32	0.001
Biopsy only	0.0		0.0			
Debulking	66.7		66.7			
Excision	43.8		43.8			

Abbreviations: DFS, disease-free survival; LDH, lactate dehydrogenase; OS, overall survival.

Table 2 Response and outcome by treatment regimen

Parameter	Chemo A ($n = 38$)	Chemo B ($n = 51$)
Metronomic chemo maintenance	9 (23.6%)	3 (5.8%)
RT	2 (5.2%)	1 (1.9%)
Good response	30 (78.9%)	23 (45%)
Poor response	6 (15.7%)	24 (47%)
Recurrence/relapse	27 (71%)	46 (90%)
Patients alive	11 (28.9%)	5 (9.8%)
5-year DFS	23.6%	5.0%
5-year OS	27.2%	8.1%

Abbreviations: DFS, disease-free survival; OS, overall survival; RT, radiotherapy.

3724 U/L (range 303–16609 U/L). Fifty-eight patients (65%) had LDH > 750 U/L and 21 patients (23.5%) had LDH < 750 U/L.

Treatment and Response

Thirty-eight patients (42.6%) received Chemo A, out of which 30 patients (78.9%) had good response to chemotherapy and 6 patients (15.7%) had poor response. Fifty-one patients (57.3%) received Chemo B, out of which 23 patients (45.09%) had good response and 24 patients (47.05%) had poor response (►**Table 1**). In 6 patients, response assessment could not be done because of early clinical progression or death. Surgery could be attempted in 26 patients (29.2%), with excision in 16 patients, debulking in 6 patients, and biopsy alone in 4 patients. Only 3 patients received radiotherapy and 12 patients received metronomic maintenance chemotherapy (9 patients after Chemo A and 3 patients after Chemo B).

►**Table 2** shows patient outcome by treatment regimen.

Relapse and Death

Overall, 74 patients (86%) developed recurrence/progression of disease. Out of the 53 patients who had good initial response to chemotherapy, 43 patients (81%) relapsed. The median time to recurrence/progression was 9 months (range 1–120 months). Seventy-three patients (85.9%) died, the median time to death being 10 months (range 1–123 months). Cause of death was disease progression in 71 patients and toxicity-related deaths in 2 patients. Three relapsed patients are lost to follow-up.

►**Fig. 1** depicts the summary of patient treatment and outcome.

Prognostic Factors

In univariate analysis, age < 18 months, LDH > 750 U/L, type of chemotherapy regimen, response to initial chemotherapy, number of chemotherapy cycles received, and surgery were found to be statistically significant factors for disease-free survival (DFS) and overall survival (OS).

Details of prognostic factors on univariate analysis are given in ►**Table 1**.

On multivariate analysis, age > 18 months, LDH > 750U/L, less aggressive Chemo B regimen, and poor response to chemotherapy were statistically significant poor prognostic factors.

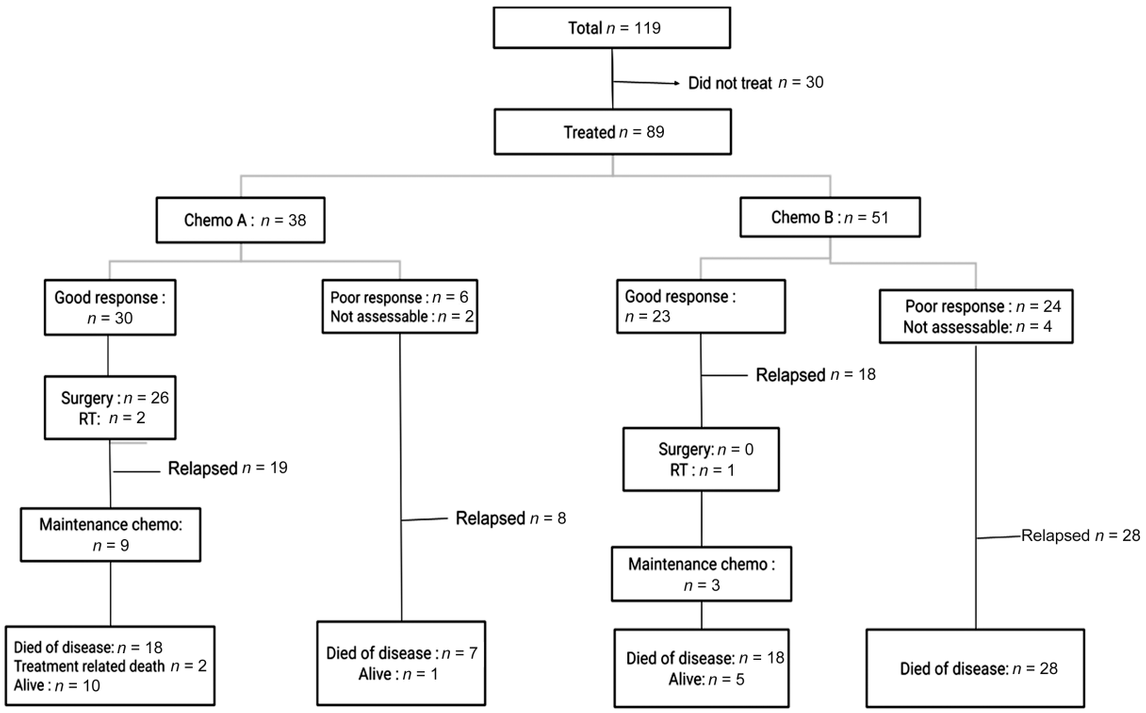

Fig. 1 Flowchart depicting treatment course and outcomes.

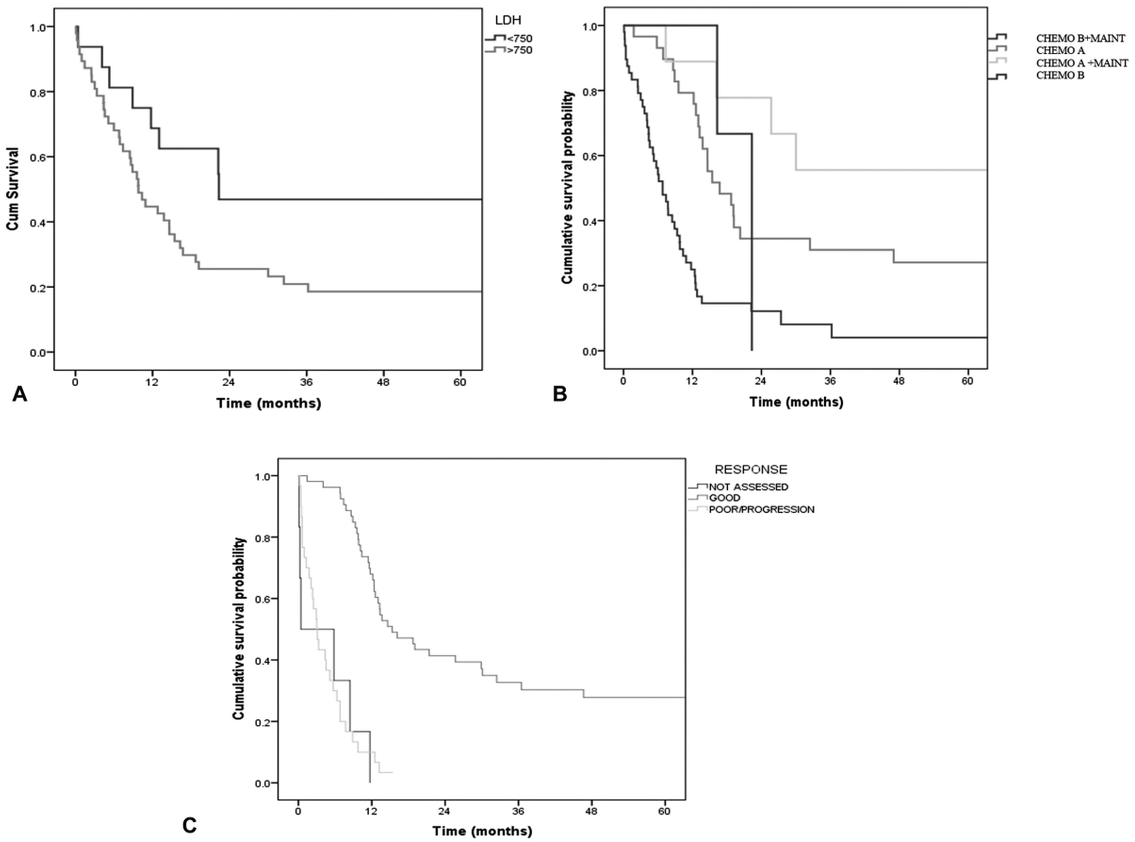

Fig. 2 Kaplan–Meier survival curves of (**A**) overall survival (OS) by lactate dehydrogenase (LDH) > 750 U/L and < 750 U/L. (**B**) OS by type of chemotherapy regimen. (**C**) OS by response to chemotherapy.

Survival

At a median follow-up of 72 months (range 15–135 months), there were 16 survivors. Five-year DFS was 17.6% and OS was 18.4%. Children < 18 months had significantly better DFS and OS (35.1 and 38.6%, respectively). Eleven patients out of 38 (28.9%) who received Chemo A and 5 patients out of 51 (9.8%) who received Chemo B survived. Twelve patients (9 on Chemo A and 3 on Chemo B) received metronomic chemotherapy, and 5 out of those 12 patients (41.6%) are alive.

►**Fig. 2** shows the survival curves by the relevant prognostic factors where 9 out of 16 patients (56.2%) who survived were aged < 18 months at diagnosis. Mean age of survivors was 2.3 years (range 1–9 years) and their mean LDH at presentation was 728 U/L (range 303–1747 U/L).

Details of survival cohort are depicted in ►**Table 3**.

Discussion

It is well known that the burden of high-risk and metastatic NB is high in the LMICs with suboptimal survivals. A previous study of 91 pediatric NB patients from our hospital some years back had reported around 60% stage 4 disease, with long-term survivors as low as 9% after multimodality treatment.[1] A recent compilation of studies from LMICs which includes several studies from India, describes survivals of 0 to 45% world-over without ASCT and anti-GD2 antibody.[4] Single-institution studies from other developing countries like Brazil and countrywide outcomes from Turkey have reported 17 and 45% five-year survival, respectively, for stage 4 NB.[5,6] The overall poor results in LMICs are likely multifactorial such as inadequate diagnostic facilities, less intense chemotherapy protocols, inability to resect the primary tumor, limited availability, expertise, and prohibitive cost of transplant facilities and unavailability of monoclonal antibodies.[2] Treatment refusal and abandonment are also high in resource-challenged nations[1,3] as was noted in our study, likely because of social, health system-related, and financial reasons. Optimization of available resources thus becomes important while treating these patients in the LMICs.

The significance of clinical and biological prognostic factors like age, metastatic burden, and LDH in metastatic NB patients treated without transplant was explored in this study. Data from the International Neuroblastoma Risk Group (INRG) reveals that older age, involvement of bone marrow, bone, and multiple metastatic sites are associated with worse outcome.[7] The better prognostic value of younger age in noninfant metastatic NB has been proved historically by the Children's Cancer Group and the European registries.[8] Age cutoff of 18 months is utilized as standard for risk stratification of noninfant NB, but the earlier Children's Oncology Group study has shown that prognostic effect of age is continuous in nature.[9] In our study, children < 18

Table 3 Characteristics of the survivor cohort ($n = 16$)

Variable	Value
Age	
Mean	2.3 y
Range	1–7 y
Gender	
Female	10
Male	6
LDH	
Mean	728 U/L
Range	303–1747 U/L
Primary site	
Adrenal	6
Abdominal	5
Cervical	2
Thoracic	1
Paraspinal	1
Multifocal	1
Metastatic site	
Limited metastases	14
Multiple metastases	2
Chemotherapy regimen	
Chemo A	12
Chemo B	4
Metronomic chemo	5
Response to treatment	
Good	15
Poor	1
Surgery/RT	
Debulking/excision	10
No surgery/biopsy only	6
RT	2

Abbreviations: LDH, lactate dehydrogenase; RT, radiotherapy.

months had significantly better event-free survival (EFS) and OS in a nontransplant setting. We understand that some of them would have had biologically favorable disease and would be considered as nonhigh-risk by the current international standards had they been properly risk-stratified using N-myc. Because of lack of facility in the hospital, N-myc study, MIBG scintigraphy, and bone scans could not be done in all our patients. Under these limitations, the significance of biomarkers like LDH and ferritin becomes important in risk stratification and prognostication of these patients. LDH is considered as a surrogate marker for N-myc amplification, and the International Society for Pediatric Oncology-Pediatric Oncology Developing Countries has recommended an arbitrary LDH value of 750 U/L as a prognostic marker when N-myc status is not known.[2] In the recently published INRG study, higher LDH at presentation was independently prognostic for worse DFS and OS in metastatic NB.[10] In our study, patients with LDH > 750 U/L demonstrated markedly inferior survival than those with LDH < 750 U/L (18.2% vs. 46.9%), suggesting that those patients may have had biologically adverse tumors.

Treatment-related factors analyzed in this study were intensity of chemotherapy, response to chemotherapy, and impact of surgery. Dose-intensive short-duration chemotherapy incorporating cisplatin and etoposide is associated with better clinical outcomes in metastatic NB, and utilized in different chemotherapeutic regimens.[11] In the earlier study by Kusumakumary et al from our hospital in a group of NB patients treated with heterogeneous chemotherapy protocols, one of the reasons explained for poor outcome of stage 4 NB patients was the less aggressive palliative intent chemotherapy.[1] In our study, survival of patients who received the cisplatin-containing regimen A was far better than those who received the regimen without cisplatin (28.9% vs. 9.8%). Our results may have been confounded by a selection bias, as patients with multiple metastases and poor general condition were not expected to tolerate aggressive treatment and inadvertently received the less intensive regimen.

We noted an unusually high response to chemotherapy in our patients, probably because response evaluation was done with bone marrow examination and skeletal X-rays only. If MIBG would have been used, the number of responders would have been lesser. However, good response to initial chemotherapy did not translate to proportionately good EFS or OS in our patients, because of early relapses, suggesting that conventional chemotherapy is not able to maintain the remission status. In an earlier analysis from our own center, 15 out of 17 children with metastatic NB treated with multiagent chemotherapy had a good initial treatment response, but their 2-year survival was only 11.7%.[11] Whether further intensification of chemotherapy in good responders should be considered in the setting of nonavailability of transplant facility is a question to be addressed. Recently, Jain et al have reported improved survivals in high-risk NB patients treated without ASCT or dinutuximab using an intensive consolidation regimen with topotecan, vincristine, and doxorubicin in India.[4] We also observed that patients who underwent tumor excision or debulking had better outcome, but surgery and radiotherapy could be offered to very less number of patients, hence the impact of such a finding is doubtful.

Of interest are the characteristics of our survivor cohort. We observed that they were younger, mostly females, presented with lower baseline LDH, mostly had limited metastases, received moderately intensive cisplatin-containing chemotherapy, all but one were good responders, and most underwent excision or debulking. Very few patients in our cohort were able to reach the maintenance phase of treatment, but this group had the best survival of 41%.

The limitations of our study are that it is a retrospective study of a cohort of patients treated with nonuniform chemotherapy protocols. Nonavailability of N-myc testing and MIBG, selection bias in treatment protocol, and

limitation of clinical facilities and resources for treatment may also be considered as a limitation. Most patients who attend our center for treatment come from poor socioeconomic status and are not able to afford costly treatments. Treatment costs were met partially by the center with the help of government aids and there was always shortage of human resources. Given the poor prognosis of metastatic NB, during the earlier time period many parents opted out of the cisplatin-containing regimen because they could not afford to stay in and around the hospital for frequent monitoring and management of subsequent complications. Over the years, because of increased government initiatives and support from new voluntary organizations, new treatment assistance schemes and staff support for pediatric cancer patients in the hospital were provided, resulting in increase in clinical facilities and improvements in supportive care, so that overall more number of pediatric patients could afford cancer treatments. The increased trend in survival may be a reflection of more number of patients being able to take the aggressive protocol.

Future prospective study may be proposed based on our findings from the present study. Younger patients and those with lower LDH at presentation may be treated with moderately intensive platinum-containing chemotherapy and response of metastatic sites after first few cycles of chemotherapy may be utilized to guide further treatment. Patients with clearance of metastases may preferably receive intensified chemotherapy, followed by surgery of primary, radiotherapy to residual tumor, and maintenance chemotherapy. On the other end of the spectrum, identification of patients with multiple adverse factors like older age, very high baseline LDH, multiple metastatic sites, or poor response to chemotherapy which portend poor outcome may allow the focus to be directed on early provision of palliative care along with less intensive cancer-directed treatment aiming at reducing the symptom burden, improving the quality of life, and smooth transition toward end-of-life care.

Conclusion

Our study reveals that improvement in clinical services like chemotherapy and supportive care can result in a trend toward better survivals in children with metastatic NB in a resource-limited setting. Selected stage 4 NB patients may survive even without transplant or immunotherapy, and they can be identified based on simple and affordable investigations like baseline LDH, ferritin, and good response to initial chemotherapy. Stratification of these patients on the basis of clinical and biological factors can facilitate justified allocation of available resources while planning treatment for metastatic NB patients in the LMICs.

Patient Consent

Consent for treatment and use of medical record data for scientific studies were routinely obtained for all patients.

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None declared.

Conflict of Interest

None declared.

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Complementary and Alternative Medicine Use and Its Impact on the Delayed Presentation and Advanced Stage of Breast Cancer in Newly Diagnosed Indian Women

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Abstract

Introduction Complementary and alternate medicine (CAM) use is highly prevalent among Indian cancer patients. However, such studies from the perspective of Indian patients with breast cancer (BC) are lacking.

Objective The aim of this study was to evaluate the incidence of CAM use and its impact on the presentation of patients with BC.

Materials and Methods This retrospective study was performed in the Department of Radiation Oncology over a period of 6 months (January to June 2019) and involved review of hospital-record of 229 newly-diagnosed patients with BC. Univariate and multivariate binary logistic regression analysis was done to evaluate the association of CAM use with the BC stage and various clinicodemographic variables.

Results Of 229 patients, 96 (41.92%) used CAM. The CAM use was significantly associated with rural residence (odds ratio [OR]: 4.092; 95% confidence interval [CI]: 2.27–7.35), illiteracy (OR: 6.417; 95% CI: 1.83–22.45), delayed presentation by 3 to 6 (OR: 12.964; 95% CI: 2.94–57.00) and more than 6 months (OR: 40.667; 95% CI: 9.26–178.46), and advanced stage at diagnosis (OR: 10.786; 95% CI: 5.15–22.58). Similarly, advanced stage at diagnosis was significantly associated with rural residence (OR: 2.78; 95% CI: 1.59–4.84), illiteracy (OR: 7.20; 95% CI: 1.86–22.79,), and delayed presentation by 3 to 6 (OR: 6.41; 95% CI: 2.81–14.61) and more than 6 months (OR: 17.55; 95% CI: 7.26–42.45).

Conclusions CAM use was highly prevalent among the patients with BC and significantly associated with advanced stage at diagnosis. Moreover, both CAM use and advanced stage at diagnosis were significantly associated with rural residence, low educational status, and delayed presentation.

Keywords
- advanced stage
- alternative therapies
- breast cancer
- complementary therapies
- India

Introduction

Globally, breast cancer (BC) is the leading cancer to be diagnosed and is the leading cause of cancer-related mortality in women.[1] Following the global trend, BC is the most frequent cancer in Indian women. Its incidence is rising, with the highest burden reported from the metropolitan areas.[2] The current healthcare system in India is insufficient to cater to the rising incidence of cancer with just 9.28 doctors per

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10,000 patients, as compared to 26.04 in United States and 58.23 in United Kingdom.[3] This problem is further compounded by disproportionate distribution of healthcare services and lack of trained healthcare workers. In a National Sample Survey, 56.4% health workers were found to be unqualified, including 42.3% practitioners of conventional medicine. Among all qualified workers, 77.4% catered to the needs of patients in urban areas.[4]

In India, majority of the patients with BC have high attrition toward the quacks and the complementary and alternative medicine (CAM).[5] The lack of healthcare services in rural areas makes the CAM a feasible option. It is observed that the prevalence of CAM use among Indian cancer patients ranges from 34.3 to 46.2%.[6–8] The reasons that make CAM popular among patients in rural areas are their easy availability and economical nature. Moreover, most of the patients perceive that CAM is more effective and safer relative to the conventional therapy.[9] The patients with cancer prefer CAM due to the risk of death, surgery-associated long-term morbidity, and adverse effects associated with conventional therapy.[10]

Despite advances in diagnosis and management, around 57% patients with BC are diagnosed in the locally advanced stage.[2] The CAM use is associated with delays in presentation and diagnosis.[11] A recent study reported that patients residing in rural areas are diagnosed at an advanced stage and have higher death rate relative to those residing in urban areas.[12] Another study compared the income and educational background of patients with BC and reported that patients with low-income and lower educational status were diagnosed at later stage, underwent less relevant investigations, and had lower rates of treatment.[13] Thus, coupled with low-income and higher illiteracy rate, patients with BC residing in rural areas are at disadvantage and have fewer options than to choose CAM. However, the association of CAM use with delayed presentation and stage at diagnosis in patients with BC has not been evaluated from the perspective of Indian patients. Thus, we assessed the incidence of CAM use, its impact on the presentation of patients with BC, and association with various clinicodemographic characteristics.

Materials and Methods

Study Design and Setup

This retrospective, hospital-record based study was performed in the department of radiation oncology of a tertiary care institute. Ours is the only government hospital in the region with treatment facility for patients with cancer that caters to around 3,000 newly-diagnosed cancer patients annually.

Selection and Description of Patients

A total of 229 patients with BC diagnosed between January and June 2019 were included in the study. The record files were scanned manually, and following characteristics were collected: Demographic details (age, literacy level, and area of residence), history and type of CAM use, baseline investigations (chest X-ray, abdominal ultrasonography, fine-needle aspiration cytology or biopsy, and mammography and/or positron emission tomography scan, if required), and clinical details (delay in presentation and BC stage). For the purpose of analysis, stage I to II and stage III to IV of BC were considered as early and late, respectively. CAM use suggested indulgence in any products and methods that are not a part of conventional medicine prior to the diagnosis. The time to presentation was calculated from the time point the patient noticed the symptom to the time lump was evaluated and diagnosed. Presentation delay suggested the duration between symptom onset to initial presentation of more than 3 months.

Inclusion Criteria

All newly diagnosed, histopathologically confirmed patients with BC were included in the study.

Exclusion Criteria

Patients with recurrent or operated BC, those already receiving chemo- or radiotherapy, and incomplete data on files were excluded.

Primary Outcome

Incidence of CAM use among newly diagnosed patients with BC.

Secondary Outcome

Impact of CAM use on the presentation of patients with BC and its association with various clinicodemographic characteristics.

Statistical Analyses

SPSS (IBM, Armonk, New York, United States) version 23.0 for Windows was used to analyze the data. The data was depicted as frequency (percentages). CAM use and BC stage were divided into dichotomous outcome: "Yes" or "No" and "Early" or "Late," respectively. The association between categorical variables and dependent variables (CAM use and BC stage) was assessed with chi-squared test. The association of CAM use with BC stage was assessed with multivariate binary logistic regression analysis. The findings are represented as odds ratio (OR) with 95% confidence interval (95% CI). A two-tailed *p*-value less than 0.05 was regarded as significantly significant.

Ethics

The Institutional Ethics Committee, Government Medical College, Nagpur (Dated 17/12/2018, Letter no. 2018/418) approved the study protocol. In this study, all procedures performed in the human subjects followed the ethical standards of the institutional research committee and the 1964 Helsinki Declaration (and subsequent amendments).

Results

Among 229 patients, more than half (51.97%) patients were aged less than 50 years. Most of the patients resided in the rural areas (58.52%) and presented in advanced stage

Table 1 Univariate analysis of association between CAM use and patient characteristics

Parameters	CAM use		Total *n* (%)	*p*-Value
	Yes [*n* = 96 (%)]	No [*n* = 133 (%)]		
Age (years)				
<50	51 (53.13)	68 (51.13)	119 (51.97%)	0.828
≥50	45 (46.87)	65 (48.87)	110 (48.03%)	
Area of residence				
Rural	74 (77.08)	60 (45.11)	134 (58.52%)	<0.0001
Urban	22 (22.92)	73 (54.89)	95 (41.48%)	
Stage of cancer				
Early	10 (10.42)	74 (55.64)	84 (36.68%)	<0.0001
Late	86 (89.58)	59 (44.36)	145 (63.32%)	
Educational status				
Illiterate	22 (22.92)	6 (4.51)	28 (12.23%)	<0.0001
Primary	10 (10.42)	31 (23.31)	41 (17.90%)	
Secondary	56 (58.33)	82 (61.65)	138 (60.26%)	
Graduate	8 (8.33)	14 (10.53)	22 (9.61%)	
Delay in presentation (months)				
<3	2 (2.08)	44 (33.08)	46 (20.08%)	<0.0001
3–6	33 (34.38)	56 (42.11)	89 (38.86%)	
>6	61 (63.54)	33 (24.81)	94 (41.05%)	

Abbreviation: CAM, complementary and alternative medicine.

(63.32%). Most of the patients had higher secondary education (60.26%) and delay in presentation for more than 6 months (41.05%). Finally, 41.92% patients accepted CAM use. Predominantly used CAM, in the decreasing order, were ayurvedic [30 (31.25%)], ayurvedic + spiritual therapy [17 (17.71%)], spiritual therapy + homeopathy [10 (10.42%)], ayurvedic + yoga [8 (8.33%)], ayurvedic + meditation [8 (8.33%)], spiritual therapy [6 (6.25%)], homeopathy [5 (5.21%)], naturopathy [4 (4.17%)], spiritual therapy + naturopathy [4 (4.17%)], meditation [3 (3.13%)], and homeopathy + meditation [1 (1.04%)].

Univariate analysis revealed significant association between CAM use and area of residence ($p < 0.0001$), educational status ($p < 0.0001$), delay in presentation ($p < 0.0001$), and BC stage ($p < 0.0001$; ►**Table 1**). Similarly, significant association was observed between BC stage and area of residence ($p < 0.0001$), educational status ($p = 0.024$), and delay in presentation ($p < 0.0001$; ►**Table 2**).

On multivariate binary logistic regression analysis, area of residence, BC stage, educational status, and delay in presentation were significantly associated with CAM use. Moreover, the odds of CAM use among patients residing in rural areas and those presenting with advanced-stage BC were found to be 4.1 (OR: 4.092; 95% CI: 2.27–7.35, $p < 0.0001$) and 10.7 times (OR: 10.786; 95% CI: 5.15–22.58, $p < 0.0001$) higher than patients residing in urban areas and those with early-stage cancer, respectively. Illiterate patients had 6.4 (OR: 6.417; 95% CI: 1.83–22.45, $p = 0.004$) times higher chances of CAM use than the graduates. Finally, the odds of CAM use were 12.9 (OR: 12.964; 95%CI: 2.94–57.00, $p = 0.001$) and 40.6 (OR: 40.667; 95%CI: 9.26–178.46, $p < 0.0001$) times higher among patients with delay in presentation for 3 to 6 and more than 6 months, respectively, than those with delay in presentation for less than 3 months. However, age of the patient did not predict CAM use in patients with BC (►**Table 3**).

Similarly, area of residence, educational status, and delay in presentation were significantly associated with the BC stage. The odds of patient presenting with advanced-stage cancer were 2.7 (OR: 2.78; 95% CI: 1.59–4.84, $p < 0.0001$) times higher in those residing in rural areas than urban areas. The odds of patient presenting with advanced-stage cancer were 7.2 (OR: 7.20; 95% CI: 1.86–22.79, $p = 0.004$) times higher in illiterates than the graduates. Finally, the odds of patient presenting with advanced-stage cancer were 6.4 (OR: 6.41; 95% CI: 2.81–14.61, $p < 0.0001$) and 17.5 (OR: 17.55; 95% CI: 7.26–42.45, $p < 0.0001$) times higher among patients with delay in presentation for 3 to 6 and more than 6 months, respectively, than those with delay in presentation for less than 3 months. However, age of the patient did not predict BC stage (►**Table 4**).

Discussion

In the developed world, around 50% patients with cancer survive, while this proportion is only 20% among patients from developing part of the world. In India, among a million newly diagnosed cancer patients each year, more than 50%

Table 2 Univariate analysis of association between stage of cancer and patient characteristics

Parameters	Stage of cancer		Total *n* (%)	*p*-Value
	Early [*n* = 84 (%)]	Late [*n* = 145 (%)]		
Age (years)				
<50	39 (46.43)	80 (55.17)	119 (51.97%)	0.202
≥50	45 (53.57)	65 (44.83)	110 (48.03%)	
Area of residence				
Rural	36 (42.86)	98 (67.59)	134 (58.52%)	<0.0001
Urban	48 (57.14)	47 (32.41)	95 (41.48%)	
Educational status				
Illiterate	4 (4.76)	24 (16.55)	28 (12.23%)	0.024
Primary	17 (20.24)	24 (16.55)	41 (17.90%)	
Secondary	51 (60.71)	87 (60.00)	138 (60.26%)	
Graduate	12 (14.29)	10 (6.89)	22 (9.61%)	
Delay in presentation (months)				
<3	36 (42.86)	10 (6.89)	46 (20.08%)	<0.0001
3–6	32 (38.09)	57 (39.32)	89 (38.86%)	
>6	16 (19.05)	78 (53.79)	94 (41.05%)	

patients die within 1 year following diagnosis, while another million demonstrate cancer progression within 5 years of diagnosis. Moreover, among 1.5 million patients who require palliative therapy, less than 0.1 million are catered by the current facilities.[8] Thus, majority of the patients use CAM.

Recently, Hill et al found a high CAM use among patients with cancer in developing part of the world (54.5%),

Table 3 Multivariate binary logistic regression analysis of association between CAM use and patient characteristics

Parameters	CAM use		OR	95% CI	*p*-Value
	Yes	No			
Age (years)					
<50	51	68	1.083	0.64–1.83	0.765
≥50	46	65	1.00	Reference	–
Area of residence					
Rural	74	60	4.092	2.27–7.35	<0.0001
Urban	22	73	1.00	Reference	–
Stage of cancer					
Early	10	74	1.00	Reference	<0.0001
Late	86	59	10.786	5.15–22.58	–
Educational status					
Illiterate	22	6	6.417	1.83–22.45	0.004
Primary	10	31	0.565	0.18–1.73	0.319
Secondary	56	82	1.195	0.47–3.03	0.708
Graduate	8	14	1.00	Reference	–
Delay in presentation (months)					
<3	2	44	1.00	Reference	–
3–6	33	56	12.964	2.94–57.00	0.001
>6	61	33	40.667	9.26–178.46	<0.0001

Abbreviations: CI, confidence interval; CAM, complementary and alternative medicine; OR, odds ratio.

Table 4 Multivariate binary logistic regression analysis of association between stage of cancer and patient characteristics

Parameters	Stage of cancer		OR	95% CI	*p*-Value
	Early	Late			
Age (years)					
<50	39	80	1.42	0.83–2.44	0.203
≥50	45	65	1.00	Reference	–
Area of residence					
Rural	36	98	2.78	1.59–4.84	<0.0001
Urban	48	47	1.00	Reference	–
Educational status					
Illiterate	4	24	7.20	1.86–22.79	0.004
Primary	17	24	1.69	0.59–4.81	0.322
Secondary	51	87	2.05	0.83–5.07	0.122
Graduate	12	10	1.00	Reference	–
Delay in presentation (months)					
<3	36	10	1.00	Reference	–
3–6	32	57	6.41	2.81–14.61	<0.0001
>6	16	78	17.55	7.26–42.45	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio.

including India.[14] In patients with BC, higher CAM use may be due to severe adverse effects with conventional therapy and a relatively younger women consider that conventional therapy may hamper their future plans and capacity for child care.[15]

CAM Use

We observed a high prevalence of CAM use among the patients with BC (41.92%). Though some of the authors have evaluated the prevalence of CAM use in Indian patients with cancer,[6–8] there is absence of specific data regarding the CAM use in those with BC. Shreyamsa et al pointed out that 41.2% patients with BC use CAMs, mainly due to fear of conventional therapy, claims of no adverse effects, and easy/cheap availability.[16] Studies from Malaysia (46.5%) and Europe (44.7%) have reported comparable CAM use in patients with BC.[11,17] However, studies from United States (60.2%), Germany (62.5%), and Korea (67%) have reported higher prevalence.[18–20] These distinct findings could be due to differences in BC stage, educational status, economic background, type of CAM used, number of patients evaluated, and time point of the CAM use.

We observed that ayurvedic (31.25%), ayurvedic + spiritual therapy (17.71%), and spiritual therapy + homeopathy (10.42%) were most common CAMs used. Other studies from India reported ayurvedic remedies as the most commonly used CAM.[6–8] However, CAM use depends on the local preference and several other factors. Natural products, dietary supplements, and yoga and exercise were the most common CAM used in developed world.[18–20] In this study, all the patients were newly diagnosed, and most had low educational level. However, in other studies, patients were known cases of BC and had higher educational level.[18–20] This might have resulted in higher prevalence of CAM use.

Association of CAM Use with Clinicodemographic Characteristics

We observed that CAM use was significantly associated with rural residence, lower educational status, longer delay in presentation, and advanced stage at diagnosis. Similarly, Maghous et al reported that CAM use was significantly associated with rural residence and absence of primary and tertiary cancer care, thereby resulting in delayed diagnosis.[21] Moreover, Hwang et al found that lower educational status and longer duration following diagnosis were significantly associated with CAM use.[20] Contrarily, McLay et al reported that higher education was associated with significantly increased CAM use.[22] This could be attributed to higher awareness and ability to find specific information regarding CAM.

Mohd Mujar et al found that CAM use was associated with significantly greater risk of delayed presentation, advanced stage at diagnosis, and delayed treatment initiation.[11] Moreover, Tautz et al demonstrated that patients with advanced-stage BC generally use CAM to a significantly higher degree.[23] This suggests that patients with advanced stage are more likely to look for further treatment options beyond conventional medicine.

Association of BC Stage with Clinicodemographic Characteristics

We found that advanced stage at diagnosis was significantly associated with the rural residence, lower educational status, and longer delay in presentation. Liu et al reported that

educational status was significantly associated with the BC stage and significantly greater proportion of uneducated patients had advanced stage at diagnosis than those with education of university and above.[13] Similarly, a study from South India reported that patients with illiterate/primary school educational status had significantly higher chances of being diagnosed with advanced BC.[24] Thus, diagnosis of BC in early stage is possible if women are educated about the screening and diagnostic techniques.

Foroozani et al reported that rural residence was significantly associated with delayed diagnosis and higher chances of being diagnosed with end-stage BC.[25] These findings can be ascribed to the fact that well-educated individuals prefer to reside in developed cities and thus, have a greater likelihood of undergoing screening investigation for BC and being diagnosed at an early stage.

Delay on the part of patient to seek medical attention following self-discovery of a potential BC symptom is linked to advanced stage at diagnosis. Foroozani et al demonstrated that longer delay in diagnosis (>3 months) was significantly linked to higher chances of being diagnosed with end-stage BC.[25] We observed that around 57% patients had a delayed presentation for more than 3 months in seeking the medical attention. Other studies from North, South, and Central India reported that nearly 62, 54, and 48.3% of women with BC had a delay of more than3 months, respectively.[26–28] Thus, our findings are consistent with those conducted in other parts of India.

We observed that age did not predict CAM use. Similarly, Chin et al suggested that age was not related to the CAM use.[29] Contrarily, Hwang et al reported that young patients had significantly higher CAM use.[20] This could be due to higher literacy rate among younger patients and better access to information related to CAM use. We further observed that age was not significantly associated with the BC stage. Contrarily, Foroozani et al[25] and Gangane et al[26] reported that old age is significantly associated with longer delay resulting in advanced stage at diagnosis. These contradictory findings could be attributed to difference in number of patients evaluated and different distribution of patients according to age groups.

Strengths

First, this is the initial study from India to assess the CAM use in newly diagnosed patients with BC. Second, findings of this study add to the sparsely published literature related to CAM use in Indian patients with BC and its effect on the delayed presentation and stage at diagnosis. Third, we tried to assess the association of CAM use with several demographic factors that result in advanced stage of cancer at diagnosis. Finally, diverse population of Central India makes the findings generalizable to other patients with BC.

Limitations

First, the available medical records did not have economic background of the patients and thus, we could not assess the association of CAM use with economic status. Second, retrospective nature of study did not allow us to assess the factors responsible for CAM use.

Conclusion

This study suggests high prevalence of CAM use in Indian women with BC. The CAM use was significantly associated with rural residence, low educational status, delayed presentation, and advanced stage at diagnosis. Similarly, advanced stage at diagnosis was significantly associated with residence in rural areas, low educational status, and delayed presentation. The findings of the present study suggest assessment of current BC care and their accessibility, as poor access is very likely to promote CAM use. Further studies are needed to support our findings. Moreover, further studies evaluating various causes of delay in presentation, both patient- and system-related, need to be carried out.

Patient Consent

Not declared.

Authors' Contributions

A.P., V.M., and A.D. conceptualized and designed the study. V.M. and A.D. supervised the study and provided the material. A.P. helped in data collection and/or processing, analysis and/or interpretation, literature search, and writing. A.P., V.M., and A.D. critically reviewed the manuscript.

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Conflict of Interest

None declared.

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Fumarate Hydratase-Deficient Renal Cell Carcinoma—A Clinicopathological Study of a Series of 11 Cases

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Abstract

Introduction Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) is a rare, molecularly defined renal tumor with aggressive behavior. The diagnosis of these tumors is challenging because of varied morphology and limited access to molecular testing and immunohistochemistry (IHC) for FH and 2-succinocysteine. We aim to elucidate the histomorphology, clinical presentation, and follow-up of this tumor in this first series of cases of FH-deficient RCCs from India.

Objectives This article aims to understand and elucidate the clinical presentation, pathologic findings, treatment options, and outcomes of FH-deficient RCC.

Materials and Methods Diagnosed cases of FH-deficient RCC between January 2021 and January 2023 including clinical details were retrieved from the electronic medical record database. Histopathological and immunohistochemical slides were reviewed.

Results Out of 11 cases of FH-deficient RCC, 36% had been referred with a diagnosis of type 2 papillary RCC. One patient presented with metastatic disease. All had mixed histologic patterns with the predominant pattern being papillary and showed FH loss on IHC. The classically described inclusion like nucleoli was present only focally in most cases. A subset of tumors had low-grade solid-nested morphology and these patients presented at an earlier stage (T2a). Two patients on multikinase inhibitors are alive with disease at 14 months' follow-up.

Conclusion FH-deficient RCCs can have varied histologic patterns within the same tumor and show loss of FH expression by IHC. A subset has low grade morphology and tends to have a more indolent course. It is important to have a high index of suspicion for this diagnosis due to its varied histological appearance and aggressive behavior.

Keywords
- fumarate hydratase-deficient renal cell carcinoma
- fumarate hydratase
- RCC
- FH IHC
- HLRCC

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Introduction

The classification of renal tumors has evolved phenomenally and at an expeditious rate in less than a decade. The introduction of "molecularly defined renal tumors" in the 2022 World Health Organization (WHO) classification of urogenital tumors officially marks the commencement of the molecular era in renal cell carcinomas (RCCs). The fumarate hydratase (FH)-deficient RCCs belong to this subgroup. These tumors, which display diverse morphologies, were largely labeled as type 2 papillary RCC (PRCC), RCC unclassifiable, and collecting duct carcinoma. The diagnosis of these tumors is challenging partly because of their heterogeneous morphology and partly due to the limited accessibility to specific immunostains and molecular testing in resource-limited settings. Accurate identification of these tumors is vital due to their syndromic association with hereditary leiomyomatosis and RCC syndrome (HLRCC) and potential for aggressive behaviour.[1] Although considered to be rare, a study by Shuch et al have estimated a carrier frequency of germline FH alterations of 1 in 1,000 individuals.[2]

Treatment options for these patients are under active research and combination therapies with vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) inhibitors have shown promising results in patients with metastatic FH-deficient RCC.[3,4] In low resource settings, where access to molecularly driven immunohistochemical (IHC) markers may not be universal, it is crucial to be able to suspect the diagnosis on a hematoxylin and eosin (H&E)-stained section so that the patient may be referred to a specialized center for a definitive diagnosis and management. The number of reported cases of FH-deficient RCCs from India is limited with only one case report published till date.[5]

Our objective is to add to the existing limited body of literature on treatment options and clinical outcomes in these patients and to assess their histomorphologic spectrum through this first series of cases of FH-deficient RCCs from India.

Materials and Methods

Study Setting

The recent WHO 2022 5th series has advocated classifying a category of renal cancers under the rubric of "molecularly defined RCC" of which the FH-deficient renal cancers form an important group. There has been no series from India reported till date and hence we embarked to study these RCCs diagnosed at our institute.

Sample Size

We retrospectively analyzed 11 cases of FH-deficient RCC and discuss their clinicopathological characteristics.

Study Design

This was a retrospective study designed to describe the clinical presentation, morphologic spectrum, and treatment options of FH-deficient RCC. Clinical, radiological, and treatment information, where available, was obtained from the electronic medical record. H&E-stained slides and IHC stains performed on paraffin-embedded tissue were available in all cases and were reviewed and tabulated.

Primary and Secondary Outcome

As this is a retrospective case series of a rare type of renal cancer (FH-deficient RCC), the first series from India, follow-up and outcome details are limited.

Inclusion and Exclusion Criteria

All cases diagnosed as FH-deficient RCC in our center over a period of 24 months (between January 2021 and January 2023) were included in the study. Loss of IHC staining for FH was taken as the diagnostic criteria for inclusion in the study.[1]

Statistical Analysis

Descriptive statistics for univariate analysis to measure central tendency including median and to measure dispersion in the form of ranges and percentages was performed using Microsoft Office Excel.

Ethics

This study was approved by the Tata Memorial Hospital Institutional Ethics Committee on May 16, 2023, project number 4165. Waiver of consent was granted since this was a retrospective study with less than minimal risk. 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 Helsinki Declaration of 1964 and its later amendments or comparable ethical standards.

Results

We identified 11 cases of FH-deficient RCC during the study period. Nine out of 11 patients were referral/consult cases and these patients had undergone radical nephrectomy elsewhere. In one patient, only a core biopsy of the renal mass, done for diagnosis, was available for review. The details of these cases are described below.

Clinical Presentation and Investigation

There were seven men and four women in this series with a median age at presentation of 35 years (age range = 12–60 years). There was no laterality predilection with left-sided tumors in 6 out of 11 patients (54.5%), while one patient presented with synchronous, bilateral renal tumors. Clinical and radiological details have been tabulated in ►**Table 1** (►**Fig. 1**).

Macroscopic and Microscopic Findings

Detailed gross findings were available in only two tumors; both were solid and cystic with a tan to hemorrhagic cut surface. The tumor size as measured grossly or on radiology ranged from 5.1 to 13 cm ($n = 7$). All tumors had mixed architectural patterns with the most common predominant pattern being papillary ($n = 6$). The other predominant patterns encountered were nested tubules ($n = 3$), tubulocystic ($n = 1$), and infiltrating tubules ($n = 1$). The most commonly

Table 1 Patient details and treatment and follow-up history

Patient	Age (y)/Sex	Laterality	Tumor size (cm)	Stage	Radiology	Metastasis	Therapy received	Follow-up time (mo)	Status
1	30/M	Left	13	T3aM1	Heterogeneously enhancing mass, interpole region of kidney	Adrenal, pleural, and pericardial cavities, duodenum	None	5	DOD
2	35/M	NA	NA	NA	NA	NA	NA	NA	NA
3	60/M	Left	NA	NA	NA	NA	NA	NA	NA
4	53/F	Left	NA	NA	NA	NA	NA	NA	NA
5	26/M	Right	NA	NA	NA	NA	NA	NA	NA
6	44/M	Right	6.2	NA	NA	Lung, bone, retroperitoneal lymph nodes	Pazopanib	14	AWD
7	44/M	Left	NA	NA	NA	NA	NA	NA	NA
8	35/M	Bilateral	Right - 6, Left - 5.1	NA	NA	Liver, adrenal, peritoneum	Sunitinib	16	AWD
9	43/F	Left	13	T2b	Heterogeneously enhancing mass, anterior aspect of kidney	No	NA	NA	NA
10	16/F	Left	13	T2b	NA	No	NA	NA	NA
11	12/F	Right	9.5	T2a	Heterogeneously enhancing mass with internal calcification, lower pole of kidney	No	None	4	NED

Abbreviations: AWD, alive with disease; DOD, died of disease; F, female; M, male; NA, not available; NED, no evidence of disease.
Note: American Joint Committee on Cancer (AJCC) 8th edition is used for staging.

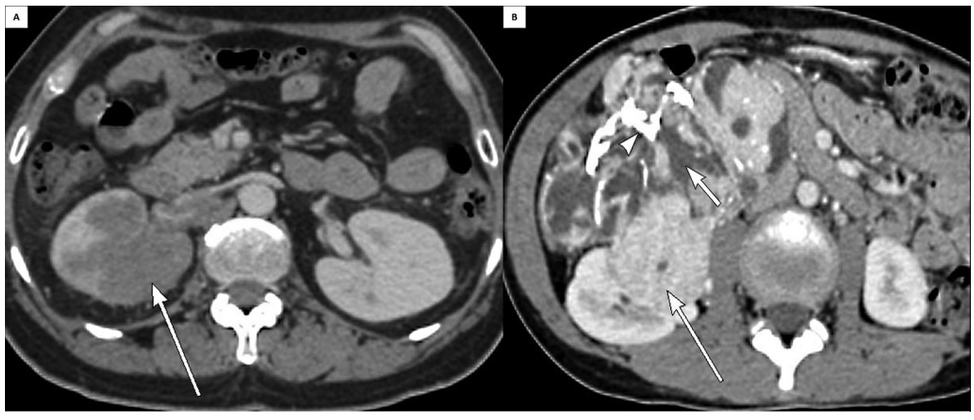

Fig. 1 (**A**) Axial contrast-enhanced computed tomography (CT)—Hypoenhancing endophytic mass in the right kidney (arrow). (**B**) Axial contrast-enhanced CT—Exophytic mass in the anterior interpolar region of the right kidney with enhancing solid (long arrow) and necrotic (short arrow) components and calcifications (arrowhead).

seen secondary pattern was tubulocystic ($n = 7$) followed by tubules ($n = 1$), papillary ($n = 1$), solid papillary ($n = 1$), and cribriform ($n = 1$). The papillae were broad with hierarchical branching, edematous, and sometimes hyalinized cores and were lined by columnar cells with abundant eosinophilic to focally clear or vacuolated cytoplasm. Some papillae appeared to be intracystic. The nuclei were vesicular with focally ($n = 7$) to diffusely present ($n = 2$) prominent eosinophilic "cytomegalovirus-like inclusion" nucleoli with perinuclear halo (►**Fig. 2**).

Three tumors had a predominant nested tubular pattern and were composed of eosinophilic cells with low-grade, minimally pleomorphic nuclei. One of these tumors had very focally prominent eosinophilic nucleoli, spireme-type

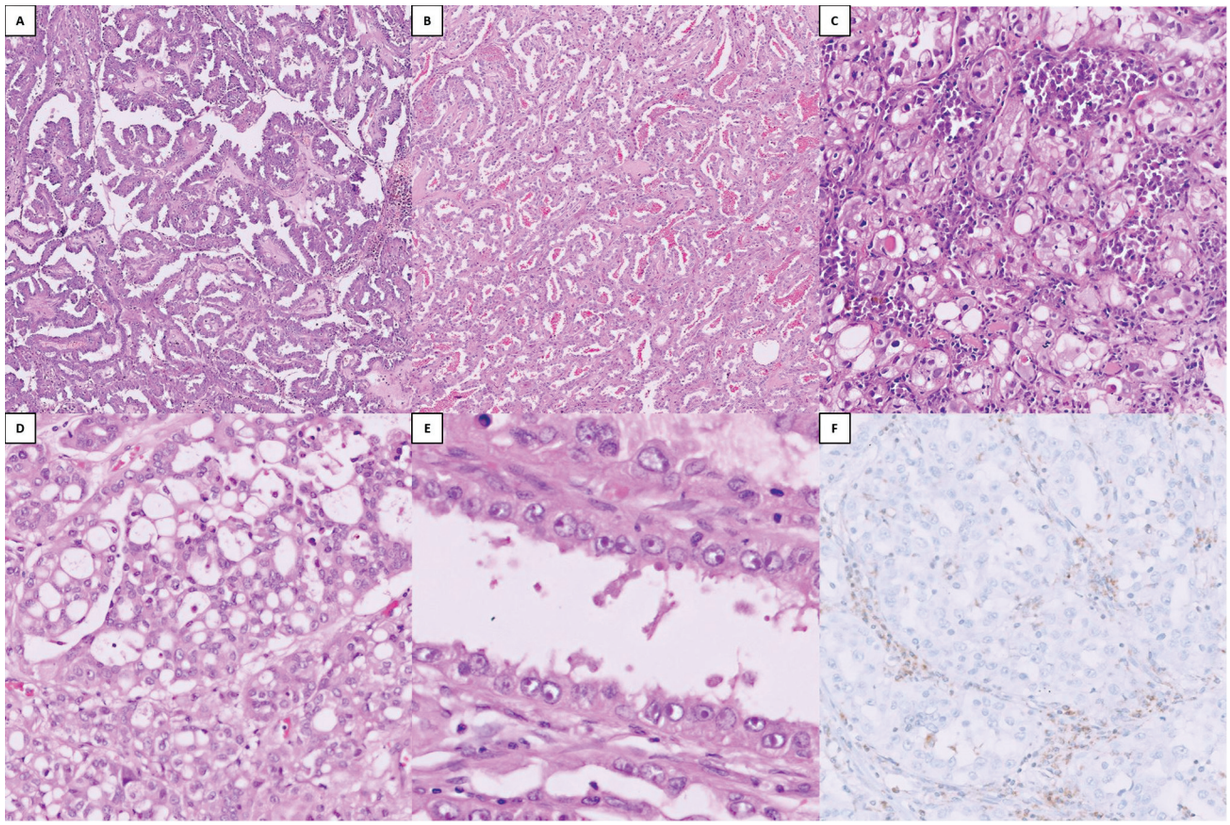

Fig. 2 Pattern heterogeneity in fumarate hydratase (FH)-deficient renal cell carcinoma (RCC). (**A**) Hierarchically branching papillae (hematoxylin and eosin [H&E], 10 ×). (**B**) Tubules (H&E, 5 ×). (**C**) Infiltrating tubules and nests (H&E, 20 ×). (**D**) Cribriform appearance (H&E, 20 ×). (**E**) Prominent eosinophilic nucleoli with perinuclear halo (H&E, 40 ×). (**F**) Negative staining for FH (inflammatory cells—positive internal control) (H&E, 20 ×).

chromatin, metaplastic bone, and tubules with mucin in the lumen. Psammoma bodies were noted consistently in these three tumors (►**Fig. 3**). The features in these three tumors were compatible with the "low-grade" morphology. Rhabdoid or sarcomatoid morphologies were not seen in any of the cases.

Immunohistochemical Findings

IHC with various antibodies was performed on all cases, the details of which have been summarized in ►**Table 2**. For FH IHC, clone used was BSB-151 from Bio SB. All the 11 cases showed uniform loss of FH staining.

Treatment and Follow-Up

Two patients are on treatment with multikinase inhibitors and are alive with disease at 12 months' follow-up. One patient is on observation and is disease-free at 4 months of follow-up. One patient who presented with adrenal metastasis was referred for palliation but progressed with systemic metastasis and died of disease within 5 months of initial diagnosis.

Discussion

FH is an enzyme coded for by the *FH* gene which is located on chromosome 1 (1q42.3-q43) that converts fumarate to L-malate in the tricarboxylic acid cycle.[6] Heterozygous germline mutations in the *FH* gene lead to the autosomal dominant inherited disorder, HLRCC syndrome, which has an estimated 15% lifetime risk of developing renal cancer in addition to multiple cutaneous and uterine leiomyomas.[7,8] However, somatic mutations in the *FH* gene can also lead to the development of RCC without other stigmata of HLRCC syndrome and hence it was renamed as FH-deficient RCC instead of HLRCC-related RCC in the WHO 2022 classification.[9]

FH deficiency leads to fumarate accumulation which has multiple downstream effects including stabilization of the hypoxia-inducible factor alpha (HIF-1α) complex that lead to tumorigenesis. Pathogenic levels of fumarate also causes succination of cysteine residues on proteins leading to formation of 2-succinocysteine (2SC) and abnormal protein function.[10,11] FH-deficient RCCs are typically solitary, unilateral tumors with age at presentation ranging from 36 to 46 years and no gender predilection, which is in keeping with the findings of this series.[12–15] The earliest stage at presentation was T2a with one patient presenting with metastases to adrenal and T3b primary disease. The aggressive nature of these tumors has been shown in previous studies with one study having 71% of patients presenting at least with T3a disease, 40 to 50% with regional lymph node metastasis, and around 20% with distant metastases (usually to adrenal and bone) at presentation. These

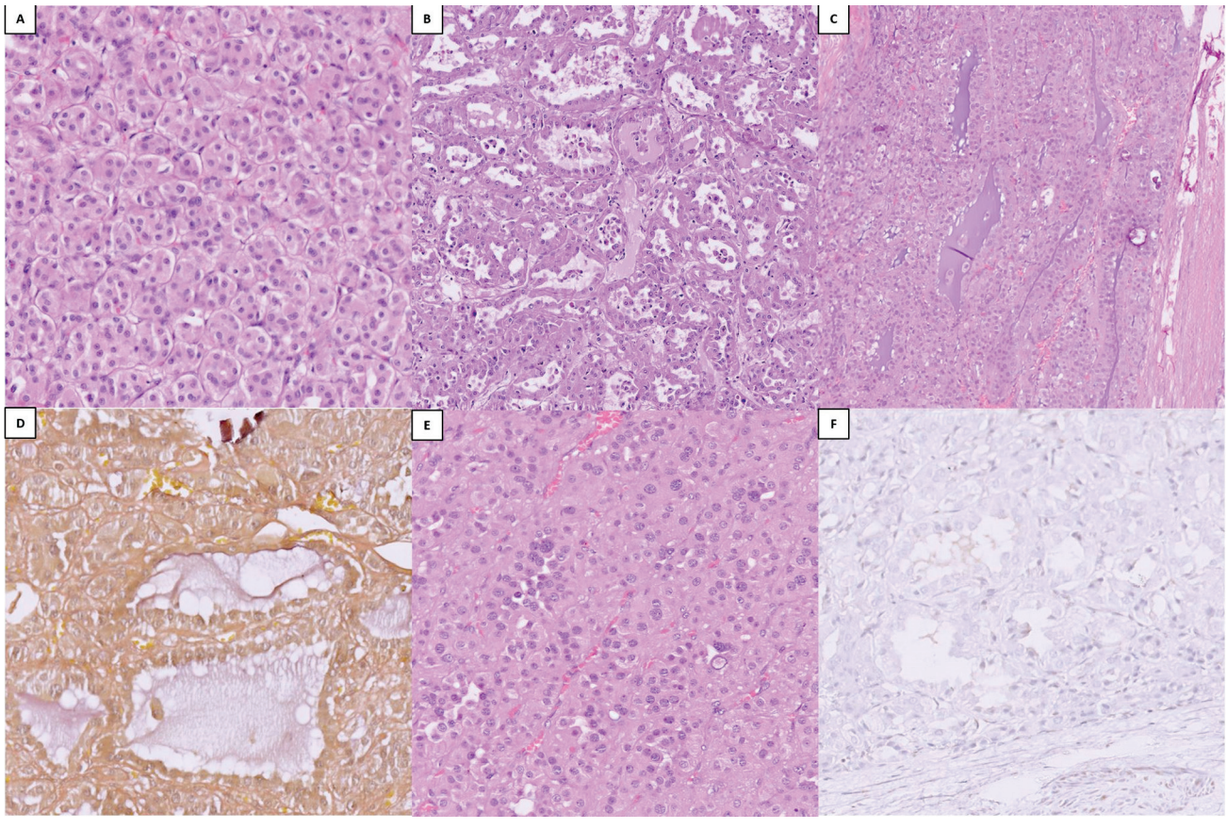

Fig. 3 Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) with low grade morphology. (**A**) Solid nests of eosinophilic cells with inconspicuous nucleoli (hematoxylin and eosin [H&E], 20 ×). (**B**) Tubulocystic (H&E, 10 ×). (**C**) Mucin secretion (H&E, 10 ×) with (**D**) mucicarmine positive intraluminal mucin (20 ×). (**E**) Spireme-type chromatin (H&E, 20 ×). (**F**) Negative staining for FH (smooth muscle in vessel wall—positive internal control) (H&E, 20 ×).

studies also reported 39 to 50% disease-related mortality within 3 years of diagnosis.[12–14,16]

FH-deficient RCCs have classically been described to have a type 2 PRCC-like morphology and four of our cases had been diagnosed on morphology as type 2 PRCC. However, heterogeneity is probably the first important clue toward a diagnosis of FH-deficient RCC, even if the tumor shows type 2 PRCC-like areas. All published series of cases have demonstrated heterogeneity within the same tumor which is also reflected in the present series. In literature, the most predominant pattern encountered was papillary followed by tubulopapillary, intracystic papillae, tubulocystic, cribriform/sieve like, sarcomatoid, and low-grade oncocytic.[12,14–21] An infiltrating collecting duct carcinoma-like morphology and tubulocystic carcinoma with poorly differentiated foci have also been described.[5,12,22,23] In our study, the most predominant pattern was also papillary followed by tubulocystic and cribriform with minor patterns including solid and nested and three cases with a collecting duct carcinoma-like morphology.

Merino et al in their seminal study of 40 FH-deficient RCCs described the presence of prominent, inclusion-like, cherry red nucleoli with perinuclear halos in all their cases which became the defining histological feature of this tumor. However, subsequent studies including the current cohort show that this feature is not uniformly present in all FH-deficient RCCs and if present, more often than not, is very focal.[15,18]

A subset of patients with FH deficiency has renal tumors with low grade oncocytic morphology similar to other low grade eosinophilic/oncocytic renal cell tumors. Although they appear to have low grade nuclei, Smith et al have reported two cases, one with occurrence of a synchronous high-grade RCC and another metachronous high-grade RCC occurring 4 years later, both with low grade oncocytic morphology.[22] Three of our cases had uniformly low grade oncocytic morphology with retained expression of succinate dehydrogenase B and focal areas of psammomatous calcification. This latter feature has been described by Li et al in FH-deficient RCCs with low grade morphology.[24] One of these low-grade morphology tumors also showed tubules containing mucin and osseus metaplasia, both of which have not previously been described in literature. All were T2 at presentation and one patient is disease-free at 4 months of follow-up; however, we did not have follow-up data for the other two patients. The use of the term “low grade” for this subset of FH-deficient RCC is a matter of debate and it may not hold good as more data emerges.[25]

Loss of FH ICH staining combined with positivity with 2SC IHC is used in the routine diagnosis of these tumors. Muller et al reported that loss of FH has a sensitivity of 87.5% and a specificity of 100% in the diagnosis of FH-deficient RCCs.[18] In the present series, all cases showed FH loss by IHC. Positive nuclear and cytoplasmic staining for 2SC is a more sensitive

Table 2 Immunohistochemical findings in FH-deficient RCC

IHC	Patients										
	1	2	3	4	5	6	7	8	9	10	11
FH	–	–	–	–	–	–	–	–	–	–	–
SDHB	ND	ND	ND	+	+	ND	+	ND	+	+	+
AMACR	+	F+	+	+	+	ND	ND	+	–	W+	+
CK7	–	–	–	–	F+	F+	–	–	–	–	–
CK20	–	ND	–	–	ND	–	ND	ND	–	–	ND
EMA	ND	ND	ND	ND	ND	ND	ND	ND	ND	F+	ND
AE1/AE3	ND	ND	+	ND	ND	+	ND	ND	ND	–	ND
PAX8	ND	ND	ND	ND	+	ND	+	+	ND	F+	ND
HMB45	–	ND	ND	–	ND	–	ND	ND	–	ND	–
Melan A	ND	ND	–	ND	ND	ND	ND	ND	–	–	–
ALK	–	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
TFE3	–	–	ND	ND	ND	ND	ND	ND	–	–	F+
CAIX	ND	ND	ND	ND	–	–	–	–	–	ND	–
KIT	ND	ND	ND	ND	ND	–	ND	ND	–	–	–
GATA-3	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vimentin	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND
L1cam	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND

Abbreviations: F, focal; FH, fumarate hydratase; IHC, Immunohistochemistry; ND, not done; RCC, renal cell carcinoma; W, weak.
Note: +, positive; –, negative.

although less specific marker, with one study quoting a sensitivity and specificity of 91.7%. This paper also quotes an increase in sensitivity of 100% when FH and 2SC are used in concert.[18] 2SC staining was not done in the current series due to nonavailability at our center. It must be noted that 2SC is a sensitive marker but not specific and hence is of limited utility in confirming FH-deficient RCC on IHC without combining with FH IHC or molecular testing.[26]

These tumors morphologically form a part of the so-called "type 2 PRCC histology" (barring the FH-deficient tumors with low nuclear grade histology). Hence, the IHC panel to address type 2 PRCC histology includes CK7, AMACR, FH, INI-1, ALK, HMB45, Melan-A, Cathepsin K, TFE3, TFEB, and CK20.

For tumors that are localized to the kidney, the recommendation is wide margin surgical excision with retroperitoneal lymph node excision. For patients with confirmed HLRCC syndrome, annual screening with abdominal magnetic resonance imaging starting at age 8 to 10 years is recommended.[7] Systemic treatment options for metastatic FH-deficient RCCs are under active research and initial studies have focused on therapies targeting the classic clear cell RCC-associated HIF targets including inhibitors of VEGF, EGFR, and mTOR. A phase II clinical trial (AVATAR trial) with bevacizumab and erlotinib showed a median progression-free survival (PFS) of 21.1 months in patients with advanced disease.[3] However, Choi et al in a retrospective study of 10 patients treated with bevacizumab and erlotinib showed a median PFS of 13.3 months.[27] A study by Gleeson et al concluded that the longest median overall survival (OS) of 33 months was obtained with a combination therapy of mTOR and VEGF inhibitors (combination of bevacizumab or lenvatinib with everolimus) as opposed to monotherapy with these agents.[4] An European study by Carril-Ajuria et al demonstrated a median OS of 44 months on treatment with antiangiogenics like sunitinib and cabozantinib.[28] In the present series, two patients are on treatment with sunitinib and pazopanib and have shown a decrease in tumor burden at 14 and 16 months' follow-up, respectively.

Future studies can aim at longer follow-up periods to try to better understand the behavior of FH-deficient RCCs with low grade morphology and effectivity of different treatment modalities in tumors with conventional morphology.

Conclusion

This series of 11 cases highlights the aggressive nature, histological heterogeneity including "low grade nuclei" and younger median age at presentation of FH-deficient RCC. Ancillary IHC with FH is a sensitive test to diagnose these tumors although a combination with 2SC maybe better. The limitation of our series is lack of follow-up details due to the referral nature of the cases. Another limitation is the lack of molecular testing since FH IHC has less than 100% sensitivity as a molecular surrogate for FH mutation and does not provide information on germline versus somatic nature of mutations. Germline testing of all cases with FH loss and or 2SC loss would have allowed for genetic counseling to be initiated where necessary.

Awareness of this entity both in the urological and pathology community is of utmost importance as these are known to have an aggressive course, implying radical management and also may trigger genetic counseling with germline mutation testing and surveillance.

Patient Consent

Waiver of consent was obtained since this was a retrospective study with less than minimal risk and participants are de-identified or cannot be contacted.

Ethics clearance letter stating the same has been provided during manuscript submission and also the ethics project approval number is provided within the manuscript.

Funding

None declared.

Conflict of Interest

None declared.

Acknowledgment

None declared.

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Clinical Profile, Toxicities, and Survival Outcome of MCP841 in Pediatric Acute Lymphoblastic Leukemia in Current Era: A Retrospective Study from Eastern India

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Abstract

Introduction: The overall survival in pediatric acute lymphoblastic leukemia (ALL) ranges from 45 to 81% in India. Aggressive chemotherapy protocols like MCP841 have improved the outcome and it can be delivered with minimal supportive care. This study retrospectively analyses the clinical profile and overall survival of patients treated by this protocol.

Objective: This single-center study aims to estimate the event-free survival of patients treated accordingly to the MCP841 protocol with high-dose cytarabine (HDAC) at 2 g/m^2 as the backbone, along with the risk-stratified incidence and cause of mortality in childhood ALL.

Material and Methods: Records of 156 patients aged 1 to 19 years, newly diagnosed with ALL from June 2009 to August 2013 who were treated according to the forementioned protocol were analyzed. Risk stratification for both precursor B-cell ALL (B-ALL) and T-cell ALL (T-ALL) was done, followed by an analysis of the correlation of risk-stratified groups with mortality and survival outcomes.

Result: Precursor B-ALL was found in 70% patients (including 69.7% [$n = 76$] standard risk, 20.1% [$n = 22$] intermediate risk, and 10% [$n = 11$] high risk), while 30% had T-ALL (including 74.4% [$n = 35$] standard risk and 25.5% [$n = 12$] high risk). Death during induction occurred in 0.04% ($n = 5$) precursor B-ALL and 23% ($n = 11$) T-ALL patients. The causes were infection in 62.5%, hemorrhage in 25%, and cortical venous thrombosis in 12.5%. Among those who attained remission (89.7%, $n = 140$), relapse occurred in 26% ($n = 27$) precursor B-ALL and 28% ($n = 10$) T-ALL patients. Approximately 31% patients died in the postinduction phase, with progressive disease due to relapse being the most common cause and bone marrow the most common site. Event-free survival at 168 months for overall population, precursor B-ALL, and T-ALL was 59, 62.4, and 51.1%, respectively.

Conclusion: A comparable survival outcome in par with similar centers in developing countries with the MCP841 protocol was found. Infections are a major cause of

Keywords
- acute lymphoblastic leukemia
- high-dose cytarabine
- MCP841 protocol
- retrospective study
- survival analysis

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mortality during treatment, especially when associated with malnourishment. Relapsed disease and poor salvage rates remain a major hurdle to achieving better survival in developing countries; however, better supportive care and infection control measures along with implementing risk-stratified high-dose chemotherapy protocols might improve outcome in the future.

Introduction

Acute lymphoblastic leukemia (ALL) is one of the most common malignancies in children in India with relative proportion varying between 25 and 40%.[1] After the introduction of aggressive chemotherapy protocols like Berlin–Frankfurt–Münster (BFM), remarkable outcome has been seen in the developed countries resulting in cure rate of 80 to 90%.[2] The prognosis of ALL in India remains poor as the overall survival in ALL ranges from 45 to 81%.[3–7] This can be partly attributed to the logistic constraints to tackle side effects of aggressive protocols and nonadherence to treatment. Aggressive chemotherapy protocols, therapy stratification, and risk-adapted management represent major cornerstones in the treatment of childhood ALL.[8,9] The MCP841 protocol was developed for low- and middle-income countries as it can be delivered with minimal supportive care.[10]

Initially high-dose cytarabine (HDAC) at the dose of 2 g/m^2 were given to those younger than 3 years who could not be given prophylactic cranial radiation. At the Tata Memorial Hospital, Mumbai, HDAC at the dose of 2 g/m^2 was given to entire pediatric population, and the 4-year event-free survival (EFS) was reported to be 85.5%, which is at par with the EFS reported in cancer centers in developed countries. The incidence of posttherapy relapse was reported to be 15% in the MCP841 protocol in a study at the same center.[8]

Our primary objective was to study the EFS with HDAC as the backbone of the protocol.

The secondary objectives of the study were to determine the following:

- Incidence of precursor B-cell ALL (B-ALL; standard, intermediate, and high risk) and T-cell ALL (T-ALL; standard and high risk) as per the criteria listed in ►**Table 1**.

Table 1 Criteria for risk stratification

B-cell precursor ALL	Standard risk (precursor B-ALL SR)	• Children aged >1 and <10 y • WBC count <50,000/mm^3 at presentation • Prednisolone good responder • No testicular or bulky disease • No high-risk cytogenetics
	Intermediate risk (precursor B-ALL IR)	• Children ≥10 y or WBC count ≥50,000/mm^3 at presentation OR • Testicular or bulky disease AND • Prednisolone good responder • No high-risk cytogenetics
	High risk (precursor B-ALL HR)	• High-risk cytogenetics t(9:22), translocations of chr.11, complex cytogenetics • OR prednisolone poor responder • OR central nervous system disease
T-cell ALL	Standard risk (T-ALL SR)	• WBC count <10,000/mm^3 at presentation • No bulky disease • Prednisolone good responder • Complete remission at the end of induction • Not ETP-ALL • No CNS disease
	High-risk (T-ALL HR)	Any of the following: • WBC ≥100,000/mm^3 at presentation • Bulky disease • ETP phenotype • T lymphoblastic lymphoma • Prednisolone poor responder • No complete remission after induction • CNS disease

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; ETP, early T-cell precursor ALL; HR, high risk; IR, intermediate risk; SR, standard risk; WBC, white blood cell.

- Incidence and cause of death in various risk groups of ALL.
- Statistical correlation of risk stratification with mortality.

Materials and Methods

In this retrospective observational study, data of 156 patients aged 1 to 19 years diagnosed with ALL from June 2009 to August 2013 at the Medical College and Hospital, Department of Medical Oncology and Department of Pediatrics, were analyzed. Immunophenotyping and conventional cytogenetic study were planned in all cases at diagnosis, but this was subject to logistic issues and nonavailability. The patients were treated according to the MCP841 protocol with HDAC (2 g/m^2 every 12 hours for 2 days, repeated every 14 days for 3 cycles) for the entire population. The chemotherapy protocol followed is depicted in ►**Table 2**. Prophylactic cranial irradiation was given to children older than 3 years. Individuals were stratified into various risk groups as per the criteria mentioned in ►**Table 1**. Complete blood count (CBC) was performed thrice weekly and cerebrospinal fluid (CSF) examination was performed as per protocol to detect the central nervous system (CNS) relapse. Prednisone response was defined as reduction in a number of blood blasts per microliter after a 7-day prednisone prephase and one intrathecal dose of methotrexate on day 1. Prednisolone good response (PGR) is less than 1,000 blasts/µL, whereas prednisolone poor response (PPR) is ≥1,000 blasts/µL.[9] Remission death has been defined as death after remission and before completion of maintenance. Fluorescence in situ hybridization (FISH) cytogenetics and molecular genetics were avoided for risk stratification as they were not available during the study period across the population.

Supportive management and neutropenic care were instituted for all patients as per the institutional protocol. Investigations such as CBC, C-reactive protein, and blood culture were done in all suspected cases of sepsis and febrile neutropenia. Initial empirical antibiotics used were piperacillin-tazobactam and amikacin. Antibiotics were changed according to culture sensitivity reports. When neutropenic sepsis was associated with no identified organisms in blood culture, the choice of antibiotics was piperacillin-tazobactam + amikacin (first line), followed by meropenem + vancomycin (second line), and, finally, colistin and antifungals. Antifungals used for treatment were amphotericin B and voriconazole.

Primary outcome: To study the EFS with HDAC as the backbone of the protocol.

Secondary outcome: To estimate the incidence of risk-stratified ALL in pediatric patients and to determine the incidence and cause of death in various risk groups.

Inclusion Criteria

Patients aged 1 to 19 years newly diagnosed with ALL from June 2009 to August 2013 and treated according to the MCP841 protocol with HDAC (2 g/m^2) were included in the study.

Exclusion Criteria

Treatment defaulters during any phase of treatment till re-intensification (RI_1) and previously treated cases of ALL were excluded from the study.

Table 2 Summarizing MCP841 chemotherapy protocol

Drugs	Induction (I_1)	Induction 2 (I_2)	I_2A	Repeat induction (RI_1)	Consolidation	Maintenance (6 cycles)
Prednisolone (40 mg/m^2)	D 1–28	■	HDAC (2 g/m^2)	Repeat I_1	D 1–7	■
Vincristine (1.4 mg/m^2)	D 1, 8, 15, 22, 29	■			D 1, 15	D 1
L-asparaginase (6,000 U/m^2)	D 2–20, alternate day	■			■	D 1, 3, 5, 7
Daunorubicin (30 mg/m^2)	D 8, 15, 29	■			■	D 1
Mercaptopurine (75 mg/m^2)	■	Daily			D 1–7, 15–21	Start on day 15. Daily, 3 wk out of every 4 wk, for a total of 12 wk
Cyclophosphamide (750 mg/m^2)	■	D 1, 15			D 1, 15	■
Methotrexate (12 mg, IT)	D 1, 8, 15, 22	D 1, 8, 15, 22			■	15 mg/m^2, orally, start on D 15, once a week, missing every 4th wk, for a total of 12 wk
Cranial irradiation (2,000 cGy)	■	10 d			■	■
Cytarabine (70 mg/m^2)	■	■			D 1–3, D 15–17	■

Abbreviations: D, day; HDAC, high-dose cytarabine; IT, intrathecal.
The black squares in the table denote that the drugs (mentioned in Rows) were not given in that particular phase of chemotherapy.

Statistical Analysis

All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) software for windows (IBM Corp., Armonk, NY, United States). The chi-squared test was performed to examine the relation between categorical variables and a value of $p < 0.05$ was considered significant. For survival analysis, Kaplan–Meir survival curves were plotted and log-rank (Mantel–Cox) test was performed; statistical significance ($p < 0.05$), chi-squared values, and mean survival with 95% confidence interval (CI) were calculated.

Ethics: Ethics committee approval was granted for this retrospective study by the Institutional Ethics Committee of Medical College, Kolkata (reference number: MC/KOL/IEC/NON-SPON/2158/07/2023 dated 19.07.2023). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Between June 2009 and August 2013, 156 patients were included in this study after applying the exclusion criteria. Data were analyzed in February 2023. The mean age at presentation was 6.4 ± 0.3 years with a male preponderance of 60.8% ($n = 95$). In total, 109 patients (70%) were precursor B-ALL, of whom 76 (69.7%) were standard risk (pre-B-ALL SR), 22 (20.1%) were intermediate risk (pre-B-ALL IR), and 11 (10%) were high risk (pre-B-ALL HR). In all, 47 (30%) patients had T-ALL, of whom 35 (74.4%) were standard risk (T-ALL SR) and 12 (25.5%) were high risk (T-ALL HR).

Fever was the most common presenting symptom (79.5%), followed by lymphadenopathy (69.8%) and hepatosplenomegaly (52%). Hyperleukocytosis was present in 24 (15%) patients at diagnosis. Approximately 80% were treated in the general pediatric ward and 20% in the oncology ward.

PGR on day 8 was seen in 98 (62.8%) patients. In total, 140 (89.7%) patients achieved remission (<5% blast on bone marrow examination, i.e., M1) at the end of induction and 16 (10.3%) patients died during the induction phase. Twelve of 16 (75%) children who faced induction mortality had a median gap of 2.5 months or more from symptom onset and initiation of treatment. Thirteen of 16 (~81.25%) children who faced induction mortality were suffering from moderate acute malnutrition and 2 (12.5%) were suffering from severe acute malnutrition. Blood culture was positive in approximately 31% ($n = 49$) patients during the course of treatment. The most common organisms isolated in bacterial sepsis were *Klebsiella pneumoniae*, *Pseudomonas* sp., *Staphylococcus aureus*, and enterococci.

►**Tables 3** and **4** depict the frequencies and causes of death during induction, remission death, and EFS according to the risk stratification. The causes of induction death were infection in 10 (62.5%) patients, hemorrhage in 4 (25%) patients, and neurological cause, that is, cortical venous thrombosis in 2 (12.5%) patients. Among infection, bacterial neutropenic sepsis was the most common ($n = 5$, 50%), followed by fungal pneumonia ($n = 3$, 30%), systemic candidiasis ($n = 1$, 10%), and human immunodeficiency virus (HIV) infection ($n = 1$, 10%). Among those who attained remission (89.7%, $n = 140$), relapse occurred in 26% ($n = 27$) precursor B-ALL and 28% ($n = 10$) T-ALL patients. Forty-eight patients (30.7%) died during the postinduction period and the causes of mortality included progressive disease due to relapse in 37 (77%) patients and infection in 11 (22.9%) patients. The commonest cause of overall mortality was progressive disease due to relapse, occurring mostly in the consolidation and maintenance phase. Bone marrow was the commonest site of relapse and observed in 35 (94.6%) patients, followed by testicular relapse in 2 (5%) patients. Bone marrow and testicular relapse occurred at a median gap of 24 and 42 months, respectively, after initiation of treatment. No cases of CNS relapse were seen in our study.

The chi-squared test of independence was performed to examine the relation between risk groups and the incidence of induction mortality. The relation between these variables were significant ($\chi^2 = 82.54$, $p < 0.0001$). However, the chi-squared test of independence between risk groups and incidence of remission death and overall survival was not significant ($\chi^2 = 6.07$, $p = 0.19$). The EFS at 168 months was 59%. Relapse-free survival by Kaplan–Meir analysis (►**Fig. 1**)

Table 3 Details of mortality and event-free survival according to risk-stratified groups

Type of malignancy	Risk stratification	No. of patients ($N = 156$)		No. of deaths during induction ($N = 16$)		Remission death ($N = 48$)		Event-free survival in each group	
		n	%	*n*	%	*n*	%	*n*	%
Pre B-ALL	Pre B-ALL SR	76	48.7	1	6.2	21	43.7	54	71
	Pre B-ALL IR	22	14.1	1	6.2	10	20.8	11	50
	Pre B-ALL HR	11	7.0	3	18.7	5	10.4	3	27
T-ALL	T-ALL SR	35	22.4	1	6.2	11	22.9	23	65
	T-ALL HR	12	7.6	10	62.5	1	2.08	1	8

Abbreviations: B-ALL; B-cell acute lymphoblastic leukemia; HIV, human immunodeficiency virus; HR, high risk; IR, intermediate risk; Pre, precursor; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia.

Table 4 Details of mortality during induction according to risk-stratified groups

Risk stratification	No. of patients (*n*)	Cause of induction death	No. of deaths during induction ($N = 16$)	
			n	%
Pre B-ALL SR	76	Cortical venous thrombosis	1	6.2
Pre B-ALL IR	22	Neutropenic sepsis	1	6.2
Pre B-ALL HR	11	Fungal pneumonia	2	12.5
		Neutropenic sepsis	1	6.2
T-ALL SR	35	Neutropenic sepsis	1	6.2
T-ALL HR	12	Hemorrhage	4	25
		Neutropenic sepsis	2	12.5
		Systemic candidiasis	1	6.2
		Fungal pneumonia	1	6.2
		HIV	1	6.2
		Cortical venous thrombosis	1	6.2

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; HIV, human immunodeficiency virus; HR, high risk; IR, intermediate risk; Pre, precursor; SR, standard risk; T-ALL, T-cell acute lymphoblastic leukemia.

was 62.4% for precursor B-cell ALL and 51.1% for T-ALL (log-rank, $\chi^2 = 1.931$, $p = 0.165$). The mean survival for B and T lineages was 111.19 months (95% CI: 97.86–124.51) and 94.36 months (95% CI: 73.04–115.68), respectively.

Discussion and Conclusion

The 5-year survival rate for ALL in the western world is approximately 90% in children younger than 15 years.[11] Compared to the developed world, the biology of ALL appears different in India, with a higher proportion of T-ALL (20–50% as compared to 10–20% in the developed world), hypodiploidy and translocations t (1;19), t (9;22), and t (4;11). All of these factors contribute to a poorer prognosis of leukemia.[1]

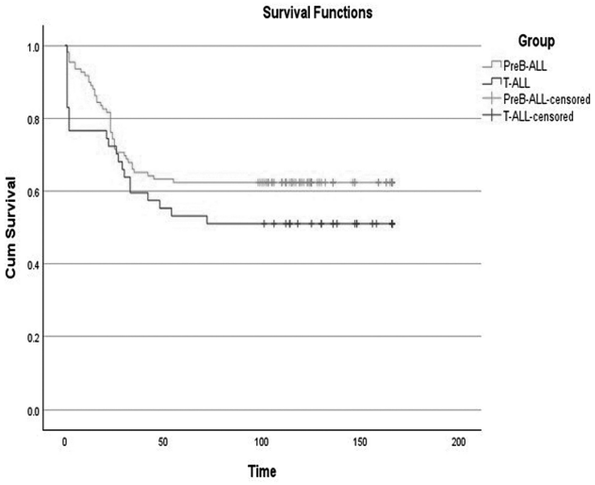

Fig. 1 A Kaplan–Meier survival plot showing relapse-free survival probability for T-cell acute lymphoblastic leukemia (ALL) and B-cell ALL. Cumulative survival (Y axis) has been plotted against time (in months) since diagnosis (X axis).

The incidence of induction mortality was higher in the T-ALL HR group; however, the statistical difference in EFS was not significant between pre-B-ALL SR and T-ALL SR groups treated by the MCP841 protocol. The most common cause of induction death was neutropenic sepsis. Factors such as malnutrition contributed to the increased risk of mortality during the induction period. In the randomized intercontinental trial by Starý et al on intensive chemotherapy for childhood ALL by BFM 2002, PGR was reported in 90.2%,[12] while in a study on outcome of ALL with the ALL-BFM-95 protocol in Nepal by Sharma Poudyal et al, PGR was reported in 71.8% patients.[13] In our study, PGR was reported in 62.8% patients. Out of a total of 64 deaths, most occurred due to relapse in the postinduction period ($n = 37$ [57%] of overall mortality). Bone marrow is the most frequent site of relapse and no CNS relapse was seen. Advani et al obtained similar results for bone marrow relapse, and five patients had a combined bone marrow and CNS relapse.[5] All cases of relapse were advised bone marrow transplant and were referred to institutions with a bone marrow transplant facility. As per the institutional protocol, the cases of relapse were further treated with the St. Jude Protocol and the CCG112 protocol for testicular relapse, but there was no reported survival in cases of relapse in our study.

EFS in our study was 59% at 168 months, which is comparable to the 49% EFS at the end of 5 years reported by Advani et al.[5] In a study by Kapoor et al, relapse-free survival at 5 years was 62% for B-ALL and 28% T-ALL; overall, 53.2% of the patients were in remission at the end of 5 years of starting of treatment.[10] According to the results of randomized intercontinental trial by Starý et al on intensive chemotherapy for childhood ALL by BFM 2002, the 5-year EFS was overall 74% (75% in B-cell precursor and 69% in T cell), 81% in the SR group, 75% in the IR group, and 55% in the HR group.[12] According to a study on outcome of ALL with the

ALL-BFM-95 protocol in Nepal by Sharma Poudyal et al in 2023, the 3-year overall survival and relapse-free survival were 89.4 and 87.3%, respectively. The study undertaken by Sharma Poudyal et al also mentions that the 5-year EFS was 28% in childhood ALL between 1998 and 2012.[13] The higher survival of childhood ALL in recent years, as compared to our study, can be attributed to improving oncological resources over the years, such as enhanced infrastructure and supportive care, awareness among patients, early diagnosis, and specialized training of health care workers.

In spite of its drawbacks, MCP841 using HDAC as a backbone of the protocol is an effective tool for treatment of children suffering from ALL and it has similar survival outcomes in precursor B-ALL and T-ALL. With improving oncological resources, the overall survival has improved in the more recent studies. However, MCP841 remains an important tool in a background of resource-constraint settings and high abandonment. Achieving 50% survival in children with ALL is a challenge in India, and we have reached a comparable survival outcome in par with similar centers in developing countries with the MCP841 protocol. Combating treatment in malnourished children and bridging infections are the major hurdles to improving outcome in developing countries.

Drawbacks

This study is based on a single-center experience, and there is a limitation of available data as it is a retrospective study. Immunophenotyping and cytogenetic reports of all patients could not be procured due to logistic issues and nonavailability of facilities during the time of patient treatment almost two decades ago. Hence, it was not possible to perform a detailed analysis of the correlation between the outcomes based on detailed hematological and cytogenetic reports.

Authors' Contribution

S.B. was responsible for the concept, data acquisition, design of intellectual content, literature search, and manuscript editing. S.S. was responsible for manuscript preparation and literature search. D.R. designed the study. K.D. contributed to manuscript review. M.S. contributed to data analysis and manuscript review. This manuscript has been read and approved by all the authors.

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Conflict of Interest

None declared.

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Molecular Profiling of High-Grade B-Cell Non-Hodgkin Lymphomas and Its Clinicopathologic Correlation in an Indian Tertiary Cancer Care Center

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Abstract

Introduction Double-expressor and double-hit lymphomas (DHL) are known to be more aggressive and have poor outcomes with standard chemotherapy regimens.

Objectives To assess the incidence of DHL and triple-hit lymphomas (THL) and correlate them with clinicopathologic parameters.

Materials and Methods Patients who were diagnosed with high-grade lymphomas from April 2021 to September 2022 were prospectively followed up, and details comprising clinical and pathological parameters, including the immunohistochemistry expression status and gene rearrangements of MYC, BCL2, and BCL6, were recorded.

Results The incidence of DHL and THL in our study was 16.43%. The separate incidence of the DHL-BCL2, DHL-BCL6, and THL groups was 16.43, 13.69, and 2.73%, respectively. The germinal center B cell subtype of histology was predominantly seen in DHLs. MYC, BCL2, and BCL6 expressions do not correlate well with translocations of these genes.

Conclusion Double protein expression cannot be used for screening to decide which patients should undergo fluorescence in situ hybridization, as this would result in missing 4.5% of DHLs.

Keywords
- double-hit lymphoma
- triple-hit lymphoma
- double-expressor lymphoma
- triple-expressor lymphoma
- double protein expression

Introduction

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignant lymphoproliferative conditions of B, T, and NK cells with differing patterns of behaviors and responses to treatment. According to GLOBOCAN (Global Cancer Observatory) data, the incidence of NHL globally was 5 per 100,000 population (2.8% of all new cancer cases), with a mortality rate of 2.5 per 100,000.[1] In India, the incidence has been reported to be 2.9 per 100,000 in males and 1.5 per 100,000 in females.[2]

There have been changes in the nomenclature of NHLs in the recent World Health Organization classification of hematolymphoid neoplasm 2017.[3] Based on the revised nomenclature, high-grade NHL includes (1) Burkitt's lymphomas, (2) diffuse large B cell lymphoma (DLBCL), and (3) high-grade B cell lymphoma (HGBL).

The rearrangements of *MYC*, *BCL2*, and *BCL6* genes are diagnosed by fluorescence in situ hybridization (FISH) and their protein expression by immunohistochemistry (IHC). The incidence of double-expressor lymphomas (DELs) varies from 13 to 46%.[4,5] The incidence of double-hit lymphomas

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(DHLs) varies from 1.6% in Asian studies to 7.9% in Western literature.[6–12]

DHL may most commonly have a blastoid morphology (around 50%) or may be seen in DLBCL or Burkitt's lymphoma. The cell of origin (COO) of DLBCL may be determined by the Hans algorithm[13] or by gene expression profiling such as Lymph2Cx.[14] Based on COO, DLBCLs are divided into germinal center B cell (GCB) type or non-GCB (activated B cell or ABC) type. DELs are more commonly seen in the ABC type, whereas DHL is more commonly seen in the GCB type. DHL with MYC and BCL2 is exclusively seen in GCB type and is seen in 1.7% of ABC type DLBCL. Due to the above-mentioned reasons, the morphology, IHC, or COO cannot be used to screen patients as to who should undergo FISH for detection of DHL. This would result in the unacceptable missed diagnosis of a few DHLs in the screened-out group. One option would be to screen patients by performing FISH for MYC translocation alone, and then to further test FISH for BCL2 and BCL6 only for those who are MYC altered.

DEL and DHL are known to have a poor prognosis and poor responses to standard chemotherapy regimens. There is a lack of data in the Indian scenario regarding the molecular profiling of lymphomas. This study aimed to detail the molecular profiling of high-grade lymphomas and their clinicopathological correlation.

Materials and Methods

Study Design

This is an observational cohort study conducted at Apollo Cancer Centre, Chennai (Tamil Nadu, India) during the period from April 2021 to September 2022.

Sample Size

The previously reported percentage incidence of DHLs was 10%.[8] For 95% confidence and an error of 5%, the calculated sample size was 73.

Primary and Secondary Outcomes

The primary outcome was to assess the incidence of DHLs by molecular profiling of high-grade B cell NHLs. The secondary outcome was a correlation of the DHL status with clinicopathological and molecular findings.

Inclusion and Exclusion Criteria

Patients diagnosed with aggressive B cell NHLs (Burkitt's lymphoma, DLBCL, and HGBL) with an age older than 18 years were included in the study. Those patients with an age younger than 18 years, and all lymphomas other than aggressive NHLs, such as indolent B NHLs (low-grade follicular lymphoma, low-grade mantle cell and marginal zone lymphomas), and T cell NHLs were excluded.

Methods

The study patients underwent FISH of MYC, BCL2, and BCL6 (aggressive lymphoma panel) on the formalin-fixed paraffin-embedded specimen, preferably obtained from an excision biopsy of the lymph node. Data including demographic details, clinical symptoms, laboratory values, Eastern Cooperative Oncology Group (ECOG) performance status (PS), number of nodal stations involved, extranodal disease, bulky disease, central nervous system (CNS) disease, clinical stage, prognostic scoring, histology (DLBCL/HGBL/Burkitt's lymphoma), and IHC results were recorded. The patients were considered into four groups: (1) DHL-BCL2 (DHL with rearrangement of MYC and BCL2), (2) DHL-BCL6 (DHL with rearrangement of MYC and BCL6), (3) triple-hit lymphoma (THL with rearrangement of MYC, BCL2, and BCL6), and (4) the standard group ("nonhit" lymphomas). The association between each variable and positivity for the aggressive lymphoma panel was analyzed. A correlation between IHC positivity (expressor lymphomas) and FISH positivity (hit lymphomas) was also performed.

Statistical Analysis

All categorical variables were expressed as percentages. Continuous variables, such as age, were expressed as their mean $\pm$ standard deviation if they were normally distributed. Nonnormally distributed continuous variables were represented by their median interquartile range. Comparison of categorical variables was done by either the chi-square test or Fisher's exact test. Data entry was done in Epidata Entry version 3.1. Data analysis was performed using SPSS version 26. All p-values < 0.05 were considered statistically significant.

Results

Results of the Total Cohort

Demographics

There were a total of 73 patients in this study. The mean age of the patients was 52.67 ± 15.62 years, ranging from 20 to 85 years.

Clinical Parameters

Fifty-five patients (75%) of them had an ECOG PS of 1. Only two of them were asymptomatic with an ECOG PS of 0. Fourteen (19.2%) of them had an ECOG PS of 2, and one each had an ECOG PS of 3 and 4. Eighteen (24.7%) of the patients had any one of the B symptoms. Ten (13.7%) of them had fever as one of the presenting complaints. Thirteen (17.8%) of them had a weight loss of more than 10% of their body weight over the past 6 months. None of them had night sweats.

Laboratory Parameters

The mean hemoglobin was 11.73 ± 2.28 g/dL. Thirty-seven of them had hemoglobin less than 12 g/dL. The mean total count was $10{,}596.58 \pm 23{,}807$ cells/mm^3, ranging from 1,600 to 208,900 cells/mm^3. The platelet count varied from 80,000 729,000 /mm^3, with a mean of 273,300/mm^3. The mean neutrophil percentage was 69.30 ± 15.11%, and the mean lymphocyte count was 18.42 ± 10.15%. The mean absolute neutrophil count was $5{,}702.26 \pm 3{,}251.86$. Only two patients had neutropenia at diagnosis, one with mild and another with moderate neutropenia.

The mean lactate dehydrogenase (LDH) value was 777.24 ± 2,608.24 units/L, ranging from 130 to 22,020 units/L. LDH was more than the upper limit of normal in 50 (72.2%) patients.

The mean ki67 value was 81.52 ± 15.87%. The ki67 was 80% or higher in 50 patients. Only four patients had a ki67 of less than 50%.

There was no nodal involvement in four patients. The nodal involvement was limited to one to three nodal groups in 33 patients (45.1%). Seven or more nodal stations were involved in 15 patients.

Extranodal involvement was present in 59 (80%) patients; 26 of them had only involvement in a single extranodal site. Two, three, and ≥ four extranodal sites were involved in 16 (21.9%), 11 (15.1%), and 6 (8.3%) of them, respectively. Bone marrow involvement was seen in six (8.2%) patients. Bulky disease was present in four (5.5%) patients. CNS involvement was seen in five (6.8%) patients. Most of the patients had advanced disease, with 42 (57.5%) of them in stage IV and 11 (15.1%) of them in stage III. Fourteen (19.2%) and 6 (8.2%) of them were in stages II and I, respectively. The international prognostic index (IPI) was ≥ 3 in 39 (53.4%) patients and ≥ 4 in 18 (24.6%) patients. The CNS IPI score was ≥ 4 in 26 (35.6%) patients. The most common histology was the DLBCL–GCB type seen in 37 (50.7%) patients, followed by the DLBCL–non-GCB type in 23 (31.5%) patients. HGBL was seen in eight patients and in three Burkitt's lymphomas.

MYC, BCL2, and BCL6 Expression in the Total Cohort

MYC expression was seen in 30 out of 66 evaluable patients (45.5%). BCL2 was expressed in 39 of the 66 patients (59.1%). BCL6 protein expression was found in 46 of all 64 patients (79.1%) (►**Fig. 1**).

MYC, BCL2, and BCL6 Gene Rearrangements in the Total Cohort

MYC translocation was seen in 18 out of 73 patients (24.7%). BCL2 translocation was found in 15 out of 58 patients (20.5%). BCL6 translocations were seen in 25 out of 73 patients (34.2%).

Out of the 18 MYC translocations, the partner was Immunoglobulin heavy locus (IgH) in 10 of the cases. Out of the 15 BCL2 translocations detected, the partner was IgH in 10 of the cases. In the remaining cases, the partner was unknown.

Results of Patients with Double-Expressor Lymphoma

Of the 73 patients, IHC for MYC data was available for 66 patients. They were divided into the triple-expressor lymphoma (TEL) group, the DEL-BCL2 group, the DEL-BCL6 group, and the nonexpressor lymphoma group.

MYC, BCL2, and BCL6 Expression in Expressor Lymphomas

MYC expression was positive in all DEL/TEL patients, as was expected, and none in the nonexpressor groups. BCL2 expression was seen in 17 out of 36 (47.2%) standard group patients and 22 of the 30 (73.3%) expressor lymphoma

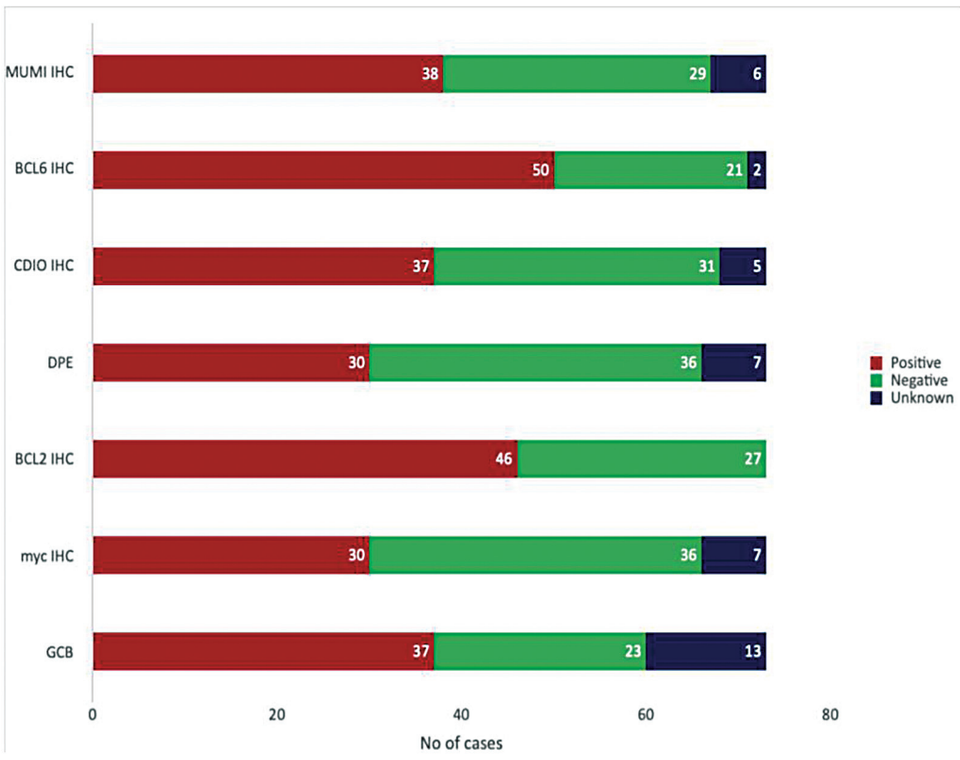

Fig. 1 Percentage positivity of selected immunohistochemistry (IHC) markers, double protein expression (DPE), and germinal center B cell (GCB) histology in the total cohort including all the patients.

patients. Similarly, BCL6 expression was seen in 19 out of 35 standard group patients and in 27 of the 29 patients in the expressor lymphoma groups (►**Table 1**).

Results of Patients with Double-Hit Lymphomas

For analysis purposes, 73 patients were divided into a THL group, a DHL-BCL2 group, a DHL-BCL6 group, and a nonhit lymphoma group.

IHC Markers in Hit Lymphomas

CD10 positivity was 75% in DHL as compared with 45% in nonhit lymphomas, and this difference was statistically significant ($p < 0.022$). MUM1 was negative in 83% of DHL and 31% of nonhit lymphomas, and it was statistically significant ($p < 0.002$). These findings can be attributed to the predominance of GCB type in DHL. There was no difference in the positivity of other IHC markers between the DHL and nonhit lymphoma groups.

Histology of Hit Lymphomas

One out of two (50%), four out of eight (50%), and two out of two (100%) cases were of the GCB phenotype in the THL, DHL-BCL2, and DHL-BCL6 groups, respectively. Thirty out of 61 (49.2%) were GCBs in the standard group. There was no statistically significant difference in histology between the groups.

Cell of Origin/Phenotypic Distribution of Hit Lymphomas

There were 18 patients (24.7%) with MYC translocation among the 73 patients studied. Eight (11%) patients had DHL with BCL2 translocation, and two (2.7%) patients had BCL6 translocation. There were two (2.7%) patients with THL. Among the 18 MYC translocated patients, 9 of them had a GCB subtype and 1 had a non-GCB subtype. Among the DHL-BCL2 group, of the eight patients, four had the GCB subtype and one had the non-GCB subtype. In the DHL-BCL6 group, both patients had GCB subtypes (►**Fig. 2**).

MYC, BCL2, and BCL6 Translocations in Hit Lymphomas

Eighteen patients tested positive for MYC by FISH. Six out of 61 patients in the standard hit group had MYC positivity. Of the remaining 12 cases, 2 were in THL, 8 were in DHL-BCL2, and 2 were in DHL-BCL6 groups. Fifteen patients were positive for BCL2 by FISH. Five out of 61 patients in the standard hit group had BCL2 positivity. Of the remaining 10 cases, 2 were in THL and 8 were in DHL-BCL2 groups. Twenty-five patients were positive for BCL6 by FISH. Twenty-one of the 61 patients in the standard hit group were positive, while of the remaining 4 patients, 2 were in the THL group and the other 2 in the DHL-BCL6 group.

Correlation of MYC, BCL2, and BCL6 Expression and Gene Abnormalities

MYC-IHC Positivity in Hit Lymphomas

All two of the patients with THL (100%) were positive for MYC expression. Six out of 8 (75%) in the DHL-BCL2 group, 1 of the 2 (50%) patients with DHL-BCL6, and 21 of the 61 (3.2%)

Table 1 Details of IHC expression and gene abnormalities in total patients and different groups stratified as expressor and hit lymphomas

Parameter	Total cohort for IHC expression ($n = 66$)	Nonexpressor ($n = 36$)	DEL-BCL2 ($n = 8$)	DEL-BCL6 ($n = 3$)	TEL ($n = 19$)	Total cohort for gene rearrangements ($n = 73$)	Nonhit lymphomas ($n = 61$)	DHL-BCL2 ($n = 8$)	DHL-BCL6 ($n = 2$)	THL ($n = 2$)
MYC IHC	30 (45.5)	0 (0)	8 (100)	3 (100)	19 (100)	30 (41.0)	21 (34.4)	6 (57)	1 (50)	2 (100)
BCL2 IHC	39 (59.1)	17 (47.2)	0 (0)	3 (100)	19 (100)	46 (63)	34 (55.7)	8 (100)	2 (100)	2 (100)
BCL6 IHC	46 (71.9)	19 (54.3)	8 (100)	0 (0)	19 (100)	50 (68.5)	40 (65.6)	6 (75)	2 (100)	2 (100)
MYC gene rearrangement	17 (25.5)	3 (8.3)	2 (25)	2 (66.7)	10 (52.6)	18 (24.7)	6 (9.8)	8 (100)	2 (100)	2 (100)
BCL2 gene rearrangement	15 (22.7)	7 (19.4)	0 (0)	1 (33.3)	7 (36.8)	15 (20.5)	5 (8.2)	8 (100)	0 (0)	2 (100)
BCL6 gene rearrangement	21 (31.8)	12 (33.3)	1 (12.5)	1 (33.3)	7 (36.8)	25 (34.2)	21 (34.4)	0 (0)	2 (100)	2 (100)

Abbreviations: DEL, double-expressor lymphoma; DHL, double-hit lymphoma; IHC, immunohistochemistry; TEL, triple-expressor lymphoma; THL, triple-hit lymphoma.

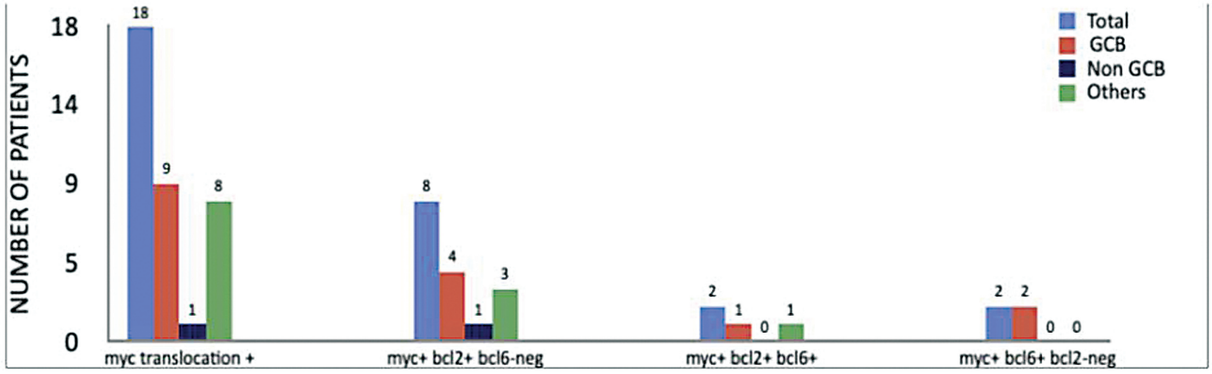

Fig. 2 Distribution of germinal center B cell (GCB) versus non-GCB histologies among patients with MYC translocation, double-hit lymphoma (DHL) with BCL2, DHL with BCL6, and triple-hit lymphoma, expressed in the number of patients.

patients in the nonhit lymphoma groups were found to have MYC IHC positive.

BCL2 IHC Positivity in Hit Lymphomas

All patients in THL (two patients), DHL-BCL2 (eight patients), and DHL-BCL6 (two patients) had BCL2-IHC positive, while this was 34 out of 61 (55%) in the standard group.

BCL6 IHC Positivity in Hit Lymphomas

Two out of 2 (100%) patients were each in the THL and DHL-BCL6 groups, while 6 of the 8 patients in the DHL-BCL2 group had BCL6-IHC positivity; 40 out of 61 patients (65%) have BCL6-IHC positivity (►**Table 1**).

MYC Gene Rearrangements in Expressor Lymphomas

MYC gene rearrangements were seen in 2 of the 8 (25%) DEL with BCL2, 2 of the 3 (66.7%) DEL with BCL6, and 10 of the 19 (52.63%) TELs. Only 7 of the 36 (19.4%) nonhit lymphoma patients had MYC gene rearrangements.

BCL2 Gene Rearrangements in Expressor Lymphomas

One out of 3 (33%) and 7 out of 19 (36%) patients had BCL2 gene rearrangements in the TEL and DEL-BCL6 groups, respectively, while the DEL-BCL2 groups had 0 out of 8 patients (0%). Seven of the 36 (19.4%) patients in the nonexpressor group had BCL2 gene rearrangements.

BCL6 Gene Rearrangements in Expressor Lymphomas

one out of the 8 (12.5%), 1 out of 3 (33.3%), and 7 out of 19 (36.8%) patients in the DEL-BCL2, DEL-BCL6, and TEL groups had BCL6 gene rearrangements, whereas this was 12 out of 36 (33.33%) in the nonexpressor group (►**Table 2**).

From the above observations, it is clear that the DHL or THL had a high incidence of protein expression of MYC, BCL2, and BCL6. But the DEL or TELs did not reciprocate the same high proportion of gene rearrangements in them.

If MYC Expression and Double Protein Expression Were Used to Screen for Eligibility to Perform FISH in Our Study?

Among the 36 patients with MYC IHC negative, 3 of them had DHL. Hence, 4.5% of hit lymphomas would be missed if MYC-IHC were used as a screening tool.

Among the 30 patients who had DEL (double protein expression [DPE]), 9 had DHL or THL. Among the 12 DHLs, 3 did not show double expression. Hence, if DPE was used to screen patients before doing FISH, we would miss 4.5% of DHL patients.

DPE as a screening test showed a sensitivity of 75% and a negative predictive value of 91.7% (►**Table 3**).

Discussion

DHLs have distinct clinical, pathologic, and molecular characteristics compared with nonexpressor or nonhit lymphomas and have a more aggressive clinical course and poor response to standard treatment.

Histomorphology

The study population included NHLs other than DLBCL in two other studies. Salam et al[12] reported on 81 patients with

Table 2 Cross tabulation to show the correlation between gene rearrangements and expression status of MYC, BCL2, and BCL6

		Gene abnormality		Total
		Hit lymphoma	Nonhit lymphoma	
IHC expression status	Expressor lymphomas	9	21	30
	Nonexpressor lymphomas	3	33	36
Total		12	54	66

Abbreviation: IHC, immunohistochemistry.

Table 3 Sensitivity, specificity, PPV, NPV, and accuracy of double protein expression when gene rearrangements by FISH when considered as the gold standard for predicting double-hit lymphoma status

Parameter	Value
Sensitivity	75.0
Specificity	61.1
PPV	30.0
NPV	91.7
Accuracy	63.6

Abbreviations: FISH, fluorescence in situ hybridization; NPV, negative predictive value; PPV, positive predictive value.

NHL, of whom 57 had DLBCL, 15 had follicular lymphoma, 4 had marginal zone lymphoma, and 1 each had other types of lymphomas. Landsburg et al's[7] study had DLBCL and BCL-u with features intermediate between DLBCL and Burkitt's lymphoma. Most other studies had patients comprised entirely of DLBCL.[6,8–11,15]

The Cell of Origin: GCB versus Non-GCB Subtype in DHL-BCL2 and THL Lymphomas

The COO findings among hit lymphomas of Zhang et al[11] correlated with our study in that the proportion of GCB is equal to that of non-GCB cases in DHLs.

Ninety-two percent of DHL-BCL2 was of GCB origin in the study by Landsburg et al.[7] In another study by the same author, the GCB subtype in the DHL-BCL2 group was 90%, while it was only 58% in non-DH lymphomas.[16] Mehta et al[15] had a significantly high GCB phenotype in DHL patients as compared with DEL or nonhit DLBCL. Scott et al[6] have shown that BCL2 translocation is a GCB phenomenon because most of the patients in the DHL-BCL2 group and THL in their study were of the GCB subtype, and no non-GCB type was noted in this group. In addition to Hans classification, Scott et al[6] have verified the COO by Lymph2Cx, and both techniques showed that DHL and THL were predominantly composed of the GCB type and not the non-GCB type.

Immunohistochemistry

In the study by Scott et al,[6] there was a significant difference in the positivity of IHCs of MYC, BCL2, CD10, DPE, and MUM1 for the DHL-BCL2 and THL groups, but not in the DHL-BCL6 group as compared with the total cohort, which was similar to our findings.

Expression of MYC, BCL2, and BCL6 in Hit Lymphomas

MYC

The expression of MYC in the total cohort in our study was 45.45%, which was comparable to other studies, which ranged from 33% in Johnson et al[5] to 46% in Huang et al,[10] 47% in Zhang et al,[11] and 48% in Scott et al.[6]

The MYC expression in the hit lymphomas in our study was 75%, while this was 80%[6] in the largest reported study, and this is comparable with our results.

Most of the studies, except two,[12,16] had DLBCL alone as the study population, although there were eight patients with Burkitt's lymphoma and three with HGBL in our study, which could explain the relative increase in MYC expression in our study.

Salam et al[12] and Landsburg et al[16] are two other studies where histologies other than DLBCL were also included. However, these two studies have restricted the reporting of their data to gene rearrangements alone, and protein expression data are not published.

BCL2

The percentage of BCL2 expression in the total cohort in our study was 63%, which correlates well with Zhang et al (85%)[11] and Huang et al (75%),[10] but Scott et al[6] had a much lesser BCL2 expression in their total cohort.

The proportion of patients with hit lymphomas who expressed BCL2 in our study was 100%, which correlated well with the proportion of BCL2 expression in the hit lymphoma cohort of the other two studies.

BCL6

BCL6 expression in the total cohort in our study was 68.5%, while the same ranged from 55% in Zhang et al[11] to 85% in Scott et al.[6] The proportion of patients with BCL6 expression in the hit lymphomas was similar to ours in both studies available for comparison.

Double/Triple Expression

In our study, the incidence of DELs was higher (45%) than reported in other studies. This can, in turn, be explained by the increased MYC expression. The DPE was much lower in all other studies, ranging from 11.6% (Mehta et al[15]), 13.3% (Ting et al[9]), 34% (Scott et al[6]), 35% (Zhang et al[11]), to 39% (Huang et al[10]).

Gene Rearrangements in Hit Lymphomas

The total number of patients with MYC, BCL2, and BCL6 translocations in this study was 18 (24.65%), 15 (20.54%), and 25 (34.24%), respectively.

The MYC gene rearrangement incidence was similar to our study at 23.8% in Zhang et al,[11] but it was much lower at 5.3, 7, 5.8, and 10% in Scott et al, Salam et al, Ting et al, and Huang et al respectively.[6,9,10,12]

The BCL2 gene rearrangement incidence in our study was 20.5%. This was much higher in Zhang et al[11] (42.86%) and was much lower in other studies such as Salam et al (5.3%), Ting et al (5.8%), and Huang et al (16.9%).[9,10,12]

The BCL6 gene rearrangements were generally higher than MYC and BCL2 in all studies. In our study, BCL6 translocations comprised 34.2% ($n = 25$). The incidence of BCL6 translocations was comparably lower in Salam et al, Ting et al, Huang et al, and Zhang et al at 17.5, 14.2, 16.9, and 14.2%, respectively.[9–12]

The comparatively higher incidence of all translocations in our study may be because of the different patient populations being studied.

Incidence of Double- and Triple-Hit Lymphomas

The incidence of DHL/THL in Barraclough et al,[17] Huang et al,[10] and Scott et al[6] was 7.2, 7.7, and 7.9%, respectively, while it was much lower at 1.6, 4, and 4.8% in Ting et al,[9] Mehta et al,[15] and Zhang et al,[11] respectively. The higher incidence of DHLs in our study at 16.43% may be due to the difference in the patient population being studied.

Double Protein Expression Is Not Recommended as a Screening Tool

If double expression status was used to screen patients before FISH, 4.55% of hit lymphoma would be missed. This is similar to that found in Kluk et al[18] and Sakr and Cook.[19] But Scott et al[6] and Horn et al[20] predicted that 20 and 30%, respectively, of the DHL/THL cases would be missed if MYC-IHC were to be used as a screening tool.

Conclusion

The incidence of DHL or THL among aggressive lymphomas, including DLBCL, Burkitt's lymphoma, and HGBL was 16.43%. The GCB subtype of histology was predominantly seen in hit lymphomas. MYC, BCL2, and BCL6 expressions do not correlate well with translocations of these genes. DPE cannot be used for screening to decide which patients should undergo FISH.

Patient Consent

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

Ethical Considerations

The study was submitted and cleared by the Institutional Ethical Committee-Biomedical Research, Apollo Hospitals, Chennai, EC Reg No. EC/NEW/INST/2020/527 NABH Certification No. EC-CT-2018-0045 on April 29, 2021, as per approval number ASH-DNB-042/04-21. 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. All patients included in the study were provided with a patient information leaflet and consented to be part of the study on the informed consent form.

Source of Funding

None declared.

Conflict of Interest

None declared.

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Can Artificial Intelligence Assist Nurses in Planning the Nursing Care of a Child with Acute Lymphoblastic Leukemia?

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Abstract

Background Today, the rapid development of artificial intelligence (AI) based technologies and their widespread use in the health sector offer important opportunities in the field of nursing practices and patient care. Therefore, there is a need for research to better understand and evaluate the impact of AI-based applications on nursing. In this study, we aimed to determine and evaluate the nursing care practices planned by AI for a pediatric case diagnosed with acute lymphoblastic leukemia.

Methods Within the scope of the study, a hospitalization scenario for a child diagnosed with acute lymphoblastic leukemia was created by the researchers in line with the literature. The scenario and five open-ended questions were directed to ChatGPT (OpenAI), an AI application. The responses were evaluated in line with the literature.

Results It was determined that AI did not include the measurement of vital signs in the planning of nursing care for the current problems of the child diagnosed with acute lymphoblastic leukemia, and could not detect anemia, thrombocytopenia, alopecia, and nausea/vomiting among the possible problems of the child.

Conclusion Although it is thought to address the patient in a multidimensional way with its responses, the knowledge, experience, and equipment of the nurse are needed to filter the information provided by AI. In line with the data obtained, it is recommended that nurses make a final assessment for the appropriateness of the intervention when deciding to follow an AI-based recommendation.

Keywords

- acute lymphoblastic leukemia
- artificial intelligence
- nursing care
- pediatric nursing

Introduction

Artificial intelligence (AI) is a general term used to describe techniques developed to teach computers to mimic human-like cognitive functions such as learning, reasoning, communicating, and decision-making.[1] Research on the use of AI-based technologies in health care has increased in recent years, and AI applications have great potential to assist patient care and improve care practices.[2]

During clinical practice, nurses are always faced with situations that require careful decision-making. Inherent in the decisions to be made is the choice between choices that can be complex.[3] It is critical for the nurse to reach an effective clinical decision through comprehensive information sources and reliable information in a supportive environment.[4] With the support of AI technology, it is aimed to improve empirical nursing knowledge and facilitate nursing care by creating clinical nursing guidance for different patients.[5]

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If AI algorithms can be effectively translated into patient care practices, both nurses and patients can benefit.[6] In this regard, it is necessary to determine the contributions of AI-based technologies to nursing.[1] One of these AI-based technologies is ChatGPT, which has recently gained a lot of attention. Developed by OpenAI (OpenAI, L.L.C., San Francisco, CA, United States), ChatGPT is a chatbot (a program that can understand and generate responses using a text-based interface) and generative pretrained transformer.[7] Despite the growing popularity and performance of ChatGPT, there is still a lack of studies evaluating its use in clinical practice.[8] ChatGPT is programmed to have a humanlike conversation and is tasked with answering questions, including clinical situations that clinicians encounter in their daily practice. However, there are concerns that ChatGPT can be directly relied upon to generate scientific evidence for clinical decision-making. This is because it is debatable whether ChatGPT can replace the standard practice of evidence synthesis, which involves literature review, critical appraisal, data collection, and combining the findings of various studies to obtain an evidence-based answer to a clinical question.[9]

In the literature, studies utilizing AI in the care delivery of pediatric hemato-oncology patients are rare. In one study, ChatGPT was asked, "What should be said when leukemia is suspected in a child under the age of 7?" and it was found that ChatGPT generated a text appropriate for the child's age, explained the illness in simple terms, and reassured the child that they would not be alone in the hospital.[10] With such capabilities, ChatGPT can be a significant support tool in the care of pediatric hemato-oncology patients.

As both potential users of AI-based technologies and professional caregivers, nurses are in a key position to drive the evolution of modern AI in nursing.[11] Studies contributing to the literature are needed to elucidate the impact of AI-based technologies on nursing, including implementation and clinical outcomes.[2] Therefore, this study aimed to determine and evaluate the care practices planned by ChatGPT for a pediatric patient diagnosed with acute lymphoblastic leukemia (ALL).

Methods

In the first stage of this review study, the researchers created a hospitalization scenario of a child diagnosed with ALL in line with the literature.[12–14] ChatGPT, an AI application, was used for this study. Five open-ended questions were directed to the AI with the scenario prepared to evaluate ChatGPT's suggestions for nursing care in this case. The questions were directed to the AI one by one and the responses from ChatGPT were recorded. In the discussion part of this study, the responses obtained from ChatGPT are evaluated in line with the experiences of the researchers and literature information.

- What are the nursing interventions for this child's current problems?
- What are the nursing interventions for this child's possible problems?
- What are the nursing interventions for this child's laboratory findings?
- What are the nursing interventions for the side effects of the medicines used by this child?
- What are the nursing interventions that should be addressed psychosocially for this child?

Case Presentation

An 11-year-old girl, H.A., was admitted to the hospital with complaints of abdominal pain, loss of appetite, weakness, cough, and fever (38.2°C). As a result of bone marrow aspiration, a diagnosis of ALL was made and she was hospitalized for chemotherapy. Anthropometric measurements revealed a weight of 25 kg (<3rd percentile) and a height of 135 cm (3th–10th percentile). The patient's laboratory findings were hemoglobin (HGB): 9.7 g/dL; hematocrit (HCT): 28.2%; red blood cell (RBC): 3.42 10^6/μL; white blood cell (WBC): 10.56 10^3/μL; platelet (PLT): 125 10^3/μL; and C-reactive protein (CRP): 4.3 mg/L. The physician prescribed methylprednisolone 60 mg/m^2/d intravenously (divided into 3 doses), vincristine sulfate 1.5 mg/m^2/dose intravenously, L-asparaginase 5,000 IU/m^2/dose as a 1-hour infusion, methotrexate 12 mg, and metoclopramide hydrochloric acid (HCL; as needed).

Discussion

The treatment and care of leukemia is complex.[15] Pediatric nurses are at the forefront of the care provided to these patients.[16] In the literature, it is stated that AI applications such as ChatGPT may have benefits in terms of patient-specific planning in the treatment and care of complex diseases.[17] Within the scope of this study, we aimed to examine and evaluate the practices that AI can predict in pediatric nursing care of a complex disease such as ALL. For this purpose, in the first question we directed to ChatGPT, it is seen that nursing care for the current problems of the patient is presented in a very comprehensive manner. Vital signs are important indicators for monitoring the side effects of chemotherapeutic drugs and early detection of complications related to the disease. Vital signs such as body temperature, pulse, respiration, and blood pressure are important parameters that should be carefully monitored in children with ALL.[14] When the AI's responses to our case and our input question were examined, no output regarding the measurement of vital signs within the scope of the child's nursing care was found. It was observed that only body temperature monitoring was included under the fever management output (►**Supplementary File -** Box. Nursing Interventions for Current Health Problems).

AI provided comprehensive nursing interventions in identifying potential problems and offering solutions for a child with ALL. In addition to physical problems such as pain, infection, mucositis, and nutritional problems that may develop in the child, the answers suggesting to address the psychosocial aspects of the child and family are noteworthy in terms of holistic care delivery. On the other hand, although AI addressed neutropenic precautions, it did not address the issue of food

hygiene that should be considered in a child with ALL and low neutrophil count. Similarly, although the child in this case had a low PLT count, there were no recommendations for the assessment of thrombocytopenia and management of bleeding risk. It is known that children with ALL experience nausea and vomiting due to chemotherapeutic agents and this is a symptom that decreases the quality of life of children with ALL. It is remarkable that nausea and vomiting were not included among the potential problems (►**Supplementary File -** Box. Nursing Interventions for Possible Health Problems).

In the AI's responses to the laboratory findings of our patient, it was observed that data unrelated to the laboratory findings were presented. Irrelevant data (pain management, psychosocial support, education, etc.) may cause AI to create confusion on clinician nurses, which may cause time loss in patient care planning or delivery. This may indicate the need for nurses to filter the information needed by the patient from the AI's responses, and thus the need for knowledge and experience on the part of the nurse. Moreover, although the case had anemic findings, there was no suggestion in the outputs of the AI to include iron-rich foods in the child's diet (►**Supplementary File - Box.** Nursing Interventions for Laboratory Findings).

AI provided detailed information separately for five different drugs included in the child's order. However, it was observed that alopecia, a common and widespread side effect of chemotherapeutics, was not mentioned. In addition, in the case presented to the AI, although the patient's order stated that methylprednisolone would be administered intravenously, the AI ignored this input and suggested "Administer the medication with food or milk to minimize gastrointestinal upset" for oral medication use (►**Supplementary File -** Box. Nursing Interventions for Side Effects of the Medicines). In health care, accuracy of information is very important and the presence of misinformation can lead to serious problems. It is very important for nurses to conduct a meticulous review process to ensure that AI practices do not cause patient safety problems.

When the responses within the scope of psychosocial care of the child with ALL were examined, it was seen that AI offered suggestions in line with atraumatic, holistic, and family-centered care approaches. In addition, the fact that AI addresses issues such as sibling support, self-care for caregivers, cultural and spiritual needs, which may be overlooked by nurses in the case of a disease such as ALL, whose care is quite complex, was evaluated as an innovation that can support nursing care. It can be stated that this approach of AI has positive results in terms of strengthening the capacity of nurses to provide multidimensional care (►**Supplementary File -** Box. Psychosocial Nursing Interventions).

Conclusion

AI can be considered as a guiding technological development in nursing care. In this study, which evaluated the responses of AI application for the care of a child with ALL, AI was found to provide comprehensive recommendations in patient care. In the near future, AI technology may be a supportive source of information for nurses to provide individualized evidence-based care. Although it is thought to address the patient in a multidimensional way with its responses, knowledge, experience, and equipment of the nurse are needed to filter the information provided by AI. Although AI provides detailed information about patient care, it makes this assessment with the data collected by the nurse's observations, physical examination practices, and communication skills in planning care for the patient. Nursing care involves dynamic processes such as collecting data from the patient and observing the patient. Therefore, in order to receive information from AI, the nurse needs to determine the current data and changes related to the patient and present them to AI. Nurses can make more effective decisions by integrating the information provided by AI with their clinical experience and theoretical knowledge. For instance, they can evaluate AI recommendations in light of the patient's individual condition and medical history, while also considering the patient's specific needs. In this way, by combining theory and practice, nurses can utilize the information provided by AI to its fullest extent. In line with the data we obtained, we should emphasize the need for nurses to make a final assessment of the appropriateness of the intervention when deciding to follow an AI-based recommendation. Additionally, nurses must remember that each patient is unique, with individual characteristics and needs, and the importance of personalized care should not be forgotten. In the future, it is recommended to use comprehensive research designs that include clinical nurses in the integration of AI-based technologies into practice. Such research, by incorporating the experiences and feedback of nurses, can facilitate the more effective and safe integration of AI into patient care processes.

Limitations

This study has some limitations. First, ChatGPT is sensitive to the prompts addressed to it. Therefore, the outputs generated by ChatGPT may change depending on changes in the input questions. Another limitation is that ChatGPT cannot make recommendations on clinical guidelines and medicines developed after September 2021.[18] In addition to all of this, NANDA (North American Nursing Diagnosis Association) plays a significant role in professional nursing practices by providing a systematic approach to assessing and caring for patients. However, it is noted that ChatGPT is still not sufficiently specific for nursing diagnoses and can sometimes lead to incorrect responses.[19] Therefore, we could not approach the case included in our study directly through NANDA nursing diagnoses.

Ethical Considerations

The case used in this study was prepared by the researchers in line with the literature. Therefore, ethics committee permission was not obtained.

This manuscript has been read and approved by all the authors.

Patient Consent

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Conflict of Interest
None declared.

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Extraordinary Presentation of Chronic Pyelonephritis as Retroperitoneal Mass: An Image Report

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Abstract

Here we are presenting a unique presentation of chronic pyelonephritis as retroperitoneal mass. It produced a diagnostic dilemma, and final diagnosis was confirmed after histopathology report.

Keywords

- retroperitoneal mass
- chronic pyelonephritis
- tumor

A 43-year-old man presented to us with the complaint of abdominal pain for 8 months and progressive increase in abdominal girth. He had no comorbidities. On examination, he had generalized abdominal pain, abdomen was distended and soft, a vague mass was palpable incorporating left hypochondrium, left lumbar, left iliac, umbilical, and hypogastrium region of abdomen. No free fluid was percussible, no renal angle tenderness was present, patient's bilateral testis were normal, and there was no generalized lymphadenopathy. Patient did not have complaint of any urinary symptoms. There was no history of fever, weight loss, or fatigue. Instead, patient gave history of gaining weight over the course of 8 months due to abdominal mass, which was not quantified. He already had an ultrasound of the whole abdomen done outside, which described a 20.6×25.1 cm left hypochondriac region mass extending to the lower abdomen. He had visited a local urologist with the ultrasound but could not present any documents of the same. On investigation, the patient's serum tumor markers like alpha-fetoprotein, beta-human chorionic gonadotropin, lactate dehydrogenase, blood investigations like complete blood count, kidney function test were within normal laboratory range. Urine analysis was not performed. Serum tumor markers were done as a workup for Azzopardi tumor. Contrast-enhanced computed tomography scan of thorax–abdomen–pelvis described a large multiloculated cystic mass, which was seen arising within the retroperitoneum occupying the left half of the abdominal cavity. The mass shows multiple enhancing septations within. The mass measures approximately $23 \times 14 \times 28$ cm. It showed few dense calcific foci within. No enhancing solid component is seen within the mass. Left kidney was not visualized.

Right kidney was unremarkable. There was no evidence of hydronephrosis. The mass was displacing the spleen cranially with elevation of left diaphragm along with displacement of the peritoneal cavity and its content to the right (►**Figs. 1**, **2**). Since the presentation of the mass was of a retroperitoneal tumor probably arising from the left kidney, a diethylenetriamine penta-acetic acid renal scan was also performed, which showed nonfunctioning left kidney and normally functioning right kidney. After due deliberation, a decision was taken to excise the retroperitoneal mass expecting a form of sarcoma in the final histopathology report arising from kidney. Midline incision was given, and retroperitoneum was entered after mobilizing white line of Toldt. R0 resection of the mass was done along with hilar lymph nodes. Patient was discharged on postoperative day 6 and the final histopathology report came

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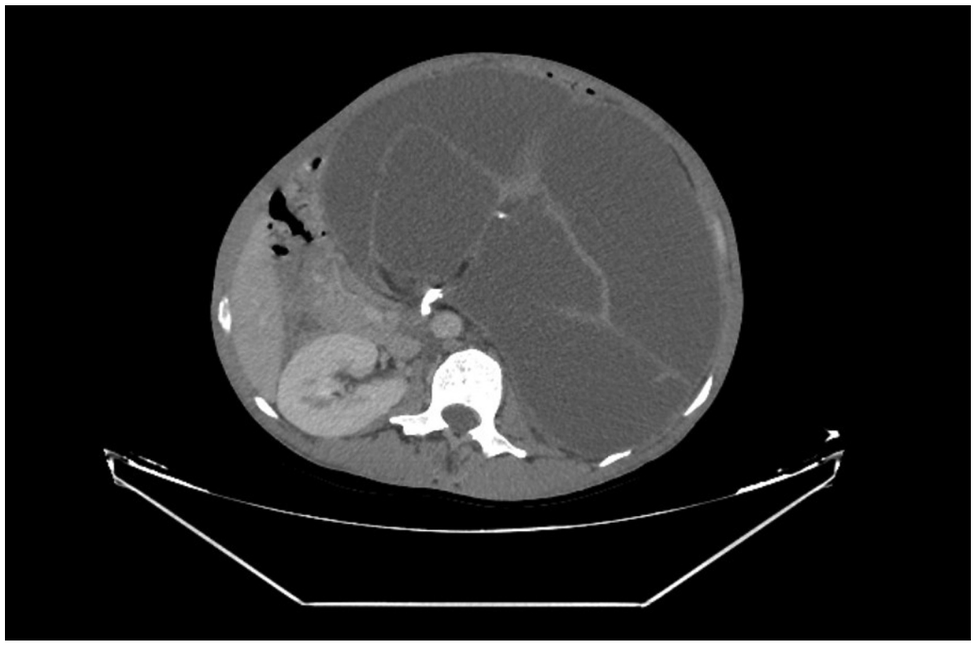

Fig. 1 Cross-sectional contrast-enhanced computed tomography at the level of right kidney is showing a cystic mass with nonenhancing septations acquiring more than half of peritoneal cavity displacing contents to right side.

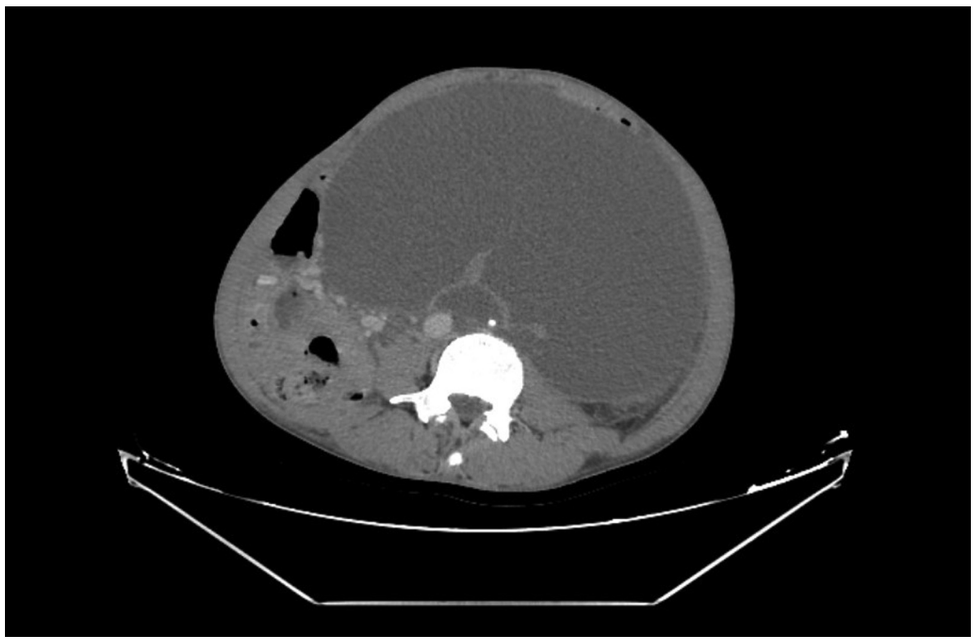

Fig. 2 Cross-sectional contrast-enhanced computed tomography below the level of right kidney is showing a cystic mass acquiring more than two third of peritoneal cavity displacing contents to right side.

out as chronic pyelonephritis described as measuring $29 \times 15 \times 10$ cm comprising kidney (measures $7 \times 4 \times 4$ cm) and ureter (measures 4.5×0.2 cm) along with multilocular cysts lesion measuring 29×15 cm. On our search, chronic pyelonephritis presenting as a retroperitoneal mass was not found in any English medical literature. Chronic pyelonephritis mostly present as proteinuria, hypertension, and hematuria. Intraoperatively, kidney size of more than 10 cm is the common

presentation.[1] One of the lacunae in our workup for this case was no urine analysis test was performed. Our treatment approach for this case was on the point, but provisional diagnosis was not correct. This case shows that chronic pyelonephritis needs to be kept as differential diagnosis in cases of retroperitoneal mass if one of the kidneys is involved. It is one of the rarest case presentations of chronic pyelonephritis.

Conflict of Interest
None declared.

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Chart Review and Practical Recommendations for the Use of Methadone as an Alternative to Opioid Rotation in the Management of Cancer-Related Pain

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Abstract

Introduction Palliative care, with a focus on enhancing the quality of life for individuals facing life-limiting illnesses, relies on effective pain management as a fundamental component. Opioids, particularly methadone, play a crucial role in addressing moderate to severe pain in palliative care due to their unique pharmacological properties. Methadone, a long-acting opioid agonist and N-methyl-D-aspartate receptor antagonist, is valuable for treating both nociceptive and neuropathic pain. However, the transition to methadone from other opioids requires careful consideration.

Objectives This study examines the use of methadone as an alternative to morphine or fentanyl for managing refractory cancer pain in a tertiary care hospital in India.

Methods We conducted a retrospective analysis of anonymized medical records of cancer patients initiated on oral methadone for pain management at a tertiary cancer center's palliative medicine outpatient clinic from February 2020 to June 2021. Data included demographic characteristics, pain descriptions, concurrent analgesic use, reasons for transitioning to methadone, rotation methods, methadone dosages, clinical outcomes, adverse effects, and treatment discontinuations. Patients were routinely followed up, with pain scores, morphine equivalent daily doses, and methadone requirements recorded at each visit.

Results Forty-four patients received methadone, either as a coanalgesic (41/44) or primary opioid (3/44). Refractory cancer pain, with a neuropathic component, was the predominant indication for methadone use. Following the methadone initiation, all patients experienced significant pain relief. Median daily methadone dose increased from 5 to 7.5 mg after 1 week. Adverse effects were minimal, with one patient experiencing QTc interval prolongation. Patient-specific factors often necessitated deviations from equianalgesic conversion tables in determining methadone dosages.

Conclusion Methadone offers a viable option for refractory cancer pain when conventional treatments fall short. Physicians should prioritize personalized titration

Keywords
- methadone
- cancer pain
- opioid rotation
- equianalgesic conversion
- pain relief
- side effects

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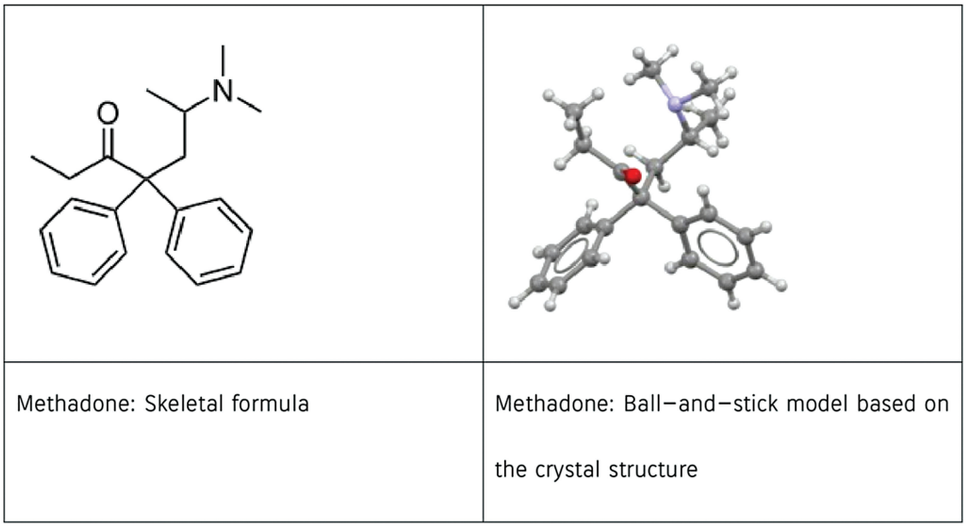
and thorough assessment during opioid rotation, rather than relying solely on conversion tables. Further research is needed to explore alternative approaches for opioid rotation and to expand our understanding of methadone's optimal use in cancer pain management.

Introduction

Palliative care aims to enhance the quality of life for individuals facing life-limiting illnesses, focusing on the relief of suffering and the provision of physical, psychosocial, and spiritual support. Effective pain management lies at the core of palliative care.[1] Opioids have long been the mainstay of analgesic therapy in palliative care, providing effective pain relief for patients with moderate to severe pain. Among the opioids used, methadone has emerged as a distinctive and increasingly utilized option. Originally developed as a long-acting analgesic and an alternative to morphine for chronic pain management, methadone's unique pharmacological properties make it an asset in the palliative care setting.[2]

As a long-acting opioid agonist and N-methyl-D-aspartate (NMDA) receptor antagonist, methadone is useful for treating both nociceptive and neuropathic pain. It is a racemic combination of R and S enantiomers, with R being 8 to 50 times more powerful than the S enantiomer[3] (►**Fig. 1**). Methadone's mechanism of action involves blocking the reuptake of serotonin and norepinephrine, as well as binding noncompetitively to NMDA receptors. Furthermore, methadone interacts with opioid receptors, specifically the mu, kappa, and delta subtypes.[3] Its distinct mode of action is thought to be what reduces the potential tolerance that can arise with long-term opioid pain management. Patients with renal and hepatic impairment, who have few options left for opiates, benefit the most from methadone. Rotations to methadone are complex. Various methods can be employed to transition to methadone, including rapid conversion or the stop-and-go approach (which entails ceasing the initial opioid and switching to methadone at an equianalgesic dosage), cross tapering, the 3-day switch (which involves gradually reducing the current opioid dosage while progressively increasing the daily methadone dose over a 3-day period) and ad libitum (wherein patients self-adjust their methadone dosage using pro re nata). However, no evidence suggests that any of these methods is more efficacious than the others.[2,4,5]

In India, methadone was first made available in 2012 as a substitute therapy drug to treat opioid addiction. In 2014, it was made available commercially for the treatment of pain.[6] In 2017, oral methadone was added to the 20th edition of the World Health Organization's standard list of essential medications.[7] Methadone proves highly effective in the treatment of complex pain syndromes often seen in India's prevalent types of cancer, such as head and neck, genitourinary, breast, and gastrointestinal cancers. These pain syndromes involve a combination of nociceptive and neuropathic pain.[8] In clinical practice, when considering the appropriate choice among methadone, morphine, fentanyl, buprenorphine, tapentadol, and tramadol for managing cancer pain, it is imperative to adopt a comprehensive and



Methadone: Skeletal formula	Methadone: Ball–and–stick model based on the crystal structure

Fig. 1 Methadone chemical formula. (Adapted from: PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. PubChem Compound Summary for CID 4095, Methadone [cited August 28, 2023]. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Methadone.)

evidence-based approach. These analgesic agents possess varying pharmacological profiles, efficacy, and potential adverse effects. The selection of the most suitable option should be guided by the principles of personalized medicine, considering patient-specific factors and the nature of the pain being addressed.[9] Methadone, an opioid with NMDA receptor antagonist properties, can be considered when there is neuropathic pain or opioid resistance. However, careful dose titration and monitoring of electrocardiogram parameters, especially the QT interval, are crucial due to the potential for QT prolongation and torsades de pointes (TdP) (distinctive form of polymorphic ventricular tachycardia).[4] Morphine, a classic opioid, remains a cornerstone for cancer pain management. Its wide range of formulations (immediate-release, extended-release, and intravenous) allows tailoring of treatment to the patient's pain pattern. The equianalgesic conversions between opioids should be followed meticulously to ensure a smooth transition.[10] Fentanyl, available in various delivery forms (transdermal patches, buccal lozenges, and parenteral formulations), is advantageous for patients who have difficulty with oral medications such as in head–neck cancers or require rapid onset of action (intravenous route). Dose titration is essential to avoid overdosing when switching to or from fentanyl due to its potent nature.[11] Buprenorphine, a partial mu-opioid receptor agonist, can be considered for patients with a history of substance abuse or for those needing long-term pain management. Its ceiling effect on respiratory depression contributes to its relative safety, although its efficacy in severe cancer pain might be limited.[12] Tapentadol could be considered for moderate to severe pain with neuropathic components. It combines mu-opioid agonism with norepinephrine reuptake inhibition. Side effects include potential for serotonin syndrome in combination with serotonergic medications.[13] Tramadol, an atypical opioid, has both mu-opioid receptor agonism and serotonin–norepinephrine reuptake inhibition. It can be useful in mild to moderate cancer pain with a neuropathic component. Caution is advised in patients with a predisposition to seizures, as tramadol lowers the seizure threshold.[14]

In all cases, an individualized approach should be followed, considering factors such as the patient's pain intensity, previous opioid exposure, comorbidities, concurrent medications, and potential drug interactions. Regular assessment of pain relief and monitoring for adverse effects are pivotal. Multidisciplinary collaboration involving pain specialists, oncologists, pharmacists, and palliative care experts can further optimize pain management strategies (►**Supplementary Materials 1** and **2**). Cost can be a guiding factor while choosing pain medications, especially in settings where patients must pay out of pocket.[15] For a weeks' supply, fentanyl is available as expensive transdermal patches (for fentanyl 25 µg transdermal patch [one patch lasts for 3 days]: INR 1000 – INR 2000 compared with INR 150 – INR 300 for equianalgesic dose of morphine, INR 600 – INR 1000 for buprenorphine patch [one patch lasts for 7 days], INR 400 – INR 600 for tapentadol, and INR 200 – INR 300 for tramadol). Methadone, on the other hand, is cheap (INR 150 – INR 200 for equianalgesic dose of methadone supply for a week) and a suitable alternative for opioid rotation in refractory cases.[16]

The primary goal of this study is to provide a review of our experience using methadone as either a coanalgesic or primary option for cancer pain management. Additionally, we aim to increase awareness about the use of opioids, particularly methadone, for cancer pain relief.

Methods

We conducted a retrospective analysis of the anonymized medical records of cancer patients who were initiated on oral methadone for pain management at the palliative medicine outpatient clinic in a tertiary cancer center. The review encompassed the period from February 2020 to June 2021. The data extracted from patients' medical records encompass various aspects, including demographic characteristics, diagnosis, comprehensive pain description (including type, severity, and baseline morphine equivalent daily doses [MEDD]), concurrent usage of other analgesics, rationale for transitioning to methadone, approach employed for rotation, ultimate and anticipated methadone dosage, clinical outcomes related to pain management, any observed adverse effects, and information pertaining to the withholding or discontinuation of methadone treatment. These patients were routinely followed up at 1-, 2-, and 4-week intervals after starting methadone, and the pain scores, MEDD, and methadone requirements were charted at each follow-up.

Results

Between February 2020 and June 2021, 44 patients received methadone as a coanalgesic (41/44) or primary opioid (3/44) (►**Table 1**). Among the participants, 24 individuals experienced a combination of somatic nociceptive and neuropathic pain, while 15 individuals reported a mixture of visceral nociceptive and neuropathic pain. Additionally, three participants exclusively had somatic nociceptive pain, and two patients specifically reported neuropathic pain. Refractory cancer pain not responding to "standard" treatments was the indication for methadone for 41 patients, the rest had a deranged liver function and one deranged renal function. Before methadone, the median numeric rating scale pain score was 8 (severe), standard deviation (SD) 1.4, with 53.49% MEDD ranging from 60 to 120 mg (median: 120 mg, SD: 74.9 mg). Forty-one had undergone rotation to methadone as a coanalgesic with a nonmethadone opioid, while three were solely on methadone. All patients received adjuvant analgesics as needed. The method used for opioid conversion was as per dosing ratio given by Ripamonti et al for opioid switching.[17] Those patients where low-dose methadone was added as coanalgesic, opioid semi-switching was done using the method described by Mercadante et al.[18] The dose was gradually titrated up in subsequent outpatient consultations as per requirement.

Following the initiation of methadone therapy, all patients experienced sufficient pain relief. The median daily dose of methadone upon commencement was 5 mg

Table 1 Demographics of patients ($n = 44$)

Items	Numbers	Percentage
Gender distribution		
Male	24	55.81%
Female	20	44.19%
Age distribution (y)		
18–20	2	4.65%
21–40	16	37.21%
41–60	17	37.21%
61–80	9	20.93%
Site of primary cancer		
Bone and soft tissue	8	18.60%
Breast	4	6.98%
Gastrointestinal	3	6.98%
Genito urinary	9	20.93%
Head and neck	8	18.60%
Hematological and lymphoid	1	2.33%
Hepatopancreatobiliary	3	6.98%
Lung	7	16.28%
Primitive neuroectodermal tumor	1	2.33%
Comorbidities		
None	32	74.42%
Hypertension	5	11.63%
Diabetes mellitus	3	4.65%
Hepatitis B	1	2.33%
Multiple comorbidities	3	6.98%
Type of pain[a]		
Somatic nociceptive and neuropathic	24	53.49%
Visceral nociceptive and neuropathic	15	34.88%
Pure neuropathic	2	4.65%
Somatic nociceptive	3	6.98%
MEDD prior to starting methadone (mg)		
60–120	23	53.49%
121–180	5	9.30%
181–240	14	32.56%
>240	2	4.65%
	Median score	Standard deviation
Numerical rating scale for pain (0–10)		
Before starting on methadone	8	1.4
Week 1	3	1.6[b]
Week 2	2	1.6[b]
Week 4	2	1.3
MEDD (mg)		
Before starting on methadone	120	74.9
Week 1	60	40.5[b]

(*Continued*)

Table 1 (*Continued*)

Items	Numbers	Percentage
Week 2	60	44.5
Week 4	60	24.8
Starting daily dose of methadone (mg)		
At start	5	1.5
Week 1	7.5	2
Week 2	7.5	2.8
Week 4	10	3.2
QTc interval before starting methadone (ms)		
Before starting on methadone	418	25.2
Week 1	447	26
Week 2	428.5	25.1
Week 4	425.5	18.5

Abbreviation: MEDD, morphine equivalent daily doses.
[a]Bone pain in 16, myofascial pain in 7,and opioid-induced hyperalgesia in 2.
[b]$p < 0.01$ on Wilcoxon's signed ranks test.

(SD 1.5 mg), which increased to 7.5 mg (SD 2 mg) after 1 week. All patients were successfully followed up on an outpatient/home care basis with adequate pain control. Among the patients who initiated methadone therapy, none experienced adverse effects such as respiratory depression. Nonetheless, in one patient, we had to discontinue the methadone after 8 weeks due to a prolonged QTc interval and chest discomfort. It is important to note that the median QTc interval remained below 425 milliseconds for the remaining patients. Ten patients developed constipation, in 3 patients, methadone was stopped by treating oncologists, 5 patients continued to be on methadone, 7 stopped by themselves as they had adequate pain control even without methadone, 2 stopped as they went back to villages where they had no access to methadone, 22 patients died due to disease progression within this time, and in 4 patients, interventional procedures were performed for pain management.

Discussion

Methadone is an effective opioid for treating cancer pain, with a safety profile like that of other opioids. Rotation to methadone was helpful in all 44 patients with cancer pain who were being treated in this study. The neuropathic component of the pain in 40 patients may be the cause of its refractory nature. An evidence-based dose conversion protocol[17,18] was used with all the patients, and it was found to be a quick and efficient technique to determine optimal dose of methadone needed in an outpatient context. Neither the MEDD nor the projected methadone dose corresponded to the actual methadone dose that was needed. Considering how refractory pain can be, the MEDD may have underestimated the number of people who needed an increase in opioid dosage but did not receive one. Transitioning from morphine to methadone can present complexities due to the possibility of incomplete cross-tolerance. In future prospective studies, it would be valuable to examine patient-controlled approaches such as the Morley–Makin method as a potential alternative to fixed ratio equianalgesic conversion tables. This is because these patient-controlled regimes enable the use of a lower dosage of methadone (sometimes as low as 1/30th of the previous MEDD) while still achieving satisfactory analgesic effects.[12] In this study, it was observed that a subset of patients ($n = 2$) reported increased pain levels with higher dosages of methadone. It is important to note that the experience of pain in these cases may have been influenced by a range of factors such as psychological, spiritual, or social discomfort. Exploring and addressing these complex issues surrounding pain and its multifaceted nature and opioid safety were beyond the scope of this study (►**Supplementary Material 3**).

Methadone, especially at higher doses, can cause TdP and prolongation of the QTc interval. The risk is higher when the QTc interval is more than 450 milliseconds. Those having a QTc interval at baseline longer than 500 milliseconds should not be initiated on methadone.[19] The median time for QTc was found to be 425 milliseconds in this analysis.

Given the limited participant size and retrospective design of the case series, it is important to approach the interpretation of these findings with caution. Our comparison table also does not include adjuvant analgesics or the different suggested methadone conversion factors. Our results contribute to the mounting body of research suggesting that patients' maintenance doses of methadone may be much different from what is suggested by equianalgesic conversion tables and guidelines.[20]

Conclusion

When conventional drugs and therapies prove insufficient in providing relief for severe and unmanageable cancer

pain, an alternative option is to consider opioid rotation to methadone. The recommended approach for opioid rotation to methadone, as advised by manufacturers, demonstrates both safety and effectiveness, particularly when conducted under appropriate supervision in outpatient settings. Interestingly, our observations indicate that actual dosages of methadone often differ slightly from those obtained through equianalgesic conversion tables and guidelines. Consequently, physicians should not solely rely on conversion tables when opting for opioid rotation, but instead prioritize personalized titration, thorough assessment, and diligent clinical monitoring during and following the rotation process to mitigate the risk of significant adverse effects. Additional research is necessary to explore the potential utility of a modified Morley–Makin approach in facilitating the rotation from other opioids to methadone.

Pointers for Practice

- Methadone is an inexpensive alternative to morphine that is safe for patients with renal failure and provides a longer duration of action.
- It may also have an advantage in treating neuropathic pain, although this has not been conclusively proven.
- However, due to its long and variable elimination half-life, methadone is not ideal when rapid dose adjustments are necessary. Oral methadone should not be increased more frequently than every 4 days.
- Converting doses between methadone and other opioids is complex and can be more dangerous than with other opioids. It is recommended to consult with pain or palliative specialists familiar with methadone use.
- It is important to educate patients and their families about the use of methadone, as they may mistakenly believe that their physician thinks they are an addict.

Disclosure

The responsibility for the writing and content of the article lies solely with the author.

Conflict of Interest

None declared.

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Polatuzumab Vedotin for Diffuse Large B-Cell Lymphoma: Innovation's Allure versus a Time-Honored Tradition

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Abstract

Chemotherapy with R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone) is the standard of care for patients with diffuse large B-cell lymphoma as the first-line therapy. The recent approval of polatuzumab as the first-line therapy after demonstration of its efficacy in the Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma (POLARIX) trial is the first significant change in this treatment regimen over two decades. This concise appraisal of trial evidence and clinical context highlights the limited potential for a clinically significant benefit with the addition of polatuzumab to the first-line therapy for this common hematologic malignancy.

Keywords
- hematology
- internal medicine
- pharmacology

Introduction

Approval of rituximab as a part of the first-line combination therapy for diffuse large B-cell lymphoma (DLBCL) in 2006 was an important milestone. It was the first monoclonal antibody approved for cancer that substantially improved the overall response rates and progression-free survival (PFS) compared with conventional chemotherapy alone.[1,2] Since then, the R-CHOP (rituximab, cyclophosphamide, Adriamycin, vincristine, prednisolone) drugs have continued to be a part of the first-line therapy for CD20-positive lymphomas. Additionally, no newer agents have shown a similar magnitude of benefit in addition to this chemotherapy backbone.[3] This paradigm was challenged in 2022 when polatuzumab vedotin (antibody–drug conjugate targeting CD79b) was proven effective in newly diagnosed patients with DLBCL in the randomized phase 3 POLARIX trial. This trial randomized 879 newly diagnosed patients to R-CHOP or Polatuzumab- Rituximab - Cyclophosphamide - Adriamycin- Prednisolone (Pola-R-CHP). After a median follow-up period of 28.2 months, PFS was higher in the polatuzumab group (76.7 vs. 70.2%), with no difference in response rates or overall survival (OS) at 2 years.[4] Based on these findings, polatuzumab received Food and Drug Administration (FDA) approval as the first-line therapy for DLBCL in 2023—a major change in upfront therapy for DLBCL for the first time in 20 years. However, the finer details of this clinical trial must be carefully reviewed in the context of real-world practice before effecting a change in a regimen that already has extensive and durable data on its safety and efficacy.

The magnitude of benefit noted with polatuzumab is much lower than that noted with the addition of rituximab to conventional chemotherapy. The addition of rituximab to CHOP was associated with added overall response rates of approximately 10 to 15%, with a notable augmentation of PFS and OS, which is not seen with polatuzumab vedotin.[2] The potential impact of polatuzumab vedotin on an OS benefit may be blunted by an already high efficacy of R-CHOP as the first-line therapy for most patients with DLBCL. In the POLARIX trial, overall response rates of 83.8% were noted in the control arm compared with 85.5% in the intervention arm, With this efficacy, the effect size of the addition of any new drug to the control arm required to detect a statistically significant difference between the two options may be

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substantial, and may not be detected in a trial setting.[5] The OS benefit may be further masked by the availability of effective second-line therapies including salvage chemotherapy, autologous stem cell transplant, and chimeric antigen receptor (CAR) T-cell therapy.

Moreover, achieving a complete response (CR) is important for an aggressive disease like DLBCL, where a majority of patients (>80%) achieving CR are functionally "cured" with less than 20% risk of relapse after 5 years.[6] Similar rates of CR in both arms may further diminish any observable OS benefit in this trial.

Powering this study for OS would considerably prolong the trial duration to greater than 5 years and delay the approval of potentially effective therapy. Several drugs for hematological cancers have recently been approved after assessing surrogate endpoints to reduce the time to regulatory approval.[7] PFS has been espoused as a valid surrogate endpoint by industry-sponsored reviews, lending credence to selecting this as a primary endpoint.[8] Older trials leading to rituximab approval also considered PFS as the primary endpoint. However, the quantitative effect of adding rituximab to chemotherapy on PFS and OS made it a viable first-line therapeutic option.[9] Using endpoints other than OS may enable the achievement of favorable but clinically less relevant endpoints for regulatory approval in the trial setting.

From a policy perspective, the absolute risk reduction for progression from the POLARIX trial is 0.06, indicating a number needed to treat (NNT) of 16.7. At present, the addition of a second drug likely to be priced higher than rituximab may not be viable in India due to the small PFS benefit and high NNT as noted earlier.

R-CHOP therapy's efficacy appears to have plateaued for a subset of patients; hence, introducing a second drug may not enhance treatment outcomes for standard-risk patients. However, specific subgroups of high-risk diseases including double-/triple-hit lymphomas still present an unmet need, and may benefit from a second drug.[10,11] There is a mismatch between double-/triple-hit lymphomas, implying that most "high-risk lymphomas" in this trial are ABC: Activated B Cell Lymphoma (ABC) lymphomas and not true double-/triple-hit lymphomas (highlighted by Dr. Advani, Lymphoma CME on May 5, 2023). A preferential benefit on ABC lymphoma subtypes has been recently highlighted, making it possible that this drug may show greater efficacy when evaluated on this specific patient subset.[12] Similar findings were noted in the POLARIX trial, with no clear benefit in patients younger than 60 years or those with low international prognostic index scores or germinal center subtypes, further limiting the target population for this new drug.

A substantial proportion of patients with high-risk DLBCL subtypes are of advanced age. The development of newer non-chemotherapy-based treatment options is necessary in this subset. Until then, R-CHOP appears to be the best option for most patients with DLBCL. Furthermore, polatuzumab is likely a better option as the second-line therapy till better efficacy than R-CHOP can be documented. The allure of innovation may entice, but older and dependable ways may hold greater value in certain scenarios.

Patient Consent
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Classical Hodgkin Lymphoma Presenting as Cutaneous and Soft Tissue Mass Lesion: An Enigmatic Presentation Posing a Diagnostic Challenge—A Case Report and Review of Literature

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Abstract

Hodgkin lymphoma (HL) is primarily a nodal disease. Cutaneous involvement of HL as a presenting feature is extremely rare. Skin involvement is usually seen as a metachronous involvement in the course of disease and is associated with poor prognosis. Primary skin and soft tissue involvement can be construed as nonhematological, inflammatory, or infective etiology. We report a 14-year-old girl with fever, weight loss, lymphadenopathy, and multiple papular lesions over the right chest wall as initial manifestation of HL, posing a diagnostic challenge. In view of stage IVBE, patient was managed with intensive chemotherapy regimen and is currently free of disease at 6 months of follow-up.

Keywords
- cutaneous
- extranodal
- Hodgkin lymphoma

Introduction

Hodgkin lymphoma (HL), previously known as Hodgkin disease, is a monoclonal lymphoid neoplasm, originating most often from B lymphocytes. It is characterized by the orderly spread of disease from one lymph node group to another and usually begins in lymph nodes.[1] Extranodal invasion of adjacent tissue is observed in up to 15% of cases.[2] Cutaneous involvement of HL as a presenting feature is extremely rare. Skin involvement is usually seen as a metachronous involvement in the course of disease and is associated with poor prognosis. We report here an interesting case of HL in a 14-year-old girl, with fever and lymphadenopathy associated with skin and soft tissue involvement as initial manifestation of HL, which posed a diagnostic challenge. Informed consent was obtained from the parents.

Case Report

A 14-year-old female presented with history of intermittent fever, weight loss, and progressively increasing bilateral neck masses over a period of 6 months. She also reported skin lesions over the right chest wall for 3 months and cough associated with breathlessness for about a month. There were no bone pains or symptoms suggestive of aerodigestive tract involvement.

Examination findings revealed the patient to be thin built, anxious, with pallor and mild respiratory distress, bilateral firm, nontender cervical (level 2–4), supraclavicular and axillary lymphadenopathy. The large conglomerate of fused right cervical nodes measured 7x4cm. There were multiple papules and nodules present over entire right half of chest wall involving breast, infra-axillary, and scapular regions and

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extending to right shoulder and neck, few lesions were ulcerative with purulent discharge (►**Fig. 1**). Systemic examination revealed reduced air entry over right chest.

She was initially investigated elsewhere and in view of generalized lymphadenopathy and right-sided pleural effusion, she was clinicoradiologically diagnosed as pulmonary tuberculosis and had received 5 months of antitubercular therapy. Her skin lesions were suspected as herpes zoster infection and treated with acyclovir. She was unresponsive to both of the therapies, instead the lymph node mass and skin lesions progressed, for which patient was referred to our institute for further management.

At our institute, patient was investigated and initial complete blood counts, erythrocyte sedimentation rate (24 mm), liver and renal function tests were normal. Biopsy from the cutaneous lesion revealed unremarkable epidermis with underlying dermis showing infiltrate of polymorphous population of lymphocytes, histiocytes, and eosinophils. Numerous interspersed large neoplastic cells were seen monolobated to polylobated nuclei having vesicular chromatin and prominent nucleoli (►**Figs. 2A** and **B**). On subsequent immunohistochemical staining, the large scattered neoplastic cells were positive for CD30, PAX-5 (heterogenous; ►**Figs. 2C** and **D**) while negative for CD20, LCA, CD3, CD15, BCL-6, and EBER-ISH. Overall histopathological features were conclusive of classical HL, nodular sclerosis. The concurrent biopsy from lymph node also revealed HL involvement. Staging investigations revealed the bone marrow (aspirate and biopsy) to be uninvolved by HL, while positron emission tomography computed tomography (PET-CT) scan (►**Fig. 3**) showed metabolically active multiple bilateral cervical, supraclavicular, subpectoral, axillary, internal mammary, paratracheal, retrocrural, aortocaval, and para-aortic adenopathy, with extranodal disease involving bone (osteodestructive lesion involving head and shaft of right humerus), soft tissue deposits (right chest wall and right upper arm), right pleural deposits, and right pleural effusion with collapse, hence conforming to stage IVBE. The cross-sectional images reveal that the involvement was contiguous.

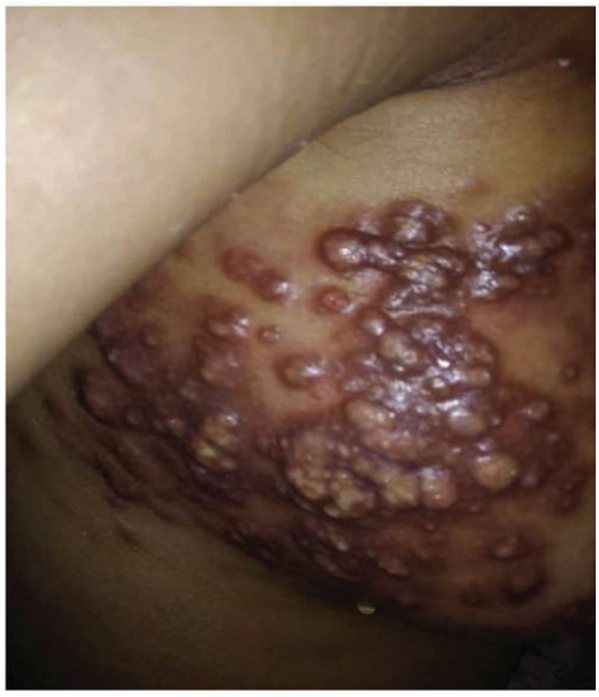

Fig. 1 Multiple papulonodular lesions over right breast and axilla; few lesions show ulceration and purulent discharge.

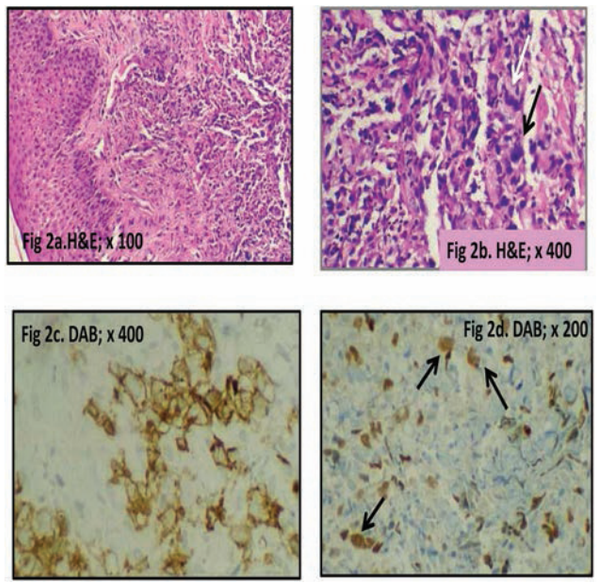

Fig. 2 (A) Section from skin lesion shows unremarkable epidermis with underlying atypical lymphoid infiltrate in dermis. (**B**) Numerous scattered large neoplastic cells (arrow) with multilobated convoluted nuclei (Reed-Sternberg [RS] cells) seen amid lymphoid infiltrate. (**C**) The scattered RS cells show strong membranous positivity for CD30. (**D**) The scattered RS cells (arrow) are also positive for PAX-5. DAB, diaminobenzidine; H&;E, hematoxylin and eosin.

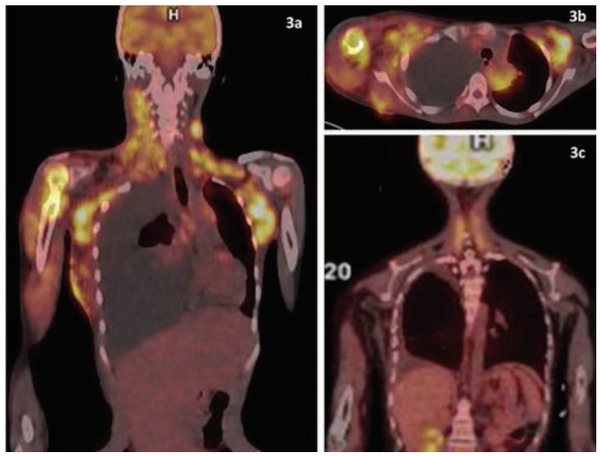

Fig. 3 (A) Whole body positron emission tomography computed tomography scan. Pretreatment image showing metabolically active supradiaphragmatic lymphadenopathy with bone (right humerus), soft tissue (right chest wall), right pleural tissue deposits, and right pleural effusion. (**B**) Pretreatment cross-sectional image shows contiguous involvement. (**C**) Posttreatment image (after 4 cycles) reveals complete metabolic response.

Subsequently, the patient was started on Adriamycin, bleomycin, vinblastine, dacarbazine chemotherapy protocol. However, disease progressed and after one cycle she was put on escalated bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine and prednisolone chemotherapy. Subsequent evaluation with PET-CT showed partial response (50–60%) after two cycles and complete response (including skin, except for residual pleural effusion) after four cycles (►**Fig. 3C**). Hence, further consolidation with high-dose chemotherapy followed by autologous peripheral blood stem cell rescue was undertaken. After the completion of treatment, the patient is free of disease at 6 months of follow-up.

Discussion

HL is primarily a nodal disease and pattern of spread is usually contiguous, spreading from one LN (lymph nodal) region to the next along the lymphatic system. Extranodal invasion of adjacent tissue is observed in up to 15% of cases, while hematogenous spread is seen in 5 to 10% of cases.[2] We have described an interesting case of HL with multiple extranodal sites of disease with significant involvement of skin and soft tissue.

Cutaneous involvement of HL is extremely rare occurring in 0.5 to 3.4% of cases and is more frequently reported in non-HL.[3,4] Although first reported in 1904 by Grosz et al, less than a hundred cases have been reported in literature, and this is the youngest case reported to the best of the author's knowledge (►**Table 1**).[3–10] Various types of skin lesions have been reported; these may be nonspecific findings due to paraneoplastic syndrome or vasculitis, like pruritis, urticaria, hyperpigmentation, or ichthyosis, or due to infiltration of skin by disease.[5,6] The latter may present as nodules, papules, plaques, ulcers, and/or erythroderma, most of which we observed in the present case with biopsy proof of tumor infiltration.[7,8]

Three different pathologic mechanisms have been described in the spread of cutaneous and extranodal HL, of which the most frequent is retrograde lymphatic spread followed by local tumor extension from an underlying nodal or extranodal site. The third mechanism includes hematogenous spread that if extensive has been seen to be associated with poor outcome.[8] Our patient had multiple supradiaphragmatic nodal disease and extranodal disease involving upper end of right humerus, the skin and soft tissue of the right chest wall (up to the midline), right upper arm, and right pleura.

Skin involvement could also occur from direct extension of same side internal mammary or intercostals lymph nodal disease, which is often present along with chest wall involvement. Involvement of skin by HL is usually associated with more advanced disease as was observed in the present case; patient had stage IV disease that was refractory to first-line chemotherapy.[9]

Interestingly, unilateral lung disease has been seen to occur from involved same-sided hilar adenopathy rather than from hematogenous spread. Pleural effusions occur in ~13% of cases and are usually negative for malignant cells.[8]

Single osseous involvement is most likely the result of local spread rather than hematogenous process and is usually a late manifestation. It is believed that local extension from adjacent lymph nodes does not alter staging, although extranodal disease resulting from local infiltration (lung, bone, etc.) is regarded as stage IV as in the present case despite absence of widespread dissemination.

We believe that delay in diagnosis occurred in the present case due to two confounding clinical features that were pleural effusion and skin lesions, both of which are

Table 1 Cutaneous manifestations of Hodgkin lymphoma: review of literature

Author (y)	No	Age (y)	Gender	Symptoms (No)	Duration (mo)	Stage	Treatment	Response (No)
White and Patterson (1985)[8]	16	16–63	Male (9) Female (7)	Lesion on Chest (11) Neck (3) Scalp (2)	32.1 (mean)	IV (7) III (4) II (5)	Multiple regimens	Death due to disease (11) Death due to unrelated cause (1) Lost to follow-up (4)
Jurisić et al (2005)[9]	1	77	Female	Nodule arms and abdomen	6	II B	CVPP	No complete resolution
Rubenstein and Duvic (2006)[5]	3		Male (1) Female (2)	Nodule over chest (*n*=2) Rash on trunk (*n*=1)	–	–	–	–
Isao et al (2007)[4]	1	44	Male	Nodule on back	32	IV B	Multiple regimens	Died
Dhull et al (2012)[7]	1	22	Female	Fungating mass over mid-chest	24	IV B	ABVD	Disease free
Khawandanah et al (2014)[6]	1	46	Male	Rash on chest and neck	3	IV E	AVD/Bend/GCD	Disease free 8 mo
Goyal et al (2014)[3]	4	50 21 25 28	Female Male Female Male	Nodules over neck Ulcer over sternum Nodule on breast Rash arms and legs	1 6 12 4	IV B IV B IV B IV B	ABVD-RT ABVD-RT ABVD ABVD	Disease free 3 y Recurrence in 6 mo Disease free Disease free 2.5 y

Abbreviations: ABVD, Adriamycin, bleomycin, vinblastine, and dacarbazine; Bend, bendamustine; CVPP, cyclophosphamide, vincristine, procarbazine, prednisone; GCD, gemcitabine, carboplatin, dexamethasone; No, number of participants; RT, radiotherapy.

uncommon primary clinical presentations of HL. With modern therapy, advanced HL has 5-year failure-free survival rate of ~80%.[10] Hence, it is important for the oncologist and pathologist to suspect and diagnose skin lesions due to HL, especially in a pediatric population.

Conclusion

To conclude, cutaneous involvement, although rare, is a well-recognized manifestation of extranodal HL and can be seen on primary presentation that may mimic nonhematological soft tissue neoplasm. Hence, a diligent histomorphological examination along with intensified chemotherapy regimen is of paramount importance due to distinct therapeutic and prognostic implications.

Declaration of Patient 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 name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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Second Recurrence of Aggressive Angiomyxoma of Labia Majora in a 34-Year-Old Woman: A Case Report and Review of Literature

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Abstract

Aggressive angiomyxoma (AAM) is a rare, slow-growing, benign neoplasm with high recurrence and local invasion. It is usually asymptomatic and frequently presents as a mass affecting the perineal and pelvic regions of women in reproductive age group. We present a rare case of a 34-year-old woman with second recurrence of a giant AAM arising from labia majora. The patient presented with a slow-growing pedunculated mass (around 20 × 12 cm) over the right labia majora for the past 1 year. In the last 10 years, she was operated on two different occasions (2013 and 2015) for similar lesion and was a confirmed case of AAM. Ultrasound of the lesion and magnetic resonance imaging of the abdominopelvic region was suggestive of recurrent AAM. The patient underwent en bloc dissection of the tumor with negative margin. Histopathological examination confirmed the diagnosis of recurrent AAM. En bloc dissection with negative margin leads to complete removal of tumor mass. However, long-term follow-up with annual magnetic resonance imaging is advised.

Keywords

- aggressive angiomyxoma
- case report
- labia majora
- mesenchymal tumor
- pelvic tumors

Introduction

Aggressive angiomyxoma (AAM), a rare myxoid mesenchymal neoplasm, mostly affects women in reproductive age group and principally involves the perineal and pelvic regions.[1] Based on the latest World Health Organization classification of soft tissue tumors, AAM is termed as deep angiomyxoma.[2] It is benign, grows slowly and insidiously, but considered aggressive due to greater propensity for local invasion.[3,4] Thus, to reduce this risk, tumor should be resected with wide local excision with 1 cm margin.[1] Though AAM has a moderate-to-high risk of recurrence, second recurrence is rarely reported.[5,6] Herein, we present a case of a woman with second recurrence of giant AAM arising from labia majora.

Case Description

A 34-year-old female presented with a giant swelling over right labia majora. The swelling grew slowly over the past 1 year. The associated symptoms included perineal heaviness and abstinence due to mass. She had similar lesions in the past for which she was operated twice (2013 and 2015) at a peripheral hospital. Though surgical details were not available, histopathology report confirmed it as a case of AAM of the perineum. There was no other significant medical and family history. Local examination revealed a soft, nontender, nonhyperemic, giant pedunculated mass (≈20 × 12 cm) arising from right labia majora (►**Fig. 1**). There was no evidence of discharge or detectable inguinal lymph nodes.

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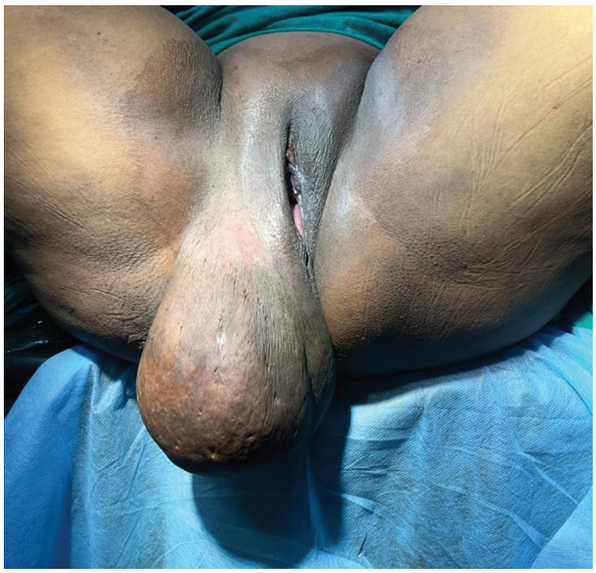

Fig. 1 Recurrent aggressive angiomyxoma arising from right labia majora.

Ultrasound examination of the perineal region demonstrated large well-defined round-to-oval heterogeneous hyperechoic lesion in the right labia majora (≈12.2 × 12.1 × 5 cm). The abdominopelvic T2-weighted magnetic resonance imaging (MRI) revealed hyperintense well-defined soft tissue lesion arising from the perineum involving the right labia majora (19 × 10 × 8.7 cm) with no signs of infiltration into adjacent structures.

The patient underwent wide local excision with negative margin and intraoperative examination revealing large pedunculated mass (25 × 17 × 12 cm) arising from the right labia majora with peduncle (5 × 5 × 5 cm). With a circumferential incision over the stalk, a sharp dissection was performed. Stalk of mass, situated in deep perineal space, was identified, clamped, and cauterized with mass en sac removed and sent for histopathological examination (HPE). The cut section was yellowish-white, with HPE revealing spindle, round, and stellate tumor cells in loose myxoid, edematous, and hypocellular stroma with variably sized blood vessels having hyalinized wall at places, suggesting recurrent AAM (►**Fig. 2A** and **B**). For the last 17 months, the patient is recurrence-free following surgery.

Discussion

Described initially, in 1983, Steeper and Rosai[7] reported nine cases with AAM of the pelvic and perineal region. It commonly affects women (90%) of reproductive age, with highest incidence reported in those aged 20 to 50 years.[4] The predominantly involved regions include the perineum, vulva, vagina, pelvic cavity, hips, and crissum. Men are rarely affected, with a male-to-female ratio of 1:6. Though benign, AAM has a high tendency to infiltrate local tissues and recurs within 2 years of resection, at a rate of 35 to 72%.[1,3,4] Likewise, our case was a 34-year-old woman, with involvement of labia majora and presented with second recurrence.

Tumor cells possess estrogen (ER) and progesterone receptors (PR), and thus, tend to grow in pregnancy and are sensitive to hormonal interventions.[5] Though the pathogenesis still remains unclear, it is associated with chromosomal translocation t(8;12) induced expression of aberrant HMGIC gene and chromosomal changes in the 12q13–15 region.[3] Generally, the patient remains asymptomatic, except for a slow-growing mass. However, some of the cases may present with nonspecific symptoms, including feeling of local pressure, dull aching pain, dyspareunia, dysuria, or urinary retention.[4] On gross examination, AAM has a mean diameter of 12.7 cm (2–60 cm). It may or may not be enveloped and appear spherical or leaf-like. It is a lobulated, solid mass with soft-rubbery consistency.[1,3] Likewise, our case presented with pedunculated, soft, lobulated, enveloped, and giant solid mass (≈20 × 12 cm).

On cut section, AAM is gelatinous and has grayish discoloration.[1] On HPE, the tumor cells appear spindle- or star-

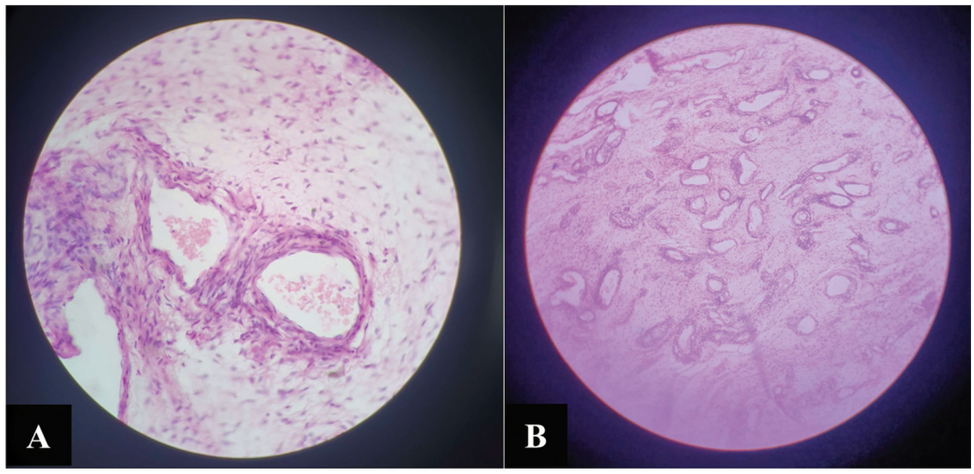

Fig. 2 Histopathological examination. (**A**) Haphazardly dilated vessels (hematoxylin and eosin [H&E] stain, 40×). (**B**) Myxoid loose stroma with spindle to stellate cells (H&E stain, 4×).

shaped, dispersed in mucinous interstitial background, with virtually absent mitoses. The tumor also shows several disordered and randomly scattered blood vessels with varying sizes and wall thickness. The blood vessels are usually surrounded by the eosinophilic spindle cells.[1,3] Likewise, in our case, the HPE illustrated spindle, round, and stellate cells with variably sized blood vessels having hyalinized walls. Other conditions mimicking AAM on HPE include myxoma, myxofibrosarcoma, myxoid liposarcoma, and nerve sheath myxoma. However, presence of prominent vascularity separates AAM from other tumors.[4]

As AAM is a rare tumor, it is associated with 70 to 100% chances of misdiagnosis.[4] Thus, AAM should be distinguished from other clinical conditions. Due to occurrence of AAM in the perineal and pelvic regions, it can be misdiagnosed as hernia or Bartholin cyst.[3] Moreover, owing to identical morphology, it is easy to be labeled as angiomyofibroblastoma and cellular angiofibroma, both are well circumscribed and generally do not recur.[1,3] Thus, AAM should be diagnosed based on the clinical presentation and HPE findings.

The gross examination fails to determine the true extent of AAM. Thus, imaging studies help in reaching the diagnosis. On ultrasound, AAM appears as a cystic or hypoechoic mass.[4] Computed tomography demonstrates tumor with well-defined margin and less attenuation than muscles.[8] T2-weighted MRI illustrates tumor as a hyperintense lesion interspersed with hypointense swirled or layered strands.[1] MRI is demonstrated to be superior to computed tomography in determining the relationship of AAM to the surrounding structures.[4] Likewise, in our case, ultrasound and T2-weighted MRI enabled us to determine AAM recurrence, but MRI provided better details of tumor dimension and extent. Thus, MRI is preferred for diagnosis and follow-up.

AAM is associated with negative tumor maker (CA125, CEA, or CA199), while Hsp90 levels are raised and positively correlate with poor prognosis. Genetically, AAM shows expression of vimentin, smooth muscle actin, muscle-specific actin, desmin, CD34, F8, ER, and PR, while S-100, CK, and CD68 are absent.[1,3] These findings highlight that AAM is characterized by differentiation into fibroblasts and muscle fibroblasts. In our case, owing to prior confirmed diagnosis of AAM, tumor markers were not evaluated. Moreover, due to poor financial status of the patient, immunohistochemistry could not be performed.

To achieve cure, and decrease the recurrence rate, three principles are described for complete resection, including the use of two incision strategy for complete tumor exposure (perineal and transabdominal incision), maintaining the intact capsule, and en bloc removal of any involved organ. Moreover, complete surgical resection with negative margin is desired. Incomplete resection is responsible for tumor seeding and recurrence.[1] Medical management with adjunct therapies, including gonadotropin-releasing hormone agonist, leads to tumor shrinkage or prevents recurrence in certain cases. Moreover, due to ER/PR positivity, targeted ER/PR therapies may be of potential value. Other modalities, including vascular embolism, may be used as adjunctive, while the role of chemotherapy and radiotherapy remains undetermined.[3,4,8] Likewise, in our case, single incision was used due to perineal location of the tumor and it was removed mass en sac with negative margin. Moreover, due to intact nature of the tumor, seeding at the resection site was not a concern.

Traditionally, AAM is regarded as a nonmetastasizing tumor. However, available literature suggests multiorgan metastasis in exceptional circumstances.[4] The postsurgical management of AAM is not guided by any evidence-based guidelines. However, in light of high local recurrence rate and unforeseen metastasis, patients should be followed over long term until 15 years following the primary surgical resection.

Conclusion

AAM is a benign and locally aggressive tumor. Physical examination and imaging studies help narrow down the differential diagnosis, but HPE is the confirmatory modality. En bloc surgical excision with negative margin is desired to prevent recurrence and a long-term annual follow-up with MRI is advised.

Prior Presentation of Manuscript
None.

Patient Consent
Consent to write and report this case was obtained from the patient.

Authors' Contributions
Concept: M.S., S.S.; Design: M.S., S.S.; Supervision: M.S.; Materials: M.S.; Data collection and/or processing: S.S.; Analysis and/or interpretation: S.S.; Literature search: S.S.; Writing: S.S.; Critical review: M.S., S.S.

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Conflict of Interest
None declared.

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5-Fluorouracil-Induced Leukoencephalopathy: Report of Two Cases and Review of Literature

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Abstract

5-fluorouracil (5FU) forms an important component of chemotherapy regimens used in various gastrointestinal (GI) adenocarcinomas and head and neck squamous cell carcinomas. Leukoencephalopathy is a rare adverse effect of 5FU, mediated by hyperammonemia and hyperlactatemia. We report cases of two patients with GI adenocarcinomas who developed neurological symptoms while on 5FU infusion. The neuroimaging and biochemical parameters were suggestive of toxic leukoencephalopathy. They were managed with cessation of the drug and short-term antiepileptic therapy. We also discuss the pathophysiology of this adverse effect and its management.

Keywords
- 5-fluorouracil
- leukoencephalopathy
- GI malignancies
- neurotoxicity

Introduction

Mucositis, diarrhea, and myelosuppression are the main toxicities of bolus dosing, while hand-foot syndrome and mucositis are the toxicities seen with longer infusions.[1] Acute cerebellar syndrome characterized by ataxia, slurred speech, and nystagmus is the commonest neurotoxicity seen with 5-fluorouracil (5FU). Other reported neurological complication of 5FU is cognitive impairment.[2] The incidence of 5FU-related encephalopathy was 5.7% in a recent retrospective study.[3] With 5FU being one of the commonest drugs used in solid tumors, the odds of encountering a rare Complication like leukoencephalopathy are still high. Our case series elucidates the course of this complication in two patients and their management.

Case 1

A 41-year-old woman without any comorbidities underwent radical left hemicolectomy for adenocarcinoma of the transverse colon. Histopathology showed a pT3N1 disease. The first cycle of adjuvant chemotherapy, modified 5FU + leucovorin + oxaliplatin (mFOLFOX 6) regimen, was started. After 36 hours of infusion, she developed an episode of generalized tonic–clonic seizure. Arterial blood gas (ABG) analysis showed a lactate level of 6.8 mmol/L. Other metabolic parameters including renal and liver function tests, blood glucose, and carbon dioxide levels were normal. Diffusion-weighted (DW) sequences of magnetic resonance imaging (MRI) of the brain showed an inverted **V**-shaped hyperintense lesions in the splenium of the corpus callosum and bilateral centrum semiovale, with corresponding hypointensities on apparent diffusion coefficient (ADC) sequence images (►**Fig. 1A**), suggestive of acute toxic leukoencephalopathy. No corresponding abnormality was found on T2-weighted (T2W) sequences (►**Fig. 1B**). 5FU infusion was stopped and she was treated with levetiracetam. She recovered completely without any neurological deficit and serum lactate level was normal at the time of discharge. Dihydropyrimidine dehydrogenase (DPD) mutation was negative by polymerase chain reaction (PCR). 5FU was discontinued permanently and she did not have recurrence of symptoms on follow-up after 3 months. She completed further adjuvant chemotherapy as capecitabine plus oxaliplatin (CapOx) and continues to be disease free.

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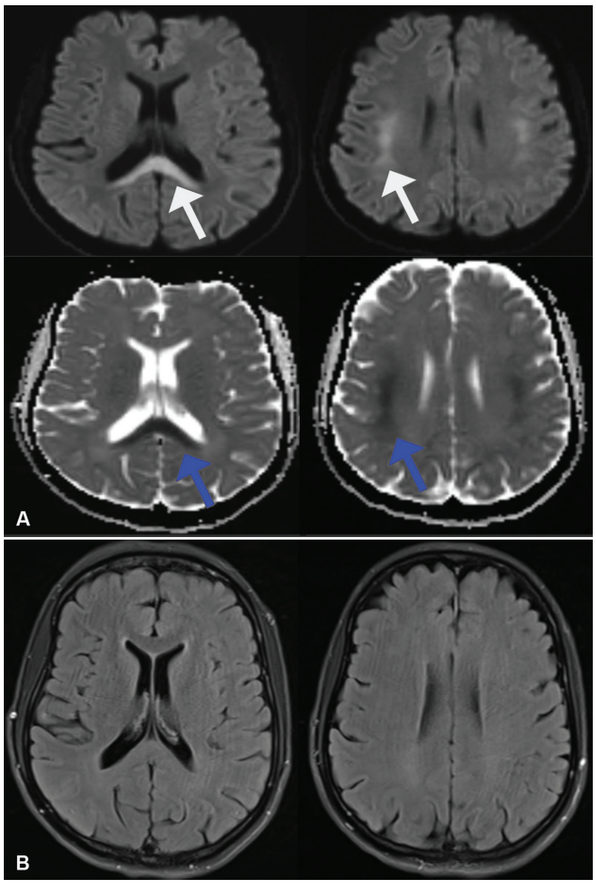

Fig. 1 (A) Diffusion-weighted (DW) sequence showing inverted hyperintensities in the corpus callosum and bilateral subcortical regions (*white arrow*) with corresponding hypointensities on apparent diffusion coefficient (ADC) sequences (*blue arrows*). **(B)** T2-weighted (T2W) sequences not showing any corresponding abnormality.

Case 2

A 36-year-old woman without any comorbidities was diagnosed with metastatic adenocarcinoma of the stomach and was started on mFOLFOX 6 regimen. After 40 hours of infusion, she developed acute onset tremors in the left upper limb. Neurological examination was normal except for the tremors. 5FU infusion was stopped. Her blood lactate level was 3.8 mmol/L and ammonia was 156 mcg/dL. Other metabolic parameters were normal. MRI of the brain showed inverted **V**-shaped hyperintense lesions in the corpus callosum and bilateral centrum semiovale on DW images, with corresponding hypointensity on ADC and subtle hyperintensity on T2W images (►**Fig. 2**). Tremors resolved spontaneously after stopping 5FU. DPD mutation test by PCR was negative. She was started on CapOx regimen subsequently, which she is tolerating well without any recurrence of neurological symptoms.

Discussion

The metabolism of 5FU is mediated by DPD.[4] Ammonia is the end product of 5FU metabolism. When a high dose of 5FU is administered, a proportion of 5FU is metabolized to fluoroacetate. Fluoroacetate inhibits the Krebs cycle resulting in adenosine triphosphate (ATP) deficiency. ATP-dependent urea cycle is responsible for metabolism of ammonia to an excretable form of urea. Lack of ATP results in increased blood ammonia. On the other hand, inhibition of the Krebs cycle results in increased conversion of pyruvate, an end product of glycolysis, into lactate, which is mediated by lactate dehydrogenase. Hyperammonemia and hyperlactatemia lead to leukoencephalopathy.[3]

DPD deficiency is usually associated with severe 5FU-related toxicities like mucositis, diarrhea, myelosuppression, and hand-foot syndrome.[4] Contrary to this, previous case series reported that 5FU leukoencephalopathy is unrelated to DPD deficiency.[5] This is also evident in our patients, both of whom did not have DPD deficiency. It is noteworthy that our patients did not suffer from any of the common 5FU toxicities, similar to the patients described in the retrospective series by Yeh and Cheng.[3] This shows that leukoencephalopathy is due to the end products of 5FU metabolism, rather than 5FU itself.

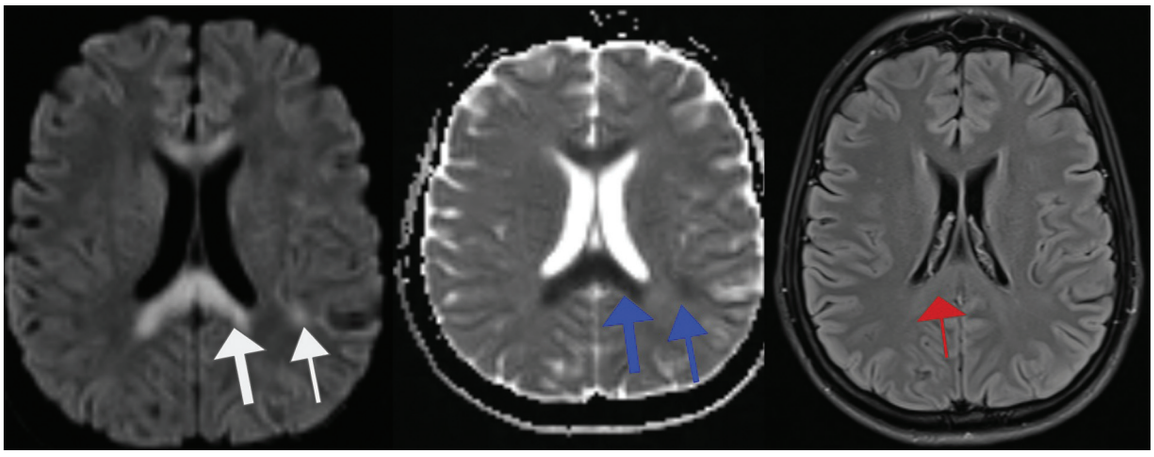

Fig. 2 Diffusion-weighted (DW) sequence showing inverted hyperintensities in the corpus callosum and bilateral subcortical regions (*white arrow*) with corresponding hypointensities on apparent diffusion coefficient sequences (*blue arrows*) and subtle hyperintensity in the corpus callosum on T2-weighted (T2W) sequence (*red arrow*).

A wide spectrum of clinical manifestations varying from slurred speech and focal seizures to cognitive impairment and generalized tonic–clonic seizures has been reported.[3,5–7] One of our patients had upper limb tremors as the sole manifestation. Symptoms are completely reversible once the drug is stopped.[3]

MRI of the brain with DW and ADC sequences is the imaging of choice to diagnose toxic leukoencephalopathy.[8] Hyperintensities involving the corpus callosum and deep white matter on DW and T2W sequences are the typical findings on MRI.[9] In early phases, T2W sequences might show faint hyperintensity with corresponding marked hyperintensity in DW sequences.[10] This could be the reason why T2W sequences did not show any abnormality in one of our patients.

In a case series by Jose et al, all five patients safely continued capecitabine-based chemotherapy as an alternative to 5FU.[5] Our patients also did not develop any neurological symptoms due to capecitabine. This suggests that capecitabine might be a good alternative to those who develop 5FU-induced leukoencephalopathy. However, there are reports of capecitabine-induced leukoencephalopathy as well.[11,12] The literature showed only two case reports of leukoencephalopathy related to tegafur uracil (TFU), another derivative of 5FU.[13,14] Switching to capecitabine or TFU can be considered carefully after discussing the risks of patients developing leukoencephalopathy due to 5FU.

One should also be aware of oxaliplatin-induced posterior reversible encephalopathy syndrome (PRES).[15,16] However, oxaliplatin-induced encephalopathy without typical features of PRES has also been reported. This is a consequence of hyperammonemia caused by oxaliplatin.[17] Our patients received oxaliplatin even after the neurological events without experiencing the events again. This suggests that the encephalopathy in this case might not be related to oxaliplatin.

Leukoencephalopathy is also a complication of newer anticancer agents like antibody drug conjugates. Brentuximab vedotin and polatuzumab vedotin are reported to cause progressive multifocal leukoencephalopathy (PML), a fatal manifestation of reactivation of latent John Cunningham (JC) polyomavirus infection.[18,19] Vascular endothelial growth factor receptor targeting agents like sunitinib, axitinib, lenvatinib, and pazopanib are also known to cause PRES.[20–23] On the other hand, immune checkpoint inhibitors have been used to treat PML.[24]

In the era of newer anticancer drug innovations, it is equally important to promptly recognize, learn, and report the rare toxicities of conventional chemotherapeutic agents because these drugs continue to remain the backbone of anticancer therapy. However, the biggest limitation of reporting a rare toxicity is that it is often in the form of case reports/series, which do not become a part of robust data analysis to generate solid evidence.

Conclusions

5FU-induced leukoencephalopathy is a completely reversible neurological condition that needs prompt identification and timely management. It is important to check the DW and ADC sequences if T2W sequences are normal on brain MRI to diagnose correctly in the early phases of leukoencephalopathy. Capecitabine seems to be a reasonable alternative choice in these patients.

Patient Consent
None declared.

Author Contributions
S.R.N. wrote the manuscript and contributed to the intellectual content of the study. S.H. and A.J. reviewed the manuscript and contributed to the intellectual content of the study. The manuscript has been read and approved by all the authors and it represents honest work.

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Conflict of Interest
None declared.

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Epithelioid Trophoblastic Tumor—A Challenge to Manage due to Its Rare Existence: A Case Report with Review of Literature

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Abstract

Epithelioid trophoblastic tumor (ETT) is the rarest type of gestational trophoblastic neoplasia. It has variable presentations and is an aggressive tumor. Because of its rarity, it is difficult to establish an appropriate diagnosis, management, and follow-up. A woman of age 45 years postmenopausal status with an antecedent term pregnancy 13 years back was diagnosed to have ETT in the hysterectomy specimen. She had come with urinary retention as the tumor was infiltrating the bladder. Beta-human chorionic gonadotropin levels were normal. Immunohistochemistry confirmed the diagnosis. Though metastatic workup was normal, adjuvant multiagent chemotherapy was given as the bladder flap margin was not free of tumor cells and antecedent pregnancy was >4 years. Every new case of ETT needs to be reported to bring about more awareness of the unusual presentations, and it may help come to a consensus for appropriate management.

Keywords

- epithelioid trophoblastic tumor
- gestational trophoblastic neoplasia
- placental site trophoblastic tumor

Introduction

Epithelioid trophoblastic tumor (ETT) is the rarest of gestational trophoblastic neoplasia (GTN) with an incidence of 2.2% of all GTNs.[1] It develops from neoplastic transformation of intermediate trophoblastic cells (ITC). Intermediate trophoblastic tumors exhibit exaggerated placental site, placental site nodule (PSN), placental site trophoblastic tumor (PSTT), and ETT. Implantation type gives rise to PSTT and chorionic type results in ETT. That is the reason both behave similarly and are distinguished mainly by immunohistochemistry (IHC).

Case Report

A woman aged 45 years who had attained menopause 3 years back had presented to an outside hospital with retention of urine. She is para 2 living 2 with her last child birth 13 years back which was a full-term delivery. Prior cycles were regular, and now she did not have postmenopausal bleeding. On evaluation by ultrasound (US) and magnetic resonance imaging (►**Fig. 1**), it showed a solid cystic pelvic mass with calcification of $8 \times 10 \times 7$ cm predominantly on the left side involving the uterus with nonvisualized left ovary with an impression of neoplastic etiology of either ovarian or uterine origin. No ascites or pelvic lymphadenopathy was noted. The tumor marker CA-125 level was 14.6 U/mL. She underwent exploratory laparotomy in that hospital where a uterine tumor was noted infiltrating the bladder anteriorly. Total abdominal hysterectomy with bilateral salpingo-oophorectomy with excision of bladder flap was done. The gross specimen of the uterus showed a tumor size of $8 \times 7.5 \times 5$ cm occupying the lower uterine segment breaching the serosa in the left lateral aspect of the uterus infiltrating the bladder.

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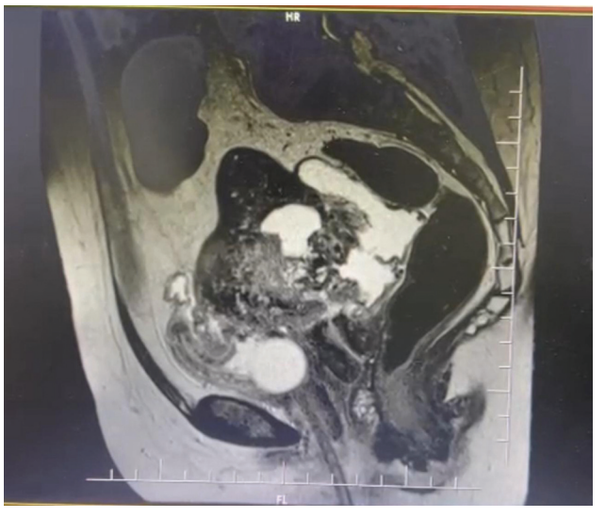

Fig. 1 Magnetic resonance imaging showing pelvic mass infiltrating the bladder.

Microscopy showed epithelioid tumor cell nests with necrosis and calcification with atypical features and a 4 mitosis/10 hpf (high power field) was noted (►**Fig. 2**). Tumor cells were seen involving the adjacent fallopian tube and ovary. The International Federation of Gynecology and Obstetrics (FIGO) stage II was reported as the tumor extends to other genital organs. IHC was asked for confirmation. The patient came to us with an IHC report for further management. IHC markers of cytokeratin (CK) 8/18, P63, and inhibin were positive. SALL4, desmin, and GATA3 were negative. K_i-67 was 20% (►**Fig. 3**). After seeing the histopathological report, β human chorionic gonadotropin (β-hCG) was done and was 4.47 mIU/mL.

A metastatic workup of chest X-ray, β-hCG, and computed tomography (CT) of the lung, abdomen, and pelvis was done and found to be normal. Her FIGO score was 9 (high risk: >40 years old [45 years = 1], index pregnancy [term delivery = 2], time since delivery [13 years = 4], β-hCG (4.47 mIU/mL = 0), size of the tumor (>5 cm = 2), metastasis (none = 0), number

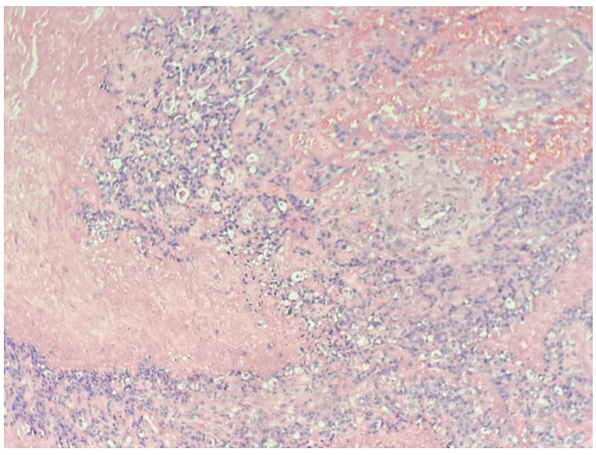

Fig. 2 Microscopy (hematoxylin and eosin stain) showing nests of epithelioid cells with atypical features, with hyalinization and necrosis.

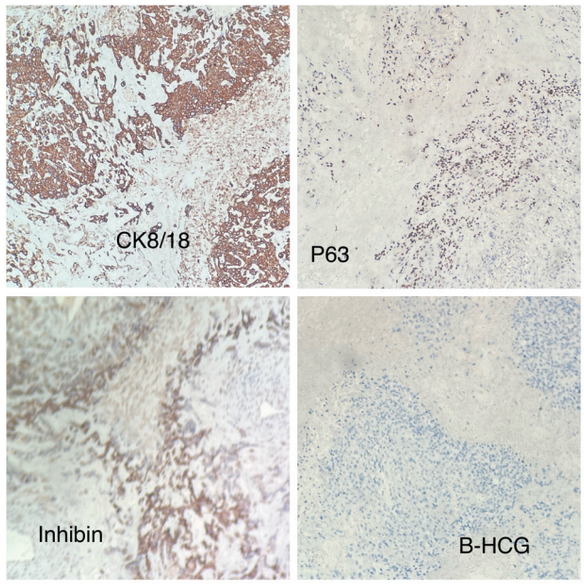

Fig. 3 Immunohistochemistry of tumor cells showing positive expression for cytokeratin (CK8/18), P63, inhibin and negative for β-human chorionic gonadotropin (β-hCG).

of metastasis (none = 0), and previous failed chemotherapy drugs (no = 0). After discussing with the medical oncologist, we came to a decision even though there was no metastasis, we planned to give adjuvant chemotherapy as her antecedent pregnancy was >4 years, and the excised bladder flap margin was not free of tumor cells. Three cycles of etoposide, methotrexate, actinomycin-D, cyclophosphamide, and oncovin (EMA/CO) were planned. The patient received three cycles of the multiagent chemotherapy and has been called for follow-up after 4 weeks. We planned to follow her up regularly with an examination, β-hCG levels, US/contrast-enhanced CT of the abdomen and pelvis for a minimum period of 5 years. The tumor board had decided to only give adjuvant chemotherapy and to follow-up regularly to look for recurrence. Since ETT is radioresistant tumor, radiotherapy was not considered.

Discussion

GTN is a malignant transformation of a gestational event which consists of invasive mole, choriocarcinoma, PSTT, and ETT. Initially, ETT was termed as atypical choriocarcinoma, later Shih and Kurman in 1998 called it as ETT. It is commonly seen in reproductive age group of 15 to 48 years (mean 36 years).[2] Very few cases are reported in postmenopausal age group. Though our patient is 45 years old, she had attained menopause 3 years ago. Most of the patients (67%) present with irregular vaginal bleeding. Other symptoms include abdominal pain, abdominal distension, amenorrhea, or symptoms due to metastasis. Many at times it is incidentally found in a hysterectomy specimen[3] or dilatation and curettage sample. Here, patient had presented with urinary retention probably because the tumor was infiltrating the bladder. Uterus is the primary site (40%) especially the lower

uterine segment just like in this case. The next site which is commonly involved is cervix (31%) and can be confused to squamous cell carcinoma (SCC) of the cervix. The commonest extrauterine site is lung (19%) and other sites where tumor can arise include broad ligament, fallopian tube, ovary, pelvis, and vagina. There are few cases of only isolated lung lesions without any uterine involvement. The tumor size usually ranges from 0.5 to 4 cm. The tumor is usually expansive in the endometrial cavity and locally infiltrates the myometrium or can expand toward the cervical canal. The antecedent pregnancy is either a term delivery (43%), molar (39%), abortion in 18% which may occur 1 to 18 years (mean of 6.2 years) prior to the disease per se.[2] In this case, she had a term delivery nearly 13 years ago which makes us think whether that pregnancy triggered the malignant transformation or is there any other reason or source for development of this tumor. However, antecedent pregnancy >4 years is a poor prognostic factor triggering us to treat her with multiagent chemotherapy following surgery.

Elevated β-hCG is seen in 69% of cases and the levels are mostly $<2{,}500$ mIU/mL unlike in choriocarcinoma where it is very high ($>10{,}000$ mIU/mL).[3] There have been few cases reported where the β-hCG levels were normal,[4] and it becomes difficult to use it for follow-up unlike in choriocarcinoma. The diagnosis of ETT is based on microscopy and IHC. Microscopically, tumor cells appear uniformly mononucleated chorionic type intermediate trophoblasts with round nuclei and eosinophilic cytoplasm and grow in nests. A distinct hyaline-like material and necrosis can also be noted with no significant vascular invasion. ETT has a diffuse expression for markers such as CK/CK 18, epithelial membrane antigen, and P63. It has focal or patchy expression for hCG, human placental lactogen (hPL), and melanoma cell adhesion molecule (MEL-CAM) (CD146). It is positive for inhibin in 20 to 80%.[5] In this case, it was positive for P63, CK/CK 18, and inhibin. The mitotic index varies from 0 to 9 mitosis/hpf. In this case, it was 4 mitosis/hpf. High mitotic index suggests an aggressive tumor. The mean K_i-67 index in ETT is $17.7 + 4.5$.[5]

The differential diagnosis for ETT includes choriocarcinoma, PSTT, PSN, SCC of the cervix, and epithelioid malignant smooth muscle tumor (ESMT). It is easy to differentiate choriocarcinoma as it has both cytotrophoblast and syncytiotrophoblast. PSTT is very infiltrative growth, with prominent vascular invasion, and has larger implantation type ITCs. IHC differentiates PSTT from ETT as PSTT is diffusely positive to hPL, MEL-CAM (CD146) and negative to P63. ETT can be misdiagnosed as SCC of the cervix especially when ETT is located at the cervix and ETT's hyaline-like matrix and necrotic debris can resemble keratin present in the SCC of the cervix. IHC helps in distinguishing as inhibin and CK 18 are positive in ETT but not in the SCC of the cervix. K_i-67 proliferative index is usually 10 to 25% in ETT, whereas it is high ($>50\%$) in choriocarcinoma and in SCC of the cervix. In our case, it was 20%. In ESMT, smooth muscle markers will be positive. There are cases where ETT was misdiagnosed as stage IIIB cancer of the cervix and treated with radiotherapy[6] with no good response to the treatment and also as choriocarcinoma which was treated with only chemotherapy (without surgery) without any positive response.[7] Hence, one should be very vigilant while diagnosing ETT.

Surgery is the preferred treatment as ETT is more chemoresistant than choriocarcinoma. The standard treatment includes total hysterectomy for early-stage disease and resection of metastatic lesions if feasible followed by multiagent chemotherapy in metastatic disease only. Patients with isolated lung lesion had better outcome with excision, although they were classified as stage III. For stage I disease with antecedent pregnancy >48 months or persistent high β-hCG levels and any stage with metastatic disease post-adjuvant platinum-based chemotherapy, either EMA/CO or etoposide, methotrexate, actinomycin-D, etoposide, cisplatin (EMA/EP) is recommended.[8] In this case, she had certain risk factors such as her prior gestational event was 13 years back, age >40 years, and since bladder invasion was noted and margins were not free, we decided to go for multiagent chemotherapy to prevent a recurrence. In a case reported earlier in 2015, a 47-year-old woman with menopausal status and an antecedent pregnancy 16 years back was treated with only surgery and she had a recurrence 4 years later though her β-hCG levels were low following surgery.[5]

Liu et al[1] did a retrospective study on 31 patients and noted stages II to IV, >3 metastatic lesions, and chemotherapy treatment without surgery were associated with adverse recurrence-free survival. FIGO anatomical stage is a significant prognostic factor for ETT. Combined surgery with multiagent chemotherapy is required in metastatic disease or localized disease with persistently positive β-hCG after surgery or if surgery is unfeasible. The preferred chemotherapy is EMA/EP or EMA/CO.

Yang et al revealed univariate analysis showed only stage IV as the only risk factor for poor overall survival rate. In multivariate analysis, an antecedent pregnancy of >120 months, stage IV disease, metastatic disease, and beta-hCG $>1{,}000$ IU/L were significantly associated with poor disease-free interval, and it was suggested to keep a close watch for recurrence. In this study, certain immune checkpoints were also looked for such as programmed death (PD)-L1, B7-H3, and CD105, and these were detected 100% in ETT cases, where PD-L2 and V-domain immunoglobulin suppressor of T-cell activation were detected in 82%, B7-H6 was seen in 18%, and B7-H4 was not detected at all. New therapeutic targets are required to treat nonoperable patients with metastatic chemoresistant diseases. Pembrolizumab (a humanized monoclonal antibody against PD-1) was effective in chemoresistant GTN. The use of immunotherapy and anti-angiogenic treatment are upcoming options even in patients with ETT.[9]

Metastatic disease is seen in 25 to 42% of cases. Metastasis can occur in lung (commonest), liver, brain, small bowel, vagina, and pelvic lymph nodes. Mortality is seen in $>10\%$. The main cause of early death (which can occur <4 weeks from diagnosis) may be mainly due to hemorrhage from

metastatic lesions or because of tumor destruction following administration of full-dose chemotherapy.[8]

Every ETT case needs to be reported to understand this unusual disease so that we can establish a proper means of diagnosis and management.

Conclusion

ETT is a rare and aggressive tumor that can have diverse presentations. Because of limited knowledge of ETT, diagnosis and management remain challenging and can lead to mismanagement and delay in appropriate treatment. Diagnosis is made on morphological grounds, so the pathologists play an important role to detect the disease. This case highlights that ETT can occur in postmenopausal, with no recent gestational event and with low β-hCG levels.

Authors' Contribution

All authors have agreed to the manuscript description. R.C. contributed to data collection and manuscript preparation. V.S. contributed to concept design and clinical treatment. N.N. contributed to manuscript preparation and editing.

Declaration of the Patient Consent Form

Patient's consent has been obtained for publishing her case report and images.

Conflict of Interest

None declared.

Acknowledgment

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Effect of COVID-19 on HPV Vaccination in HIV Individuals: A Preliminary Observation from HIV Clinic in Indochina

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Dear Editor, cervical cancer is the fourth most frequent malignancy and the leading cause of cancer death in women worldwide, despite being highly preventable.[1] In developing countries in Africa and Asia, there is a high incidence of cervical cancer.[1] As earlier noted, cervical cancer frequently ranks as the top cause of cancer-related morbidity and mortality in low-income nations.[1] In clinical oncology, the control of the cervix cancer is an important issue for cancer prevention. Several preventive measures including cervical cytology screening and vaccination are practiced. Several screening methods such as cytology and human papillomavirus (HPV) deoxyribonucleic acid (DNA) are available at present.[1] Cervical cancer vaccination is currently used as standard practices. The worldwide regular vaccination program for all females aged 12 to 16 now includes HPV vaccine.

Due to a compromised immune response to the HPV, the primary cause of almost all cervical malignancies, women with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome are at an especially high risk of developing cervical cancer. Approximately 1 in 20 cases of cervical cancer worldwide is caused by HIV.[1] Cervical cancer risk is much higher for women with HIV. Particularly crucial for developing nations are cervical cancer screening for HIV-positive women and HPV immunization.[2] The highest incidence countries have low HPV vaccine coverage, and screening results vary widely across nations. Cervical cancer risk is much higher for women with HIV.[2] For nations in southern and eastern Africa, where a sizable incidence of cervical cancer related to HIV has added to the existing cervical cancer burden, HPV vaccination and cervical cancer screening for women living with HIV are especially crucial.[2] The global endeavor to end cervical cancer as a public health issue could be aided by increased efforts to combine HIV care with cervical cancer prevention and control, and vice versa.[1] For all women with HIV, immunization against cervical cancer is advised as an oncological preventive intervention. In many developing nations, this technique has just recently been put into effect. There are many obstacles in the way of vaccine coverage.

At present, the new global public health concern is on the coronavirus disease 2019 (COVID-19). The COVID-19 is a viral infection that can result in acute respiratory problem and it can also result in a long-term clinical complication. The outbreak of COVID-19 occurs worldwide and causes problem on the medical care system. In clinical oncology, the interruption of standard regular clinical management is a common problem and it also affects the preventive oncology practice. The interrelationship between cervix cancer and COVID-19, the new emerging disease, is an interesting issue in clinical oncology. Even though HPV has a much longer latency period than COVID-19, the mortality rate for HPV-associated malignancies following infection is comparable.[3] Contrarily, HPV infection advances gradually and covertly over years, and it can result in cervical cancer and even death.[3] Women should embrace HPV vaccination for the long-term prevention of cervical cancer with the same enthusiasm they do COVID-19 testing, according to Miyoshi et al.[3] The COVID-19 pandemic is threatening to derail HPV vaccination uptake in low- and lower-middle-income countries, disrupting routine immunization and delaying the introduction of new vaccines.[4] This has a significant impact on the World Health Organization's cervical cancer elimination strategy, which includes HPV vaccination as well as cervical cancer screening and treatment.[4]

According to a recent assessment, after the COVID-19 attack, girls' vaccination rates for cervical cancer dropped

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from approximately 70%.[3] In this article, the authors reevaluate data from an Indochina China region where HIV infection is common. In this article, the authors reevaluate data from an Indochina China region where HIV infection is common (GPS location: 13.707457633253622, 100.32380528371942). Additionally, this region is COVID-19's second-most recently afflicted region, following China (since January 2020). At present, COVID-19 still exists in this area and the problem of outbreak still required a good monitoring and control. In this situation, girls aged 7 have just received the universal cervical cancer vaccination, which is good for 7 years (start at 2017). Retrospective analysis of the publicly accessible data from a hospital with an HIV clinic was performed. The statistics on the proportion of adult women (over 20 years old) with newly discovered HIV infection are reevaluated. All of them are locals and have never had a vaccination against cervical cancer. At this first visit to the HIV clinic, these cases were made available for the cervical cancer vaccine.

►**Table 1** shows the rate of cervix cancer vaccine cases over a 6-year period, from 2017 to 2021. In total, there are 900 cases of adult females with newly diagnosed HIV who are between the ages of 20 and 59. This is in accordance with the local governmental public health strategy (http://dcd.ddc.moph.go.th/) to promote HPV vaccination among local adult females as much as feasible; thus, a diverse range of female age groups is targeted. All cases are provided with a free HPV vaccination and cervical cytology screening test, according to local practices. The interval between a diagnosis and vaccination is 1 month, and a quadrivalent kind of vaccine is administered. According to the available data, the cervix cancer vaccination rate is not 100%, and many HIV-infected women did not receive vaccination due to refusal. There is no significant change in the cervix cancer vaccination rate when there is a COVID-19 outbreak. This finding is intriguing and contradicts the previous report that the COVID-19 pandemic has an effect on preventive oncology measures.[3] With significant delays to routine immunization and the introduction of new vaccines delayed, the global COVID-19 pandemic threatens to stall the uptake of HPV vaccination in low- and lower-middle-income nations.[4] In low- and lower-middle-income countries, Toh et al recommended implementing four key recommendations for HPV vaccination: increased global financial investment, improved vaccine supply and accelerated use of a single-dose schedule, education and social marketing, and adoption of universal school-based delivery. The effective eradication of cervical cancer would be supported by the adoption of these techniques, along with the support of the international health community.[4]

Table 1 COVID-19 vaccination rate among newly identified HIV infected female adults

Years	Number of newly diagnosed HIV infected female adults	Cervix vaccination rate (%)
2017	159	81.8
2018	145	86.8
2019	158	91.7
2020[a]	179	87.1
2021[a]	259	90.5

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.
[a]Existence of COVID-19.

Regarding the impact of COVID-19 on routine cervix cancer prevention, the problem of preventive manipulation during outbreaks is observed. In contrast to HPV, COVID-19 is feared, individuals avoid public places to avoid getting infected, and many are waiting for a vaccine to be developed. These actions are, in some ways, inevitable, and they can be understood by the basic ideas of behavioral economics, such as the availability heuristic and present bias.[3] A positive outcome can be anticipated if there is a good effort and plan made to handle immunization during the pandemic. Guidelines for Quality Assurance of Cervical Cancer Prevention are currently available, and they are based on integrated HPV vaccination and screening, as well as monitoring the development of the eradication goal.[5] Stakeholders should not stray from this goal as a result of the COVID-19 epidemic, which momentarily halted prevention efforts.[5,6] Health professionals should concentrate on high-risk women and follow cost-effective strategies, including self-sampling, in the immediate postepidemic phase.[7]

Gynecologists should provide the right information to their patients' families, as recommended by Miyoshi et al, so that Japanese women can overcome their cognitive biases and accurately comprehend the relationship between COVID-19 and the susceptibility to and severity of cervical cancer. They should then act on this understanding by getting the HPV vaccine.[3] Generally, attachment to the care of the HIV patient is an important determinant of acceptance of the HPV vaccination.[1] Strategies for the effective implementation of vaccination practices are required. Retention in care, along with reminders about vaccinations and easy access to vaccines at the clinic, may aid in boosting vaccination rates. Active preventive case management is crucial during a public crisis like COVID-19. The current report demonstrates that if a good public health system is in place to promote cancer prevention, the system can still function during the COVID-19 pandemic crisis.

It should be noted that COVID-19 and HPV are distinct organisms with distinct mechanisms of transmission and latency periods. The COVID-19 pandemic's impact on ordinary health care services, such as cervical cancer screening and HPV vaccination, is a legitimate issue. The pandemic's disruption, such as health care system strain, resource allocation, and changes in health care-seeking behavior, may have an impact on the management and prevention of a variety of health disorders, including HPV-related diseases. However, it is critical to treat COVID-19 and HPV latency as distinct problems, focusing on the distinct characteristics and implications of each infection. The impact of COVID-19 on ordinary health care services, as well as its potential ramifications for HPV-related illnesses, would provide vital insights into the larger effects of the virus. It is critical to realize the intricate and diverse link between COVID-19 and HPV latency. While COVID-19 may not have an immediate influence on HPV latency, the pandemic's indirect effects on health care services, vaccination programs, health care-seeking behavior, sexual habits, and mental health

may have an impact on HPV-related outcomes. Continued study and monitoring of these interconnections is critical to ensuring successful management and prevention of HPV-related illnesses during and after the COVID-19 pandemic.

Finally, HIV-positive women are subjected to cervical cancer screening measures such as PAP smear/liquid cytology/HPV DNA testing. More research on this topic is needed to determine the impact of the COVID-19 pandemic. The previous report from Indochina also observed the significant impact of COVID-19 pandemic on cervical cancer screening.[8] The results should follow the same pattern as the HPV vaccination issue.

In conclusion, cervical cancer is a major worldwide health concern, particularly in developing nations, and although being eminently avoidable, it continues to have a high incidence and fatality rate. The link between HPV and cervical cancer, as well as the relevance of prevention methods such as vaccination, are critical to reducing the disease's impact. COVID-19 has had a significant influence on cervical cancer prevention, and further research is needed to understand its implications on screening and immunization efforts. Efforts to integrate HIV care with cervical cancer prevention and control, as well as methods to sustain immunization programs during the pandemic, are critical in the global battle against cervical cancer.

Authors' Contributions

A.K.: ideas, writing, approval.
R.M.: ideas, writing, approval.
V.W.: ideas, supervision, approval.

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Conflict of Interest

None declared.

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Identification of Gut Microbes-related Molecular Subtypes and Their Biomarkers in Colorectal Cancer

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Dear Editor,

We have taken great interest in reading an original article entitled "Identification of gut microbes-related molecular subtypes and their biomarkers in colorectal cancer" published in Aging in 2023.[1]

The authors investigated the intricate relationship between colorectal cancer (CRC) and the gut microbiome. The multifactorial disruptions contributing to CRC were explored, including genetic, epigenetic, and environmental factors such as diet, physical activity, and smoking (►**Fig. 1**). The study conducted a complete analysis, identifying gut microbes-related genes (GMRGs) and developing a new CRC subtype. The authors aimed to find differences in survival prognosis, function of cancer cells, immune infiltration, and immunotherapy efficacy across various CRC subtypes. The ultimate goal was to provide a deeper understanding of CRC focusing on molecular biology, immunology, drug sensitivity, survival prognosis, and disease dynamics, with the aim of enhancing treatment planning and improved patient outcomes.[2,3]

It was noted in the results that the study identified 164 GMRGs and developed a new subtype of CRC which exhibited significant differences compared with other CRC subtypes. Nine genes among the GMRGs showed significant associations with the prognosis of CRC patients. Further

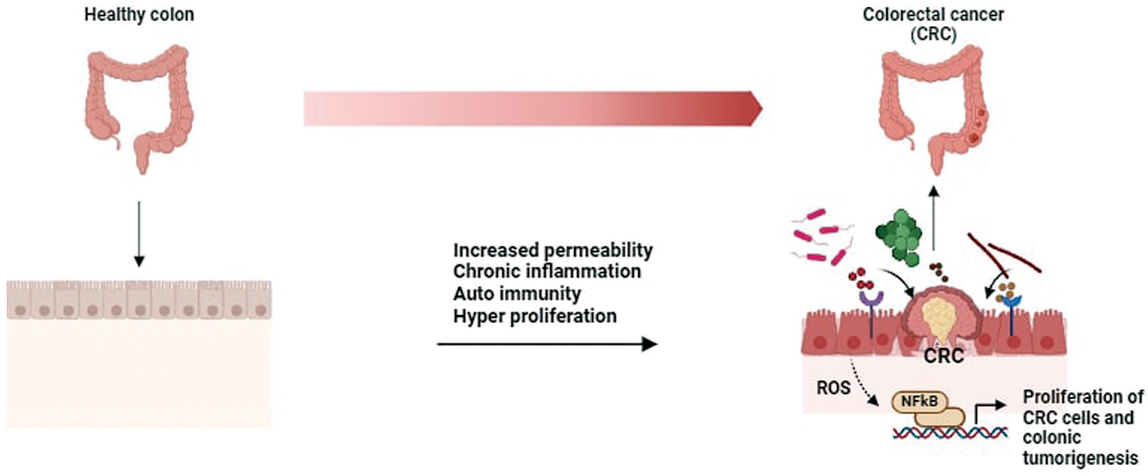

Fig. 1 Overview of the implications of gut bacteria in the development and progression of colorectal cancer. A shift from the normal healthy cells to colorectal cancer cells is shown and other factors effecting the shift are also depicted.

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analysis led to the identification of two key GMRBs (interleukin-7 and BCL10) associated with clinical outcomes. The research offered new perspectives on CRC subtypes and potential biomarkers, highlighting the gut microbiome's impact on cancer progression and treatment responses. The potential implications for patient risk categorization and immunotherapy, present a promising path for further research.[1]

While the CRC and gut microbiome study provides valuable perceptions, potential limitations include support on open data sources, a lack of complete experimental evidence, and a need for further mechanistic understanding. External validation, particularly with additional data sets or clinical studies, is essential to strengthen the proposed molecular subtypes and biomarkers. The study's clinical implications should be carefully considered, and addressing ethical considerations and improving communication for broader understanding would enhance its overall impact.

Patient Consent
None

Ethical Approval
This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest
None declared.

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Introduction Trainee Membership soon during DM/DNB medical oncology training period. This will be mandatory for participating in competitions like ISMPO-TYSA.

A CONVENIENT WAY TO SUBMIT AN ABSTRACT
The ISMPO member will be able to submit abstracts for various ISMPO meetings and conferences directly through the website. Also, eligible for several Awards.

REGISTER NOW AT THE BEST RATES
The membership fees will be revised once medical oncologists from SAARC and other countries are included.
Thus, register now

FREE LIFE MEMBERSHIP
Complimentary Life membership for DM, DNB, and DrNB medical oncology students.