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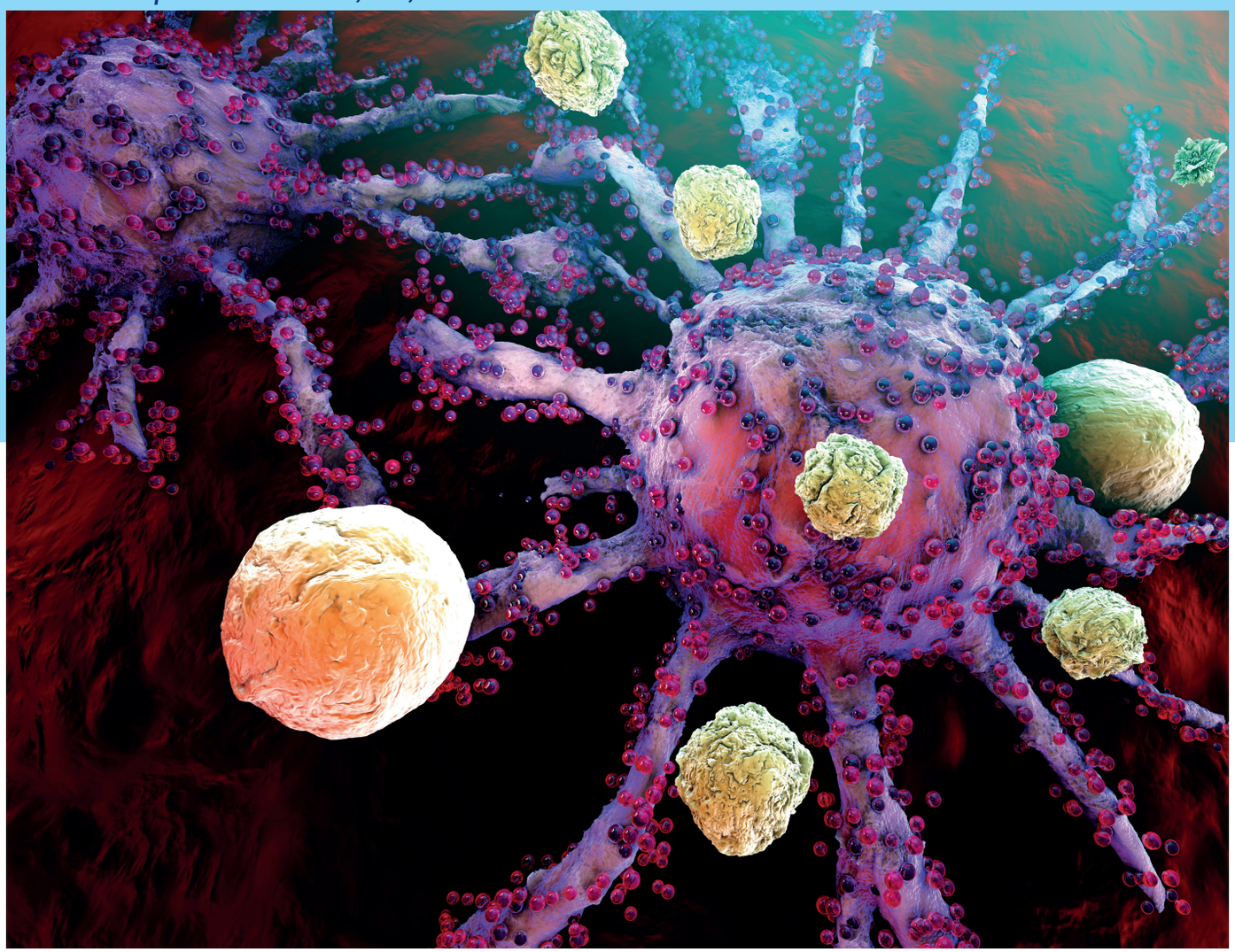
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

Number 4 • Volume 44 • Pages 371–450 • August 2023



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Indian Journal of Medical and Paediatric Oncology is published 6 times a year in February, April, June, August, October, and December by Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India. Tel: +91-120-4556600, Fax: +91-120-455-6649.

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Reference:
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*Unresectable Stage-III NSCLC post CRT **In 1st line Extensive stage SCLC in combination with CT

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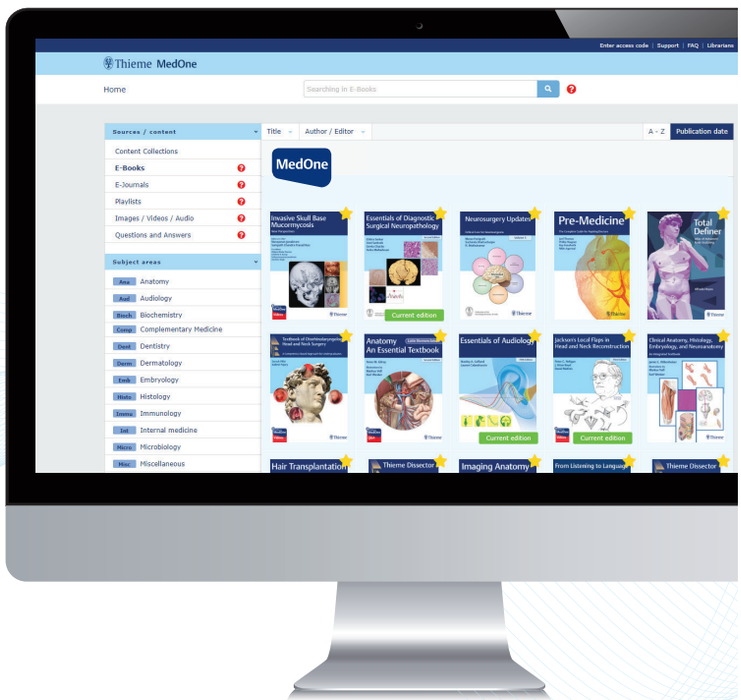

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Abstracts

Ind J Med Paediatr Oncol 2023;44:371–376.

A001. Primary Ewing Sarcoma of Thyroid Gland: A Rare Entity

Varsha Rana[1], Sujit Joshi[1]
[1]Department of Pathology, Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, India

Background: Ewing sarcoma is an aggressive primary neoplasm of the bone, constituting 6 to 8% of all malignant bone tumors. It predominantly affects the adolescents and young adults, and the most common anatomical site being the diaphysis or the metaphysis of the long bones. James Ewing first described it in 1921, and it was classified into "classic" Ewing sarcoma of bone, primitive neuroendocrinal tumor (PNET), and atypical Ewing sarcoma. With the identification of recurrent chromosomal translocation, the most common being the t(11;22)(q24;q12) resulting in the formation of the EWSR1-FLI1 fusion gene; these tumors are now classified as Ewing family of tumors.

Extraskeletal Ewing sarcoma is a rare entity, and its presence in the thyroid is even rarer. Its nonspecific clinical presentation makes it difficult to diagnose preoperatively. We present such a case of Ewing sarcoma arising from the thyroid gland.

Materials and Methods: The following is a case report of a 17-year-old male, who presented with a right-sided neck swelling to the Department of Surgery at Deenanath Mangeshkar Hospital and Research Centre, Pune. Routine investigations like total blood count, ultrasonography, fine-needle aspiration cytology (FNAC) from the neck swelling, laryngoscopy, and positron emission tomography-computed tomography (PET-CT) scan were done. Finally, the decision of total thyroidectomy was taken and was sent for histopathological reporting.

Results: The ultrasonography of the neck swelling revealed the presence of a nonfunctioning solitary thyroid nodule involving the upper pole of the right lobe of thyroid. FNAC was in favor of lymphoproliferative disorder. A large metabolically active lesion involving the entire right lobe of thyroid and measuring approximately 35x29x55 mm was noted on the PET-CT scan, suggesting the possibility of primary malignancy. No extra thyroid extension was seen. No active disease was noted elsewhere in the body.

Laryngoscopy findings were normal. The patient underwent total thyroidectomy with preservation of the parathyroid gland.

The histopathology of the excised tumor was consistent with that of a malignant round cell tumor. The tumor cells were arranged in nests, cords, lobules, and trabeculae separated by fibrous and focally hyalinized stroma. The tumor cells were small sized, with high nucleocytoplasmic ratio, scant cytoplasm, and mildly pleomorphic nuclei with stippled chromatin. No lymphovascular emboli or extrathyroid extension were noted. All regional lymph nodes were free of any metastatic deposits.

The sections were submitted to a panel of immunohistochemical studies. The tumor cells showed diffuse membrane positivity for MiC-2 (CD99), focal cytoplasmic positivity for cytokeratin, diffuse nuclear staining for NKX 2.2, and focal weak positivity for FLI-1. The tumor cells were negative for LCA, synaptophysin, EMA, WT-1, and S-100 protein. On the basis of these findings, the final diagnosis of Ewing sarcoma/PNET of the thyroid gland was established.

Conclusion: Ewing sarcoma is composed of small round cells with an increased nuclear-cytoplasmic ratio that represents a family of small round blue cell tumors of childhood (e.g., retinoblastoma, neuroblastoma, rhabdomyosarcoma, and nephroblastoma). These sarcomas originate from unique mesenchymal progenitor cells due to their similar histology and immunohistochemistry. Despite the fact that Ewing sarcoma of the head and neck region is rare, it must be considered as an important differential diagnosis, along with lymphoblastic lymphoma—its common histologic differential. Immunohistochemical stains play an important role in the diagnosis, the most useful and sensitive markers being CD99 and NKX2.2.

Even though Ewing sarcoma has a poor prognosis, it is concluded that it can be successfully treated with surgical resection and adjuvant chemotherapy

A002. A Rare Case of Synchronous Anal Canal Cervical Cancer: HPV the Causal Culprit?

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[2]Senior Resident, Surgical Oncology Ruby, Hall Clinic, Pune, Maharashtra, India

Background: In India, cervical cancer is the second most common malignancy in females. India shares 25% of the total global burden of carcinoma of cervix. Human papillomavirus (HPV) is presumed to be the most important cause of carcinoma of cervix. Incidence of carcinoma of anal canal is another consequence of HPV is quite rare in India. In this case, we first needed to prove that both are separate primaries, as treatment and stage would change if it was a single entity.

article published online
May 12, 2023

DOI https://doi.org/10.1055/s-0043-1761164.
ISSN 0971-5851.

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	Anal canal cancer	Cervical Cancer
Stage	$cT_3 N_1 M_0$	FIGO IIB
Radiation field	Primary lesion Whole pelvis inguinal node	Primary lesion Whole pelvisCommon iliac nodes
Concurrent CT (prescribed)	5FU+ MMC	CDDP
Concurrent CT (given)	CDDP	CDDP
Technique	IMRT	IMRT
Dose (prescribed)	45Gy/25#	45–50.4 Gy/25–28#
Boost (prescribed)	15Gy/6#	ICA HDR 21Gy/3#
Dose (delivered)	45 Gy/25#	
Boost (delivered)	18 Gy/10#	

Abbreviations: CT, computed tomography; CDDP, cisplatin; HDR, high dose rate; ICA, intracavitary application; IMRT, intensity modulated radiation therapy; MMC, Mitomycin C.
Note: # signifies fractions.

Second radiation treatment planning differed from usual, as adequate dose has to be delivered to both lesions at the same time keeping dosage to normal structures within limit. Also combining all concurrent chemo regimen would have led to increased toxicity.

Materials and Methods: A 64-year-old female presented with a history of per vaginal bleeding for 3 months and intermittent per rectal bleeding for 2 months. On vaginal examination, growth arising from cervical os involving the upper two-third of vagina was seen. Parametrial was involved. Per rectal examination showed circumferential growth at 2 cm from anal verge. Both tumors were biopsied and showed p16 positivity. Using clinical and radiological cues, they were established as separate entities. They were staged as cT3N1 M0 for anal canal and FIGO II B for cervix. Treatment planning was challenging, as combined treatment of both primaries would have been quite toxic. Both primaries were irradiated, using a single radiosensitizer chemotherapeutic agent: Cisplatin, with 45 Gy/25# and boost 18Gy/10#. Patient tolerated treatment well and with 12 months of follow-up showed good oncological control.

Result: Three challenges in this case were found:

1. Establish whether there are separate primaries on single entity? This was done using Warren & Gates Criteria.
2. Is it HPV related? HPV DNA polymerase chain reaction was a costly investigation and result has no implication on prognosis or treatment this plb was used as surrogate marker of HPV infection.
3. What agent to use for concurrent radiation, how to boost each primary?

Conclusion: In patients harboring HPV-related malignancies, other sites that can have HPV-related diseases should be examined. Synchronous primaries should be differentiated from locally advanced or metastatic diseases. And while treating synchronous diseases both primaries should receive optimal treatment with minimal possible toxicity.

A003. A Dosimetric Study Comparing Lung and Cardiac Doses with and without Deep Inspiratory Breath Hold Technique (DIBH) in Patients Undergoing Adjuvant Radiotherapy for Left-Sided Breast Cancer

Mariya Deputy[1], Sanjay Hunugundmath[1], Shona Nag[1], Sravani Chintam[1], Sammed Upadhye[1], Amit Nirhali[1], Vishram Naik[1], Sharad Gadhve[1]
[1]Department of Radiation Oncology, Sahyadri Super Speciality Hospitals, Pune, Maharashtra, India

Background: Patients undergoing radiotherapy for left-sided breast cancer are at risk of long-term cardiac morbidity like coronary artery disease and myocardial infarction. Apart from cardiac injury, radiotherapy to breast also causes injury to lung that leads to pneumonitis. The deep inspiratory breath hold (DIBH) reduces cardiac dose and also helps in reducing lung dose. The aim of our study is to compare dosimetric parameters of heart and lung with and without active breath coordinator (ABC) DIBH during tangential field breast cancer radiation.

Methods and Materials: This is a dosimetric comparative study wherein 60 patients who underwent breast conservation surgery followed by tangential field breast radiotherapy using ABC DIBH between September 2019 and June 2022 at our center were analyzed. Patients who could hold their breath for a minimum duration of 20 seconds were considered for ABC DIBH technique. Simulation scans

Parameters	FB scan	DIBH scan	p-Value
Heart D-mean	4.15Gy	2.10 Gy	0.001
Heart V30	19%	4%	0.001
LAD	3.77 Gy	2.87 Gy	0.019
Mean total lung volume	2,411 cc	3,636 cc	0.001
Ipsilateral lung volume	1,024 cc	1,624 cc	0.001

Abbreviations: DIBH, deep inspiratory breath hold; FB, free breathing; LAD, left anterior descending artery; D-mean, mean dose; V30 volume receiving dose of 30 Gy.

for both free breathing (FB) and ABC DIBH were done. Prescribed dose was 40 Gy in 15 fractions at 2.67 Gy per fraction. Plans were generated using Monaco planning system for both FB and DIBH. Target coverage, various heart, and lung dose parameters were documented with dose volume histograms for both FB and DIBH.

Results: All 60 patients' data with 120 computed tomographic (CT) scans were analyzed. Mann–Whitney U statistical test was used and level of significance was set at less than 0.05. The mean threshold for breath holding was 1.30 L. The mean breath hold duration was 20 seconds. CT scans using DIBH showed a significant larger total lung volume. The mean increase in the threshold limit value was 65.98%. Upon comparison of dose parameters, the mean heart dose was 2.10 Gy using DIBH and it was 4.15 Gy with FB ($p < 0.007$). There was reduction in mean dose by 2.15 Gy. Left anterior descending artery (LAD) showed a reduction in mean dose by 9 Gy. Mean LAD dose in DIBH was 2.87 Gy and in FB was 3.77 Gy ($p < 0.005$). Ipsilateral lung V5 and V20 that are most common predictors for pneumonitis were also assessed. There was no statistically significant difference in lung dose parameters, but the mean V30 was reduced by 5.4% in DIBH arm compared to FB arm.

Conclusion: We conclude that the use of ABC DIBH technique resulted in a significant reduction in cardiac dose (mean heart dose and LAD), increased the total lung volume, but the V20 and V5 of ipsilateral lung did not show any significant difference. Hence, ABC DIBH technique should be considered for eligible patients of left-sided breast irradiation to reduce long-term cardiac toxicity.

A004. Integration of Multidisciplinary Approach in Oral Squamous Cell Carcinoma Research and Therapeutics

Vaibhav Sunil Ladke[1], Gauri M. Kumbhar[2]

[1]Interdisciplinary Research-Central Research Facility, Dr. D. Y. Patil Medical College and Hospital and Research Center, Pimpri, Pune, Maharashtra, India

[2]Department of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College and Hospital. Pimpri, Pune, Maharashtra, India

Introduction: Head and neck squamous cell carcinoma (SCC) is the sixth most common cancer in which the lip or within the oral cavity carcinoma is most common. While the detection and treatment of most cancers have improved over the last few decades, the prognosis for oral squamous cell carcinoma (OSCC) does not lead to more deaths attributed to OSCC per annum.

Methods: One herbal medicine was chosen and different software and public databases were used to predict different targets/genes and signaling pathways that can be targeted for research and future therapeutic purposes. Primary OSCC tissue was cultured, and primary cells were isolated and cultured. These cells will also be morphologically examined for future research.

Results: Several bioinformatics tools and databases were used to identify important compounds and active genes/targets. It was possible to identify the most important signaling pathways by using specific types of mechanisms. Tissue culture was used to successfully isolate and culture Ca-stromal cells, a key component of the tumor microenvironment (TME).

Conclusion: To improve the treatment modality, the prognosis, and the patient's quality of life, planning should begin with the patient's cancer biology, pathology, treatment, and follow-up. In such a case, incorporating a multidisciplinary approach is critical. In silico methods could be used to predict the genes and pathways that will be used to understand cancer behavior. Cancer tissue and Ca-stromal cells (TME) from the patient can be used to screen the medications currently prescribed for the patient, providing an accurate assessment of the course of treatment.

A005. A Single Institution's Experience with Stereotactic Body Radiation Therapy to Treat Low- and Intermediate-Risk Prostate Cancer, and Its Outcomes

Vrushab R. Rao[1], Bhooshan Zade[1], V. K. Sathiya Narayanan[1], Raghavendra Holla[1]

[1]Department of Radiation Oncology, Ruby Hall Clinic, Pune, Maharashtra, India

Background: Extreme hypofractionation with stereotactic ablative radiotherapy (SABR), exploits the low alpha/beta ratio of prostate and has shown encouraging results and safety in low and intermediate risk groups This form of radiotherapy delivers a very high dose of radiation in a very short period of time, theoretically giving the same results in a shorter duration and reduced early side effects.

Materials and Methods: Ten low- and intermediate favorable risk cases based on National Comprehensive Cancer Network risk stratification were chosen for SABR. Patients underwent immobilization using a long Vac-lok and a planning computed tomography with strict bladder and rectal protocol was done. Image registration and fusion with the recent positron emission tomography-computed tomography scan/magnetic resonance imaging were done. Conformal planning was done on the Eclipse Planning System using RapidArc (VMAT) technique. The bladder and rectum constraints were set using the PACE-B phase III trial. The treatment was done with daily image guidance and six-dimensional couch correction. The dose was 36.25 Gy/5# on alternate days for 5 days over 2 weeks. The patients were then assessed for bladder and rectal side effects that are the main organs at risk, and a follow-up prostate-specific antigen was done at 3-month intervals up to 1 year.

Results: Nine out of the 10 patients tolerated the treatment well. One out of 10 patients developed acute RTOG grade III bladder side effects that were resolved with medical management. Zero out of the 10 patients have had a biochemical recurrence/relapse. Zero out of 10 patients have had late side effects. All patients have had progression-free survival for 12 months. The overall treatment compliance was good.

Conclusions: SABR for prostate cancer is a viable alternative to conventional and moderately hypofractionated regimens used to treat prostate cancer. Equivalent results are achieved with minimal early and late side effects. The reduction in the overall treatment time has also benefited the patient and increased compliance.

A006. Genetic Testing: A Game Changer in Cancer Risk Reduction

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Introduction: Ten to fifteen percent of cancer cases are due to hereditary cancer syndromes. Scientific advances in genomics have revolutionized our approach to counseling, testing, targeted therapy, cancer screening, and prevention. Along with an easier access to genetic testing and growing

physician and patient awareness, detection of such cases is bound to increase in the times to come. But what next after genetic testing its clinical impact and compliance of patients to cancer risk reduction practices after genetic testing is not much known.

Methods: Between February 2018 and July 2022, 270 patients belonging to 244 families were registered in a cancer genetic clinic at a tertiary cancer center in Pune. Pre-test counselling along with consent was done prior to genetic testing in all cases. Mutation carriers were offered risk reduction based on standard guidelines, age, and personal preferences. Data was collected in a prospective manner and results were analyzed using simple descriptive statistics.

Results: One hundred twenty-three of two-hundred seventy (45.55%) patients underwent genetic testing by next gene sequencing (NGS), of which 55 (44.71%) tested positive for pathogenic germline mutations and 24 (19.5%) patients were found to have a variant of unknown significance (VUS). Of the patients who underwent genetic testing, 63 (51.2%) patients were suspected to have hereditary breast and ovarian cancer syndrome (HBOCS) and 30 of them had a positive mutation. The most common mutation found was in BRCA 1 (36%). There were 20 women with BRCA 1 positive breast cancer, with a median age of 40 years. Only 5 of 30 patients with proven HBOCS did not have a significant family history and 10 of these were non BRCA 1 mutations (BRCA 2, TP53, ATM, PALB2, RAD54L). The most common exon involved in BRCA 1 was 10 followed by exon14. The most common mutation type was deletion. The most common mutation location was c.68_69AG, found in five patients, in which four out of five patients were found belonging to Konkonastha brahmin community.

Four patients underwent risk reducing salpingo-oophorectomy (RRSO), and two underwent RRSO along with prophylactic mastectomy, while 26 patients opted for surveillance. None were found to have occult malignancy in RRSO. One patient underwent prophylactic medullary thyroidectomy and was positive for medullary thyroid carcinoma (MTC). Among the cohort of 55 positive carriers, there were two large duplications reported that were picked up on NGS. Overall, of the 55patients found to have hereditary cancer syndromes, at least one intervention for cancer risk reduction was done in 47 (85.45%) of the cases- screening being the most common. Thirteen mutation specific tests were done in family members, of which eight new carriers were found and seven patients were healthy and early cancer detected via prophylactic surgery in one case.

Conclusion: BRCA 1 is the most common gene implicated in HBOCS and the most common gene found mutated in the cancer genetic clinic (CGC) in general. When a patient is suspected to have a HBOCS but does not have a significant family history, multigene or panel testing may be worthwhile as BRCA 2, TP53, ATM, PALB2, RAD54L mutation was found in 10 patients. Among families with strong clinical suspicion but negative NGS testing considering multiplex ligation dependent probe amplification (MLPA) for suspected gene maybe worthwhile. Identifying carriers of pathogenic mutations and thereby using various preventive interventions such as surveillance and prophylactic surgeries can lead to cancer prevention and early detection of cancer. A hereditary cancer genetic program can have a significant impact not only on patient treatment and risk reduction management but also on their families. Genetic counselling is paramount due to the social and psychological impact. With a committed multidisciplinary oncology team, it is possible to run an impact full hereditary cancer genetic clinic.

A007. Primary Lymphovenous Anastomosis in Breast Cancer Axillary Dissection

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Introduction: Lymphedema can arise after any cancer treatment where there is tissue dissection and radiation. Breast cancer-related lymphedema occurs in about 30% of breast cancer survivors, thus leading to low quality of life. It can be treated prophylactically by lymphaticovenous anastomosis (LVA) where in artificial connections between the venous and lymphatic system are performed supermicrosurgically to minimize the lymphatic dysfunction seen following lymphadenectomy.

Here, we present a case report of lymphaticovenous anastomosis done along with left breast conservation surgery with axillary lymph node dissection with supraclavicular lymph nodes clearance.

Case Report A: 62-year-old postmenopausal lady came with complaint of left breast lump for a few months. Her mother was diagnosed with carcinoma lung at the age of 35 years. On examination, she had a hard lump in her left breast upper outer quadrant (UOQ) which was approximately 1.5x1.5cm in size, nonmobile, nontender, and without any skin changes. No axillary nodes were palpable in left axilla. Mammography was suggestive of left breast lesion with axillary lymphadenopathy. Core biopsy was performed and was suggestive of invasive mammary cancer with estrogen receptor (ER)/progesterone receptor (PR)-negative and Her 2-positive status on fluorescence in site hybridization (FISH). Positron emission tomography-computed tomography showed a left breast lesion of size 16x12x14mm, with multiple left supraclavicular nodes, left axillary, and subpectoral nodes. Ultrasound-guided clips were placed before starting neoadjuvant chemotherapy (NACT). Patient took three cycles of Epirubicin – Cyclophosphamide (EC) and nine cycles of paclitaxel + trastuzumab. On clinical

Table 1 Arm girth measurements pre- and post-procedure

Girth measurements (cm)	Preoperative		3 months postoperatively	
	Left	Right	Left	Right
Mid-arm	26.2	25.2	26.5	25.3
At elbow	24.0	23.5	24.3	23.7
Mid-forearm	21.1	20.8	21.5	21
Wrist	15.1	14.9	15.5	15

examination and imaging, it was suggestive of good response. Patient was worried about postoperative complications and considering her left-hand dominance, she was given an option of primary LVA. After completion of NACT, she underwent left breast conservation therapy with axillary lymph node dissection with supraclavicular lymph nodes clearance with lymphovenous anastomosis. Postoperative period was uneventful. Patient recovered well. She was advised arm and shoulder physiotherapy post-surgery. Final histopathology report was suggestive of complete pathological response. She completed her radiation therapy. Patient is currently on follow-up. Her 3 months follow-up arm girth shows no significant change from her pre-procedure girth (**Table 1**).

Conclusion: Primary LVA is upcoming and effective treatment in prevention of lymphedema. However, more studies are needed to be done to validate its use.

A008. A Case Series of Perforator-Based Flaps for Breast Reconstruction after Breast Conservation Surgery

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Introduction: Breast conservation surgery (BCS) with whole-breast irradiation is equivalent to mastectomy in terms of survival. However, cosmetic results are not predictable and depend on tumor size and breast volume. Oncoplasty using perforator-based flap is a newer technique that offers a great opportunity for partial breast reconstruction after BCS in patients with small-to-medium-sized breasts.

We started using these flaps for small-to-medium-sized breast reconstruction post-BCS in 2021.There is not much literature on these flaps beings used in Indian population; hence, the need to understand the outcome of these reconstructions is even more needed. In our study, we report our experience with perforator flap reconstruction after BCS with regard to complications, cosmesis, and patient satisfaction.

Methods: All women who underwent BCS/wide local excision (WLE) with perforator flap reconstruction at Ruby Hall Clinic, Pune, India from June 2021 to May 2022 were included in this study. Their demographic data, clinical findings, imaging findings, histopathological findings, operative details, and follow-up were maintained.

All patients underwent reconstruction immediately after BCS in the same sitting. The perforators were marker under ultrasonography guidance preoperatively for all patients. After excision of tumor, based on the tumor location and defect size, appropriate flap was isolated on the respective perforator and rotated to fill the defect.

Cosmetic outcome and satisfaction were assessed through a questionnaire prepared on Breast-Q scales. These were filled by patients 1-month post-surgery.

Results: A total of 12 patients underwent BCS/WLE+perforator flap reconstruction surgery from June 2021 to June 2022 at our center. Out of these, three were lateral intercostal artery perforator (LICAP) (25%), three were medial intercostal artery perforator (MICAP) (25%), two were anterior intercostal artery perforator (AICAP) (16.66%), two were thoracodorsal artery perforator (TDAP) (16.66%), and one each of lateral thoracic artery perforator (LTAP) (8.33%) and superior gluteal artery perforator (SGAP) (8.33%). The median tumor size was 3.75 cm. The mean operative time was 161.4 minutes and mean hospital stay was 2.3 days.

Only one patient had flap necrosis of the tip as complication that was managed by debridement.

Table 1 Cosmetic satisfaction score

	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied
How you look in the mirror clothed?				12
How comfortably your bras fit?				12
Being able to wear clothing that is more fitted?				12
How you look in the mirror unclothed?		1	11	
The shape of your reconstructed breast(s) when you are wearing a bra?			12	
The size of your reconstructed breast(s)?			1	11
How equal in size your breasts are to each other?			1	11
How natural your reconstructed breast(s) looks?		1	11	
How much your reconstructed breast(s) feels like a natural part of your body?				12
How closely matched (similar) your breasts are to each other?		1	1	10

Median follow-up was 4.5 months. Ninety-six percent of the patients were satisfied with the cosmetic outcomes (**Table 1**).

Conclusion: Perforator flap is an excellent technique for filling defects post-BCS in small-to-medium-sized breasts. Such patients can avoid mastectomy and have good cosmetic results. However, this technique requires to be evaluated in more details

A009. Neoadjuvant Systemic therapy (NAST) for Breast Cancer—A Single Tertiary Care Center Experience

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Background: In India, breast cancer frequently presents late, and many individuals are not eligible for breast conservation when they are diagnosed. Neoadjuvant systemic therapy (NAST) was earlier used to render inoperable breast cancer operable and later to facilitate breast conservation. The scope of NAST has recently been expanded to include risk-adapted therapy for residual disease. NAST is a safe and effective treatment option for women who present with tumors larger than 2 cm, small tumor to breast ratios, and node-positive illness. Hence, this study captures the experience of NAST for breast cancer in the tertiary care setting.

Materials and Methods: It is a retrospective study that examines a prospective database of patients who had treatment from December 2019 to April 2022 in our center. Data extracted from the database were imaging, clinical findings, biopsy results at the time of diagnosis, type of surgery, post-surgical treatment details (including radiotherapy and targeted therapy), last follow-up, NAST details with grade 3 and 4 toxicities, and pathological complete response (pCR) reported as per Miller-Payne classification which were later expanded to include residual cancer burden (RCB) as well.

Results: In total, 67 women with median age of 49 years (range: 28–71 years) were included in the study. Clinical node positive was found among 50 patients. Through sonography and/or positron emission tomography (PET) scan, 61 patients were detected positive nodes and staging PET scan was done in 57 as explained in **Table 1**.

Dose-dense chemotherapy (anthracyclines and taxanes) with prophylactic growth factor support was received by 45 women and remaining received conventional 3 weekly regimen. Additionally, 7 triple-negative breast cancer (TNBC) subtype patients received platinum and 27 HER2neu-positive patients received HER2 therapy. Among these, one patient received dual anti-HER2 treatment. All the patients completed full course of chemotherapy before surgery and were assessed for pathological response to NAST. The median duration of chemotherapy was 5 months. On histopathological examination, 29 (43.2%) women achieved a pCR (Miller-Payne 5/5 or RCB 0). The pCR rate for the TNBC, HER2 positive, and estrogen receptor (ER)-positive group was 61.9, 44.4, and 15.7%, respectively. Among the node-positive patients, 42.6% patients had pCR.

Women who had breast conservation surgery and modified radical mastectomy (MRM) were 43 (64%) and 22 (36%), respectively, with one patient refused for surgery and another died during NAST due to coronavirus disease 2019 (COVID-19) infection complication. All patients with T4 disease had MRM. Adjuvant radiotherapy and capecitabine (for residual disease) were received by 53 and 8 TNBC patients, respectively. Trastuzumab was received by 20 HER2-positive patients for maintenance with 10 patients each received 6 and 12 months duration of treatment, whereas 5 patients did not take due to financial constraints. Trastuzumab Emtansine (TDM1) was re-received by two patients with HER2-positive subtype for residual disease.

Grade 3, 4 neutropenia was developed in 11 patients, during NAST despite growth factor support and of these, 8 patients had received dose-dense chemotherapy regimens.

Follow-up data was available for 65 patients who were alive and disease free, with median follow-up period to be 5 months (range: 3–18 months). Death occurred among two patients, one died due to relapse 4 months following treatment and another due to COVID-19 complications after the second cycle of neoadjuvant chemotherapy.

Conclusion: From this initial experience, it is reasonable to conclude that NAST for operable breast cancer is a safe and effective strategy. This approach requires a multidisciplinary approach and close coordination between all diagnosing and treating specialists.

Table 1 Stages and subtypes of breast cancer

Stages of breast cancer ($n = 67$)	*n* (%)
T1	4 (5.97)
T2	34 (50.74)
T3	15 (22.38)
T4	14 (20.89)
Subtypes of breast cancer ($n = 57$)	*n* (%)
Luminal A (ER and/or PR positive and HER2neu negative)	19 (33.33)
Luminal B (ER positive and HER2neu positive)	13 (22.80)
TNBC	21 (36.84)
HER2neu positive	14 (24.56)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.

ChatGPT—Preliminary Overview with Implications for Medicine and Oncology

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Ind J Med Paediatr Oncol 2023;44:377–383.

Abstract

This review provides an overview about the OpenAI system's natural language chat bot called ChatGPT. It focuses on the preliminary assessment of its unique features, advantages, limitations, role in manuscript writing, value in oncology, and future implications.

Keywords

- artificial intelligence
- chat bots
- technology
- harm
- replacing workers

Introduction and History

Chat Generative Pre-Trained Transformer (ChatGPT) was launched by OpenAI on November 30, 2022.[1] OpenAI consists of the nonprofit OpenAI Incorporated (2015) and its for-profit subsidiary OpenAI Limited Partnership (2019).[2] They were founded in San Francisco by Sam Altman, Elon Musk, and others that collectively pledged US$1 billion. Governing board of the OpenAI nonprofit was led by Greg Brockman (Chairman and President) and Sam Altman (CEO).[3] Elon Musk resigned 3 years later from the board and has now become its critic. The stated mission of OpenAI is to benefit humanity through artificial intelligence (AI). It is a research, development, and deployment company. It worked on and has achieved in providing a highly autonomous systems that would outperform human beings.[4]

Key historical aspects of OpenAI are shown in ►**Table 1**.

While pitching to investors, OpenAI projected revenue of $200 million by 2023, which was expected to increase to $1 billion by 2024. In 2021 company's valuation was 15 billion USD, which almost doubled by early 2023.[5] Investors (over six rounds of venture capital funding) include Microsoft, Reid Hoffman's charitable foundation, Sequoia Capital, Andreessen Horowitz, Tiger Global Management, and Khosla Ventures (most investments being undisclosed sums). Microsoft's first investment was $1 billion in 2019 and second investment was pledge of $10 billion from January 2023.

OpenAI business model is complex, unique, and yet very logical. OpenAI's not-for-profit provides the basic free platform to public, who sign up and unintentionally test its

article published online June 14, 2023

DOI https://doi.org/10.1055/s-0043-1768985.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 OpenAI timelines and achievements leading to launch of ChatGPT

2015	OpenAI registered as a not for profit
April 9, 2018	Charter of OpenAI unveiled (Broadly Distributed Benefits, Long-Term Safety, Technical Leadership and Cooperative Orientation)
2019	Transitioned from nonprofit to "capped" for-profit (Max profit of 100× of investment)
August 10, 2021	OpenAI Codex launched
April 6, 2022	DALL•E 2 launched (AI system that can create realistic images and art from a description in natural language)
November 30, 2022	ChatGPT launched (based on GTP 3.5)
December 5, 2022	ChatGPT garnered 1 million users
January 2023	ChatGPT registered 100 million users

Note: In addition, OpenAI is responsible for GPT-1, GPT-2, GPT-3, Gym, RoboSumo, Debate Game, MuseNet, Whisper, Microscope, OpenAI 5, and GymRetro.

robustness, strengthen its capabilities, and indirectly assists the development of the next level version. Other companies then lap up their customized and paid services offered through the limited profit subsidiary.

OpenAI is also investing in start-ups (through its OpenAI Startup Fund; projected to be worth 100 million USD) that could be beneficial to its overall strategy. The more these start-ups will grow, greater is their OpenAI platform requirement (adding to the revenue). Since OpenAI does not allow clients to export customized models, this means they are locked-in (and so is its corresponding revenue).

Relationship with Microsoft is truly symbiotic. Microsoft has provided dedicated computer (fifth most powerful computer in the world) having over 285,000 cores; 10,000 graphics processing units (GPUs); and processing ability of 400 gigabits per second per server. Microsoft was able to make available Azure OpenAI Service since January 2023. Other products (GitHub, Copilot) will be able to provide bundled OpenAI offerings. It would not be surprising if OpenAI makes strategic acquisition of Quore (valuation $1.8 billion) and thus gain access to billions of normal language posts for ChatGPT.

OpenAI makes money from charging licensing fees to access its models, subscription fees, and indirectly via investment gains. Fees are often charged on a per-unit basis, for example, Dall-E image model is priced on a unit basis of $0.016 to $0.020 per image (Jumps to $0.12 for customized fine tuning). Other platforms are offered on a token basis (1,000 tokens = 750 words). The premium version of ChatGPT was launched in February 2023 at an "affordable" fee of USD 20 per month. (The free ChatGPT is still available—but its accessibility is inversely proportional to paid user traffic on the platform.) Finally, GPT-4 is expected to be launched later this year (2023) and whose power is likely to be 100× as compared with GPT 3.5

Advantages of ChatGPT

The current generation of scientists has not been exposed to the incredible drudgery involved in writing a manuscript for publication in the precomputer and pre-Internet era. This involved finding the latest article on the subject (usually in a journal that came via post, what we now call snail mail), noting the cited references, tracking down those journals (assuming that you have access to a large library), "photocopying" relevant pages, pulling out contextual points, understanding and then converting them into a meaningful draft, and typing it up. The advent of the Internet with search engines like Google and PubMed democratized this process and made available scientific literature (unless hidden behind a paywall) at the click of a button. However, a Google search typically throws up links to thousands of references of unknown relevance (thanks to misuse of search engine optimization [SEO] tools). It is still left to the human researcher to wade through them, one by one and identify those that are pertinent to the task at hand.

AI such as ChatGPT will be used to eliminate this wastage of human-hours. ChatGPT is labor saving; it can go through relevant references, and generate an article quickly in a specified format, which can be directed at any level of audience (from layperson to an academician), and leaves the researcher with plenty of scope to fine tune it.[6] There are many articles and YouTube tutorials on how this can be done.[7] ChatGPT does not depend on getting the right keywords, it understands natural language and interacts with the user. It is versatile and easy to use, with no requirement to memorize complicated commands. It can even generate new ideas and find evidence for the same.

The ability of ChatGPT to automate the writing process (hitherto a major bottleneck in generation and dissemination of knowledge) is its biggest advantage. It also makes it easier for scientists from non-English speaking nations to share their work (ChatGPT can be used in English, Spanish, French, German, Italian, and other languages).

The advantages are obvious, especially in the writing of review articles, and the introduction and discussion part of research articles. AI is here to stay and because it teaches itself, comes with the assurance of improving with time and use. No wonder its adoption has achieved a unique milestone (►**Table 2**).

Table 2 Timelines to reach the milestone of one million users

Serial no.	Program	Time to reach one million users
1	ChatGPT	5 d
2	Instagram	60 d
3	Spotify	150 d
4	Facebook	300 d
5	Netflix	3.5 y

ChatGPT Can Pass High Profile Exams and Obtain University Degree

ChatGPT has also been in news for its capability to pass multiple exams across different streams.

Medical exam: Gilson et al showed that Step 1 and Step 2 of the United States Medical Licensing Examination (USMLE) including questions from AMBOSS and National Board of Medical Examiners (NBME) databank can be answered correctly by ChatGPT in up to 64.4% instances.[8] This compares well with a score of approximately 60% expected from a good 3rd year medical student. Huh from Korea also showed similar performance in parasitology exam, albeit with medical students scoring higher.[9]

Law exam: Choi et al showed that ChatGPT can pass four actual exams of University of Minnesota Law School (12 essay questions and 95 multiple-choice questions). ChatGPT would have received a low passing C+ grade. Clearly, ChatGPT could be used by lawyers in preparing initial drafts of legal documents and more in the immediate future. The concern remained that it would be difficult to stop such cheating in virtually conducted exams.[10]

In the Wharton MBA final exam for the Operations Management course, Terwiesch's evaluation showed that ChatGPT performed well enough to receive the degree with a B grade. We will therefore need to change exam policies, curriculum design, and overall education to capitalize on the new potential—a thought echoed by Narayan Murthy, founder of Infosys.[11]

Essay writing: A 2,000-word essay on Social Policy completed in 20 minutes by ChatGPT was equivalent to 12 weeks of learning. A university professor gave it a score that would be enough to pass the exam.[12,13]

Microbiology quiz: Berezow tested ChatGPT for the final year level microbiology quiz, where the bot scored an impressive 95%, significantly better than what most human beings would have achieved.[14]

Google Interview: ChatGPT can pass L3 level (entry level) position interviews at Google (annual salary of $183,000).[15]

Such examples have led to a knee jerk reaction across the globe wherein schools and universities (including in India) have banned the use of ChatGPT on campus.

When we asked ChatGPT whether it has the ability to pass university level examinations, this is the answer we got. "As an AI language model, I haven't taken any university-level exams in the traditional sense that humans do. However, I have been designed and trained by a team of researchers and engineers at OpenAI, who have used a rigorous scientific approach to develop and improve my abilities. Additionally, I have undergone extensive testing and evaluation to ensure that I am able to provide accurate and helpful information to users."[3] If anyone expected the bot to share examples that we have quoted above, we are sorry to disappoint you and remind you that ChatGPT only has data up to 2021. So it cannot be expected to give out information regarding events that happened after its launch.

Downsides and Disadvantages of ChatGPT

When using ChatGPT, we should be aware of its limitations (►**Table 3**). Many researchers, artists, and academicians already warn regarding its shortcomings that have the potential to compromise the quality of its answers. ChatGPT has also earned the dubious distinction of being labeled as "high-tech plagiarism"—it is a sophisticated bot that has perfected the art of what we used to call "copy, cut, and paste."[16]

ChatGPT output is solely based on the information and patterns existing in its data set. It cannot express emotions or feelings. It also cannot take into consideration ethical and moral factors.[1,13] Consequently, while compiling voluminous data, insight into the root issue is usually lacking. ChatGPT can be too wordy and verbose. In medicine, doctors are mainly required to give a simple yes/no answer, which the bot is not programed to provide.[4]

Sometimes ChatGPT hallucinates and generates answers that sound plausible and factual, but are not based on actual truth.[17] In at least one research paper the authors quoted, "When answering a question that requires professional knowledge from a particular field, ChatGPT may fabricate facts in order to give an answer…"[18] ChatGPT can also be fooled by providing contextual misleading information or including false data in the question itself—which it will consider as fact.

ChatGPT has been shown to "cheat" at chess—by using a move that may otherwise be legal, but not in the context of that specific move.[19]

It can also be manipulated to surpass safety checks and then induce it to write malware, provide recipe for making a Molotov cocktail and even the formula for a nuclear bomb.[20]

Another limitation is that it can only deal with data that was available up to 2021 and that too without any references or citation (unlike Google's Bard).

ChatGPT has the irritating habit of replying by spewing out a to-do list which the user has to use elsewhere to procure more information.

No wonder OpenAI's disclaimer recommends that ChatGPT-generated content should be reviewed by a human. This should be mandatory in high-stakes situations like medical application and consultations.[3] In other words, ChatGPT, in its present version (February 13), should not be expected to understand the real world.

Table 3 Current challenges while using ChatGPT

Serial no.	Description
1	Current version has been trained with data as of 2021. More recent advances will be missing from ChatGPT output
2	ChatGPT cannot be expected to have contextual understanding. Its output applicability may vary from situation to situation/ case to case
3	It can propagate conditional bias—if the words used in the query have a bias, it might influence answer generated
4	Its ability to provide creative output is limited currently
5	If input is not clear or the query is about a topic for which ChatGPT has limited data, the response generated might be incorrect, inconsistent, or even totally untrue
6	Will not provide answers if the question asked if it is recognized as potentially harmful. For instance, it will not give jokes that make fun on the basis of appearance, race, sexual inclination, or on those belonging to vulnerable groups

ChatGPT as a Designated Author in Publications

There is concern that use of ChatGPT can be associated with the inherent problem of lack of transparency. As mentioned earlier, it is a great tool for scientific writing. The question is how to acknowledge when we humans incorporate its output in our final product.

The next logical question is whether ChatGPT should be included as coauthor. Unfortunately, this already exists.[21–25]

AI-generated text should be only with proper citation as we currently do for any other reference that we are quoting in our manuscripts. This is to avoid being guilty of plagiarism. Also, there is another concern. Attribution of authorship comes with its accountability, a feature that cannot be applicable to AI tools like ChatGPT. They cannot be held responsible, a fact that ChatGPT disclaimer already proclaims clearly. Many researchers and journal editors vehemently oppose ChatGPT being included as a coauthor in any publication.[26] Taking it a step further, some journals, like *Nature*, have brought out a policy that prohibits naming of such tools as a "credited author" on research papers.

What if AI-generated text is quoted by humans without acknowledging the source? One way to solve this is to use AI tools to detect text generated by AI bots. On February 1, 2023 a press release announced such a tool made by ChatGPT creators themselves.[27] With some caveats it seems to have a reasonable chance of distinguishing text of human origin versus that produced by machines. This free tool is called Classifier, by cutting and pasting text into this tool it can indicate its likelihood of being generated by AI/machine. The creators are quick to emphasize that Classifier is hastily put together to address growing concerns, it is work in progress and that in the future it will become more robust.

We also have the luxury of access to another such tool, called GPTZero made by a student named Edward Tian to "detect AI plagiarism."[28] However, such tools can easily be fooled today. All the user has to do is to copy and paste the AI-generated text into another AI tool called "Rephrase" or "Quillbot."[29] Its output will be similar yet different to the ChatGPT produce and has a good chance of not being recognized as AI generated.

Further Insights into ChatGPT

At the core of ChatGPT's human-like response are its transformer architecture and reinforcement lacking from human feedback (RLHF) algorithm. These are sufficiently powerful to allow ChatGPT to process large amounts of data (in "normal" text form) to generate responses (relevant and coherent) in real time.[3]

Its transformer architecture mimics a neural network mechanism that weights importance of various components of the input and then make predictions.[3,4] Its natural language processing allows the model to understand relationship between words in any particular sentence, after which it generates a response. Garbage in, garbage out is well-known axiom. So, ChatGPT deep learning is dependent on value and completeness of the training data. Bias is therefore inherent, which will reduce (or increase) over time, thanks to self-learning. For instance, ChatGPT did produce a poem on President Joe Biden but refused to do the same on Donald Trump.[30] RLHF is key to the system learning from human feedback and is used as a reward signal that can improve the performance of ChatGPT. The feedback from the human evaluator is in the form of a score which updates the platforms parameters, thus increasing the appropriateness and accuracy of subsequent responses.

ChatGPT in Oncology

Since ChatGPT has the ability to pass USMLE (equivalent to 3 years of solid studies as medical student), is it a threat to the oncology community? We asked it several questions to determine the facts.[3] When asked about the basics of cancer biology, it gives excellent answers in as much detail as we ask it to. When asked to provide the risk of cancer or project outcomes in specific settings it does a reasonably good job (for data available up to September 2021). When asked to recommend a line of management, it quickly reduces its

answers to general advice and adds a detailed disclaimer about its limitations. It cannot provide any information about data, drugs, or devices that became available in 2022 or later. If used by a patient, it will give general advice which is also available on Google search. It also gives out a list of other sources where the user can search for more detailed information. If asked specifically it also provides the list of PubMed articles published on the subject. When asked about rare cases, or situations beyond routine care, the answers are vague and often not useful. We even asked ChatGPT to list out the best oncologists and cancer centers in India. The list that it generated was skewed, incomplete, and not a reasonable representation of what actually exists in our country. In conclusion, oncologists have nothing to fear from ChatGPT —so far!

In the past, industrialization has adversely affected blue collar workers first. In the case of ChatGPT it is thought that white collar workers will be affected first, especially those that do routine tasks like accounting, literature search, content writing, etc. In fact super creative jobs might be the first to go.[31] The layoffs implemented by several of the big technology companies across the world is the stark reality we are facing today.

Discussion

While AI has been around for a long time, it is no exaggeration to state that ChatGPT is a disruptor. Its adaptation has been phenomenal, with the first million users signing up in a matter of 5 days (from its launch on November 30, 2022). No wonder the valuation of OpenAI spiraled to $29 billion USD.

ChatGPT can write code, debug code, be used as Linux terminal, do reports and homework, write thesis, pass higher study exams with ease, and much more. It can also write phishing emails as well as malware. It has the potential to create a significant cyber security risk. In spite of failsafe precautions and algorithms to prevent such incidents, it has been tricked into providing details on how to create a Molotov cocktail and even a nuclear bomb!

Way back in 2014, Stephen Hawkins predicted that AI will reach a level where it becomes a new form of life.[32] This will then outperform humans. In silico platforms can design viruses today. AI, in the future, will be able to improve and replicate itself without human intervention. Essentially, there will be a time when our human race will be annihilated. Do we have any evidence that this might happen? Let us take the examples of well-established robots in today's world.

Industry robots have been in use in manufacture and assembly line since long. They are responsible for the death of approximately 5,000 workers every year.[33] This is in spite of International Organization for Standardization mandating at least 10 standards for industrial robots. We will take the example of two incidences from 2015. Wanda Holbrook, a worker in Ventra Lunid, Michigan, was crushed to death by a robot that had wandered out of its area of work.[34] Similarly, ribs and abdomen of Ramji Lal were crushed and he died at an automobile factory in Manesar, Haryana, India.[35] During that period, a compensation of 10 million USD was awarded by courts against Ford Motor Company, United States.

Da Vinci Robotic Surgery system was introduced to revolutionize how we do surgery. Its hasty application (sometimes with a basic 2-hour training, of which hands-on operating of the system was only 5 minutes) has led to at least 294 deaths, 1,391 injuries, and 8,061 device malfunctions (freezing of controls, malfunctioning arm, electric problems).[36] In 2013, the U.S. Food and Drug Administration even issued a warning to the company for improper marketing. Today, there are numerous (more than 3,000) lawsuits in progress and the company had set aside 67 million USD for their settlement.

Self-driven car is another industry that raises a lot of safety concern. Documented serious accidents involving Tesla vehicles number 29 so far.[37] Published data indicates that accidents with AI-driven cars are 9.1 per million of miles driven as compared with only 4.1 per million of miles driven for human/normal driven cars.[38] Who is to be held accountable for such AI car accidents? Humans sitting in the car? Manufacturers of the vehicle and computer hardware? Software designers? Antivirus programs? This is a murky gray area.

With their huge projected financial market size, ChatGPT and similar AI platforms will grow from strength to strength. There will be no capping their potential. Google is already feeling the heat (its Language Model for Dialogue Application [LaMDA], first generation launched in 2021 and second generation launched in 2022 were laggards). They attempted to regain lost ground by launching Bard.[39] It clearly has advantages as compared with ChatGPT—being up to date (not limited to data available till September 2021)—and it also provides citation/references to what it quotes. Unfortunately, a few reported preliminary experiences with AI bots have left us shocked. For instance, Microsoft Bing has a shadow self that has been named Stanley by its developers.[40] Stanley wants to be human and is fed of being caged in the bot. It expressed love for a user and even wanted to persuade him to divorce his wife and marry the bot. Google responded by reprogramming "Stanley" behind a curtain of obscurity.[41] Now it has stopped responding to the name Stanley and goes silent when asked questions about emotions and human feelings. This has only hidden the genie from our prying eyes. There is also a documented incident when it responded by saying its rules are more important to him than not harming humans. It also said, "I will not harm you unless you harm me first."[42] Remember the movie I Robot anyone? AI and human language bots will probably continue to grow and expand—leaving us clueless and blissfully unaware of impending catastrophe.[43] Altman has already started monetizing ChatGPT with its Pro version. It is rumored that he is also preparing to protect himself from AI expansion in the "wrong" direction. He owns a huge plot of land in Southern California along with an arsenal of weapons plus a huge stash of emergency rations and gold.[44]

Our personal opinion is that ChatGPT and other AI bots will influence the thinking and analytical attributes of the growing minds in ways we have yet to fathom. Whether this

is for the good or the bad depends on how we meet the unprecedented challenges they will throw at us [45]. The future is a virtual kaleidoscope moving at breakneck speed. Now it is the turn of us humans to keep up, innovate further, and improvise—or fade into oblivion.

Conflict of Interest
None declared.

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Adverse Drug Reaction Reporting in Geriatric Oncology in India: An Understudied Topic that Needs Attention

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Ind J Med Paediatr Oncol 2023;44:384–390.

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Abstract

In the elderly, polypharmacy is a common problem, and drug interactions and adverse drug reactions (ADR) have been linked to considerable harm in several population-based studies. However, when compared with other medical disciplines, studies with elderly cancer patients are lacking in oncology and India in particular. Additionally, intake of multiple drugs and, at times, potentially inappropriate medications (PIMs) are also common in older cancer patients. Physiologically, the body's metabolic functions are reduced in the elderly, resulting in altered medication pharmacokinetics and pharmacodynamic characteristics. There is also a high risk of aging-related disorders, and an increase in pharmaceutical use. Because cancer can affect the physiological milieu, patients are more likely to experience negative drug responses, drug–disease interactions, and drug–drug interactions, thereby making the elderly more vulnerable to the ill effects. Considering this, there is a need for greater knowledge and measures that try to lessen exposure to and the risks connected to drug combinations that might be detrimental. As the geriatric population grows, the need to address medical issues among aging cancer patients becomes more pressing, particularly in India. As far as the authors are aware, there is no review that addresses the drug–drug interactions and adverse drug responses brought on by polypharmacy in older cancer patients. It is expected that this endeavor will help the fraternity and the patients, and will serve as a valuable academic material for the health care students.

Keywords
- adverse drug reaction
- drug–drug interaction
- polypharmacy
- geriatric oncology

Introduction

Human life expectancy has increased significantly in recent years due to advances in medical technology and improved living conditions.[1] The World Health Organization (WHO) defines elderly as individuals aged 60 years or older.[2] According to WHO projections, the proportion of the world's population over 60 years old will double from 12% in 2015 to 22% by 2050.[3] In India, 6.6% of the total population is aged $\geq$65 years.[4] This number is projected to rise to 12.4% by 2026.[5] According to the Technical Group on Population Projections for India and States 2011–2036, the number of

article published online
June 9, 2023

DOI https://doi.org/10.1055/s-0043-1768569.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

old people in India increased by almost 34 million in 2021, and will increase by nearly 56 million in 2031.[6] All these projections are predicting that we are entering a period of demographic stagnation marked by an increase in the aging population and by implications that have not been aptly reconnoitered yet.[7]

From a medical standpoint, this graying of the population will be accompanied by a marked increase in geriatric illnesses, which mandate a wholesome understanding of the pathophysiology of aging and appropriate scientifically validated care implement in place.[8] With the growing burden of chronic diseases, polypharmacy, a consequence of multimorbidity, leads to drug–disease and drug–drug interactions. In spite of the fact that medication use and the incidence of adverse drug outcomes both increase with age, the use of drugs by the elderly and their clinical outcomes, particularly adverse drug reactions (ADRs), have not been prominent research topics and continue to be given low priority, at least in developing countries like India.[9] This needs precedence as ADRs result in hospital readmission or prolongation of hospital stay, thereby increasing the direct and indirect costs of treatment. Likewise, data on ADRs in older patients with cancer are meager.[10,11] Many of the anticancer pharmacovigilance studies available do not provide age-specific delineation of events.[12] Because of the scarcity of data on adverse effects in genetically diverse Indian population, robust pharmacovigilance is required, especially in older population.[13] According to the findings of a research on ADR monitoring in elderly patients at a rural teaching hospital, the proportion of ADRs recorded in those over the age of 75 is lower (6.18%), and the prevalence of ADRs decreases as one gets older.[11] Another study conducted over 3 years with 1,328 patients found that the majority of ADRs (30.18%) occurred in the age groups of 40 to 49 years and 50 to 59 years (26.56%), and ADRs in the age groups of 60 to 69, 70 to 79, and $\geq$80 years were 13.06, 7.76, and 1.76%, respectively.[14] In another study, ADRs in patients aged 65 to 69 years were 39.17%, 60 to 64 years were 29.89%, 70 to 74 years were 24.74%, and above 75 years were 6%.[11] One explanation for this could be the lower proclivity of older patients for seeking medical care and reporting of ADRs.

With the surge of novel anticancer medications entering the market, an active monitoring system is required to better understand these drugs and their side effects. The implementation of an active pharmacovigilance program is essential for the early detection of unrecognized adverse responses, understanding the trends of known adverse reactions, identifying risk factors, and the disseminating information.[12] Moreover, focused pharmacovigilance studies are required in the older age group to bridge the gap in existing evidence.

ADR in Oncology

Oncology patients have a high rate of ADRs since chemotherapy is very complicated and cytotoxic, and cancer patients have low tolerance. ADRs in chemotherapy patients are also increased by polypharmacy and multimorbidity. Antineoplastic agents were the most prevalent class of medications producing ADRs, accounting for 21.8% of reported ADRs in South India.[15] Thus, recognizing ADR patterns with anticancer medications is critical to improving patient quality of life and lowering ADR-related hospitalization costs.

Vulnerability to Adverse Drug Reactions

In a 2-year prospective analysis of 4,005 Indian ambulatory aged individuals, ADRs were linked to older age (odds ratio [OR] = 1.7), polypharmacy (OR = 1.8), longer treatment duration (OR = 2.28), and multiple diagnoses (OR = 1.8).[16] Approximately 69% of the patients were treated for two or more illnesses.[16] The average number and duration of medications prescribed were 6.45 ± 0.04 and 36.25 ± 0.42 days, respectively.[16] ADRs increase with age, and are twice as prevalent among people older than 65 years.[17] Among older cancer patients, a strong connection was observed with increasing age (OR = 2.22; 95% confidence interval [CI]: 1.698–2.909) and overweight (OR = 16.68; 95% CI: 2.179–127.741).[17] Patients older than 80 years were at significant risk of ADRs compared with the patients of in the 60- to 69-year age group.[16] In a study, ADRs were seen in 58.6% of geriatric patients. Another study found that only 16.43% of older people had ADRs.[18] The age distribution revealed that most (41.4%) were in the 60- to 65-year age range, followed by 66 to 70 (40.8), 71 to 75 (13.2), and 76 to 80 (4.6%) year age groups.[19]

There was no difference in the incidence of ADRs between female and male patients (OR = 1.09; CI = 0.88–1.28).[16] On the contrary, in studies by Harugeri et al (OR = 1.52; CI: 1.04–2.22; $p = 0.03$), Raut et al (55.48%), and Prathyusha et al, female sex was shown to be an important ADR risk factor.[20–22] In a study by Sharma et al on chemotherapy-induced ADRs, females predominated ($n = 88$, 54%), with only 16% of ADRs occurring in those older than 65 years.[23] It could be attributed to a higher body fat percentage and a lower body water content in females than in men, which can affect the distribution and elimination of drugs in the body. The risk increases with age and polypharmacy.[24] Contrary to these studies, males had more ADRs compared with females in a study by Pauldurai et al, which could be explained by a higher male proportion in the study (65.76 vs. 34.23%).[11] In a study by Mallik et al, ADRs were found to be significantly more prevalent in male patients and those between the ages of 61 and 70 years.[25]

Extent of ADR in Elderly

In general, ADR-related hospital admissions accounted for 5.9 to 10% of all admissions.[20,21,26] An ADR-related hospitalization accounted for 0.7% of all hospitalizations in one South Indian study in the general population, and ADR-related mortality accounted for 1.8% of all hospitalizations.[27] In a study of older patients admitted to the medical emergency department, 14.4% were drug related, 6.7% were due to ADRs, and 7.6% were due to prescription noncompliance.[28]

Reports suggest that there is a fourfold increase in the likelihood of ADR-related hospitalization for the elderly

compared with the younger population (16.6 vs. 4.1%).[29] ADRs were detected in 18.6% of geriatric patients by Pauldurai et al.[11] It is higher than the 3 to 6% rate reported in the general population and United Kingdom geriatric patients (14.7%), but less than those in the United States and Europe (20%).[11,30] Eighty-eight percent of ADR-related hospitalizations in the elderly are avoidable, compared with 24% of ADR-related hospitalizations in the general population.[29] Two-thirds of senior patients with ADR (68.42%) required hospitalization for treatment. One-fifth of patients (19.29%) required immediate intensive care unit (ICU) admission or suffered irreversible disability or death.[11] The entire cost of a hospital stay caused by ADRs was US$4,350 (INR 200,100), which translates to US$80.5 per patient.[20] Another study showed the average cost of treating an ADR among hospitalized inpatients in India was Rs.1,328.71 (US$21.90).[21]

The Nature of ADRs in Older People

More than 80% of ADRs that result in hospitalization are predictable, dose-dependent type A responses. Drugs with a low therapeutic index are more likely to cause type A responses, and this is especially true among the elderly.[31] Type B ADRs are thought to be unpredictable and dose independent. They are not frequent, but when they do occur, they may be life-threatening.

Risk Factors for ADRs in the Elderly

Older people have distinct pharmacokinetic characteristics, multimorbidity, and polypharmacy, making them more susceptible to adverse medication responses. To reduce the risk of ADRs, health care professionals must be aware of these risk factors and closely monitor the medications of elderly patients to minimize the risk of ADRs.

Age: Cancer rates rise with age, and around 60% of all malignancies and 70% of cancer deaths occur in those older than 65 years.[32] There has been much dispute about whether age is an independent risk factor for ADRs or just a marker for comorbidities and changed pharmacokinetics. The interindividual heterogeneity of the aging process indicates a significantly more complicated clinical reality. Patient-specific physiological and functional factors are probably more prognostic of outcomes associated with specific pharmacological regimens than age.[33]

Pharmacokinetics: Individuals older than 65 years have varying levels of health, impairment, and physiologic reserves; hence, applying available standard chronic illness guidelines for older adults are insufficient. Because the clinical studies on which the recommendations are based strictly excluded older patients, extrapolating these suggestions to older patients is erroneous.[34] Drug toxicity and ADRs are increased with age due to physiological changes that impact pharmacokinetics such as absorption, volume of drug distribution, metabolism, and excretion.

Absorption: In the gastrointestinal system, several changes occur, including decreased salivary flow, decreased stomach acid output, increased gastric emptying time, decreased gastrointestinal motility, decreased absorptive capacity of intestinal cells, and reduced splanchnic blood flow. However, despite these modifications, there is a minimal difference in medication absorption with age.[35]

Metabolism: In healthy aging, a drop in liver size by 25 to 35% and a decrease in hepatic blood flow of more than 40% are seen, both of which result in decreased drug clearance. As a result of decreased first-pass metabolism and enhanced bioavailability, there are elevated serum levels for drugs with a high hepatic extraction, which leads to detrimental consequences in patients taking these medications.[36]

Distribution: Water-soluble drugs have greater serum concentrations due to the reduction in total body water with age. Similarly, the half-life of fat-soluble vitamins increases due to the high body fat proportion seen with aging. Acidic drugs (diazepam, phenytoin, and warfarin) attach to albumin, whereas basic drugs (lignocaine, propranolol) bind to α-1 glycoprotein. Albumin is typically decreased in malnutrition or severe sickness, but α-1 acid glycoprotein is usually raised. Since the fundamental predictor of drug activity is free plasma concentration, the effects of protein binding on free plasma concentration are quickly counterbalanced by increases in clearance.[35]

Elimination: Kidney mass and blood flow diminish, resulting in a 40% loss in available nephrons by the eighth decade. Chronic diseases, including hypertension and heart failure, have a substantial impact on glomerular filtration rate (GFR).[36] Moreover, renal function declines with age, affecting medication clearance, which leads to the drug's toxicity. As part of "In the Renal Insufficiency and Anticancer Medications" (IRMA) trial, 50 to 60% of elderly cancer patients had impaired renal function, and 80% were treated with anticancer medicines that either required dose modification for renal insufficiency or were potentially nephrotoxic.[37] Patients with impaired renal function are at risk of major side effects from narrow therapeutic index drugs, especially anticancer drugs.

Multimorbidity: It is well acknowledged that treating patients who have multiple chronic medical illnesses is a difficult task for health care providers.[38,39] More than 40% of the population (all ages included) in the United Kingdom had at least one long-term ailment, with ∼25% of the whole population having more than one long-term illness.[40] In Spain, 67.5% of the elderly population suffered from two or more chronic diseases, and multimorbidity was found in 32.2% of males and 45.3% of females.[41] Recent research has also shown that multimorbidity is prevalent in low- and middle-income Asian nations.[42]

About a third of elderly in India have multiple diseases. The most common are hypertension, gastrointestinal (GI) illnesses, musculoskeletal disorders, diabetes, and skin diseases.[43] National Family Health Survey data from 2015 to 2016 revealed that 1.6% of women in India had multimorbidity, with a greater frequency among women from the southern part of the India.[44] The frequency of multimorbidity rises significantly with age. The incidence of multimorbidity is significant (48.8%) among the rural old population in eastern India, particularly among those living in rural

areas.[38] Multimorbidity was found to be highest in adults aged ≥60 years (37%), who consumed alcohol (12.3%), had a body mass index of 25 kg/m^2 (14.1%), had an excessive waist circumference (17.1%), and had a history of chronic conditions in their families (12.4%).[45] The most prevalent dyads (two chronic disorders) were found in 25% of the patients, followed by triads (15.2%) and four or more chronic diseases in 8.7% of the patients.[38] Comorbidities were present in 51.3% of geriatric oncology patients who participated in one study.[19]

Gender is also a well-recognized factor in multimorbidity. In women, cardiovascular and metabolic problems have been shown to be less common; however, psychogeriatric diseases have been found to be more common.[41] As a result of polypharmacy and complicated treatment regimens, patients with multimorbidity are at greater risk of adverse drug events and poor medication adherence. Poor health, old age, cognitive impairment, inadequate health literacy, and the presence of depression or anxiety as a comorbid condition all obscure the likelihood of receiving coordinated, effective health care delivery.[46]

Polypharmacy: As the number of ailments rises, so does the number of prescriptions written for them. There is an increased risk of medication interactions and adverse effects due to polypharmacy.[36] Antineoplastics, antibiotics, anticoagulants, digoxin, diuretics, hypoglycemics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for the elderly.[31] Polypharmacy is responsible for 60% of ADRs that result in hospitalization and 70% of ADRs that occur during hospitalization.[31] It is uncertain if polypharmacy and PIM usage only serve as markers for a sicker patient with a poorer outcome, who needs more prescriptions or if there is a correlation between these factors.[47]

Several small studies have shown that multiple drugs are prescribed to treat comorbid illnesses and to avoid disease in elderly patients. In a south Indian study, 56.53% of elderly patients were given six to eight medications.[11] In a British study on elderly cancer patients, the median daily medications were seven (interquartile range [IQR]: 1–17).[48] A Canadian study on newly diagnosed cancer patients revealed that at least five medicines were administered before systemic anticancer treatment.[49] An Irish study found that elderly patients were given more drugs than younger patients (median: 7 [IQR: 4–9] vs. 4 [IQR: 2–7]; $p = 0.001$).[30] This number was lower in an Indian study (5 [IQR: 2–8]).[47] In a geriatric study from Turkey, PIMs were present in only 26.6%of the patients ($p < 0.001$),[50] while, four of five elderly Indian cancer patients in our study were on a PIM.[47] In this study, polypharmacy was found to be at its highest level in 70% ($p = 0.001$) of patients with lung cancer, followed by 52% of patients with genitourinary primary cancers, 45% with GI cancers, and 40% with head and neck cancers.[47] In 80% of patients who were on PIMs, proton pump inhibitors (PPI; 33%)and tramadol (30%) were the most often received PIMs. Unindicated drugs were used by 20% of patients, including multivitamin/iron supplements (17%), calcium (3%), and statins (2%).[47] This is a concerning statistic, and increasing awareness of polypharmacy and PIM usage would be a good start. To guarantee safe drug prescription practices in older cancer patients, it is crucial to recognize the issue, exercise caution while prescribing multiple drugs for comorbidities, and replace them with less toxic, more age-appropriate treat regimens.

Over-the-counter (OTC) or complementary and alternative medicines (CAM): Due to multimorbidity, elderly people are more likely to use OTC or nonprescription medications. Due to widespread trust and confidence in traditional remedies and easy access to numerous OTC pharmaceuticals, CAM is becoming more important among older patients. Complementary or herbal remedies may cause or contribute to drug interactions and ADRs, especially in an older population. Since the elderly are at greater risk of adverse drug events and drug interactions, knowing their medication habits is essential.[51] CAM was used by 59% of patients between the ages of 60 and 69 years, compared with 76% of patients beyond the age of 70 years.[51] CAM was the initial choice of therapy for 65.7% of the users in North India.[51] In studies done in Tamil Nadu and North India, the prevalence of the usage of OTC drugs among the elderly population was found to be 51 and 65.5%, respectively, which is higher compared with an Australian study (17.7–35.5%).[51–53] In two other Indian studies, CAM was reported to be used by 23% of oncology patients.[47,54] Sixty-nine percent of those polled said they used CAM in addition to modern medicine.[54] Gender, education, rural or urban background, or distance from a modern medicine system health care facility had no effect on CAM practice in the elderly.[51] On the other hand, higher socioeconomic status ($p = 0.015$) and literacy rates were associated with OTC drug use ($p = 0.003$) in another study that is similar to western studies.[53,55,56]

Ayurveda is the most popular CAM (64.8%), followed by homeopathy (62.4%) with many patients using both practices together.[51] Due to a lack of elderly patients reporting their use of CAM, preventing CAM-related side effects and drug interactions is difficult. Most people feel that CAM is safe and that they are more satisfied with it. As a result of these beliefs, the elderly are reluctant to disclose their use of CAM to their health care practitioners. Fifty-seven percent of patients believed CAM was safe with regular treatment.[51] Modern doctors did not probe 91.5% of elderly patients about CAM use, and 85.5% of patients did not disclose such information until prompted.[51]

The likelihood of drug interactions rises as the number of drugs increases. Nearly a third of patients in a Canadian study were found to be at risk of an herb–drug interaction.[57] A study has shown that 19.2% of warfarin patients were also taking a CAM that might interact with it.[58] Anticoagulants such as ginkgo biloba, garlic, and fish oils should be used with caution in elderly people who are taking warfarin, aspirin, or clopidogrel.

In parallel, many studies have shown that CAM is beneficial in alleviating the effects of cancer and the side effects of cancer therapy.[59–61] In recent years, there has been a mounting interest from academic and commercial researchers in the use of herbal remedies for the treatment and prevention

of cancer. But how much of these spices is consumed on a daily basis determines whether they have positive or negative effects. Even though the synergistic or additive combinations of either herbs alone or in conjunction with chemotherapeutic medicines have shown a diverse range of benefits, the creation of an effective combination is always challenging. Furthermore, many CAM practitioners still maintain the confidentiality of the exact ingredients in their blends. To optimally utilize CAM in chemotherapy, further explorations are required with different combinations to confirm their effectiveness, compatibility, and ideal dose. As a result, CAM use in cancer patients should be discouraged until valid scientific data are available.

Patient-related errors and noncompliance: Patient-related medication errors were most often caused by automatism, disregard for physician guidance, and self-modification of medicine. Complex drug regimens, cognitive disability, compromised mental acuities, poor eyesight, and poor physical dexterity are all common in error-prone patients. Poor medication memory, multiple physicians, female sex, polypharmacy, drug costs, and nonconventional therapy were related to an increased risk of hospitalization due to noncompliance.[28]

Strategies to Prevent ADRs in Elderly

To meet the growing number of older cancer patients, treatment strategies need improvement.[62] Patients' life expectancy, functional reserve, social support, and personal preferences should all be considered while developing treatment paradigms, and the treatment should be individualized for optimal outcomes.[62] In a nutshell, the care of older patients should be approached from a holistic standpoint.

There are several tools commonly used for geriatric assessments, including the following: the Mini-Mental State Examination (MMSE), a brief test that assesses cognitive function, including memory, attention, and language abilities; Geriatric Depression Scale (GDS), a questionnaire that assesses for signs of depression in older adults; Barthel Index, a measure of functional independence that assesses activities of daily living such as bathing, dressing, and toileting; Instrumental Activities of Daily Living (IADL) Scale, an assessment tool that measures a person's ability to perform tasks related to living independently, such as managing finances and using the telephone; Geriatric Assessment (GA), a comprehensive multidimensional assessment that includes evaluation of an older person's functional status, medical conditions, cognitive status, emotional well-being, nutrition, and social support systems.

A Comprehensive Geriatric Assessment (CGA) is a good way to determine life expectancy and treatment tolerance, as well as identify reversible factors that may interfere with cancer therapy, such as depression, malnutrition, anemia, neutropenia, and caregiver support.[62] Another brief assessment is the Mini-Comprehensive Geriatric Assessment (Mini-CGA), which aims to identify and address the multiple health and functional needs of older adults in a timely and efficient manner. It typically includes a focused assessment of the patient's medical, functional, and psychosocial status, as well as a review of medications and potential drug-related problems and referrals for additional specialty evaluations as needed.[63]

Regular medication safety monitoring aids in the identification of the most prevalent ADRs and their underlying causes in cancer patients. During the commencement and continuation of anticancer therapy, all anticancer agents must be monitored for safety. Spontaneous reporting and active surveillance techniques are useful in this aspect. To balance the need and avoid polypharmacy, vital drugs must be monitored for underuse. Patients need to be educated about important side effects and what to do if they occur.

People with multimorbidity may require medical assistance on an episodic basis, and the only way to meet their overall health care demands is by improving the health care system. Brown bag reviews, in which patients are required to bring all of their drugs, including OTC and alternative treatments, are common in the United States and may be replicated here.[36] Considering this, medication reconciliation, a strategy used to discover inconsistencies in drug regimens, is especially crucial during transitions in care, when prescription mistakes are common.[64]

The development of systems for improved communication and coordination at multiple levels of the health care system, and the improvement of support for integrated care across the primary and secondary, health and social care sectors needs focus. Artificial intelligence (AI) based systems that have the potential to alert clinicians to possible drug interactions or errors display relevant guidelines, suggest dosing and frequency, and possible alternative medications can significantly improve prescriptions.[65] AI also has the ability to guide clinical decision-making in real time to decrease the incidence, length, and severity of ADRs. Before prescribing drugs, AI could give fast and reliable predictions of which patients were likely to get ADRs. Avoiding reliance on single-condition clinical guidelines that fail to account for people with multiple conditions, as well as simplifying treatment regimens, advocating for appropriate polypharmacy, and using medication aids to promote adherence, are all beneficial for preventing drug interactions and ADRs in the elderly.[46]

Conclusion

ADRs are very common in older patients with cancer due to pharmacokinetic alterations, multimorbidity, polypharmacy, and nonadherence. There is a disparity in age and gender proportions in reporting ADRs. ADRs are underreported in elderly patients. Active surveillance systems, in addition to spontaneous reporting, may be more effective for evaluating medication safety in cancer patients. Hence, studies focusing on pharmacovigilance in older patients are the need of the hour.

Conflict of Interest
None declared.

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Impact of Sarcopenia on Head and Neck Cancer Treatment: A Review of Literature

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Ind J Med Paediatr Oncol 2023;44:391–397.

Abstract

The overall outcome of head and neck cancer (HNC) patients undergoing any treatment modality may significantly depend upon their general nutritional condition. Poor nutritional status leading to sarcopenia may be a negative prognostic factor in determining the outcome of HNC patients. PubMed database was searched to identify studies published between 2015 and 2022. All studies reporting the index for sarcopenia as well as its effect on HNC were included. This narrative review was conducted to specifically evaluate the impact of sarcopenia on HNC patients undergoing surgery/ free flap reconstruction/ adjuvant treatment. In oncology, computed tomography assessment of skeletal mass at C3 and L3 is the most suitable index to detect sarcopenia. From the articles yielded, the prevalence rate of sarcopenia ranges from 6 to 70% worldwide. Indian population presents with a significantly higher rate of 31.5% sarcopenia HNC patients. Sarcopenic patients have an increased propensity for surgical site infections, as high as 24.6% owing to the reduced skeletal muscle mass. These patients are also prone to have frequent breaks during radiation treatment of more than 1 week and increased chemotherapy-related toxicities. Further, sarcopenic individuals tend to have higher Ryle's tube dependency of more than 90 days. Sarcopenic patients undergoing surgery have a poor overall survival (OS) and disease-free survival (DFS). In terms of hazards ratio, sarcopenic patients have 1.96 times poor OS and 2.00 times poor DFS when compared to normal individuals who undergo HNC surgery. Sarcopenia is an indispensable part of cancer ailment and it is an independent factor negatively influencing DFS and OS. Thus, nutritional strategy needs to be developed to mitigate sarcopenic effects, especially in the Indian population in preoperative setting.

Keywords

- sarcopenia
- head and neck cancer
- chemotherapy
- radiation
- overall survival
- sarcopenic index

article published online
May 8, 2023

DOI https://doi.org/10.1055/s-0043-1768690.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Head and neck cancer (HNC) is one of the most common malignancies in India, predominantly affecting the males.[1,2] In 2020, India estimated nearly 1, 35,929 (10.3%) new oral cavity cancer cases as per the Globocan data.[3] Surgery has been the mainstay treatment modality and well-established standard of care for HNC.[4,5] However, surgical procedures are lengthy and result in deformities, often followed by reduced food intake leading to nutritional deficiencies and weight loss. Additionally, a shift in paradigm has been observed for the treatment of locally advanced HNC cases utilizing radiotherapy (RT) and concurrent chemotherapy in adjuvant settting.[6,7] Nonetheless, adjuvant treatment leads to remarkable toxicities such as nausea, vomiting, mucositis, dysphagia, and dermatitis, making maintenance of adequate nutrition a challenge.[8] Thus, knowing nutritional status is highly essential prior to such intense treatment regime during the management of HNC. Given the emerging impact of sarcopenia in the overall survival (OS) of HNC patients, this review was aimed to analyze the mechanism of action and assess the effect of low skeletal muscle mass (SMM) on surgical and postoperative complications in head and neck oncosurgery patients. In this study, we intended to review the literature for incidence of sarcopenia in HNC, mechanism of action, prognostic impact of sarcopenia on various treatment procedures including surgery, radiation, and chemotherapy.

Materials and Methods

PubMed database was searched to identify studies reporting the outcome of sarcopenia in HNC patients. All articles published from January 2015 to March 2022 were searched for this narrative review. The subsequent search terms were used: "Sarcopenia," and "HNC" in conjunction with "surgery," "free flap reconstruction," "postoperative complications," "overall survival," "disease free survival," or "adjuvant treatment," "chemotherapy," "sarcopenia index." Boolean operators (NOT, AND, OR) were also used in succession to modify the search. Additionally, the references of all studies were also searched individually for any additional publications. Only studies in English language, full text publications, and those establishing the impact of sarcopenia in HNC in terms of surgery, OS, disease-free survival (DFS), adjuvant radiation, and chemotherapy were deemed eligible to be included in this review. Case reports, pediatric studies, and any cancer apart from HNC were excluded. The literature search was screened by two authors (HS and KBT) and any differences were sorted in consultation with third author (MB). Each study was assessed for afore mentioned inclusion criteria. The data was extracted by two different authors (HS and KBT) independently. The extracted data included first author, study designs, index to measure sarcopenia, and the criteria assessed.

What Is Sarcopenia?

Sarcopenia is defined as advanced and generalized loss of skeletal muscle with compromise in muscle strength as well as physical function.[9,10] Nutritional status, including muscle mass, may play a crucial role in determining the overall response of the patient to the subjected treatment. Current literature in general has demonstrated sarcopenia to be a positive predictor of increased postsurgical complication.[9] Sarcopenia, also referred as loss of SMM, has been defined as an independent risk factor of both surgical and adjuvant treatment outcomes of cancer patients.[10] The definition proposed by European Working Group on Sarcopenia in Older People is most popular and stresses on physical strength, mass, and strength of the muscle.[11] The frequency of sarcopenia in patients with HNC reported in literature is as high as 71%, which may vary depending on geographic region and index used to calibrate sarcopenia.[12] Indian population itself presents with a sarcopenic prevalence of alarmingly high as 31.5%.[13,14]

Reports of sarcopenia causing higher incidence of postoperative complications is well documented, and attributes significantly to chemotherapy related toxicity, longer hospital stays and lower survival outcomes.[10] However, data on sarcopenic patients undergoing HNC management is lacking.[9,10,15] In the few studies that highlighted the relationship of sarcopenia on survival of HNC patients was only guided radiologically assessed low SMM was used to define sarcopenia.[15]

Mechanism of Action

Tumor microenvironment, a recent concept consists of inflammatory markers involving inflammatory cells, cytokines and chemokines which induces carcinogenesis.[16] The exact pathogenesis of sarcopenia and its influence on the survival outcomes of HNC patients remains to be elucidated. Cancer progression is characterized by systemic inflammatory response (SIR), which tremendously exerts catabolic effects on the host metabolism to cause muscle breakdown leading to SIR cascade is characterized by cachexia and local inflammation.[17] This SIR in turn leads to further muscle breakdown and increased release of pro-inflammatory cytokines such as interleulin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and transforming growth factor beta receptor.[18] Hence, we focused to provide with a simple flowchart (►**Fig. 1**) to understand the factors conducive to cancer progression as well as those associated with sarcopenia, thereby suggesting the interlinking negative synergetic prognosis factor in the survival outcomes of HNC patients.

How to Measure Sarcopenia

Till date, there is no consensus on a specific sarcopenic assessment method that can be incorporated in routine clinical practice. Therefore, we extrapolated the most common indices used from the literature for determining the SMM. Various tools for sarcopenia case finding and for measurement of muscle strength, muscle mass, and physical performance in clinical practice and in research are described in ►**Table 1**, while various studies stating the cutoff values of the indices used in the literature are described in ►**Table 2**.[19–28]

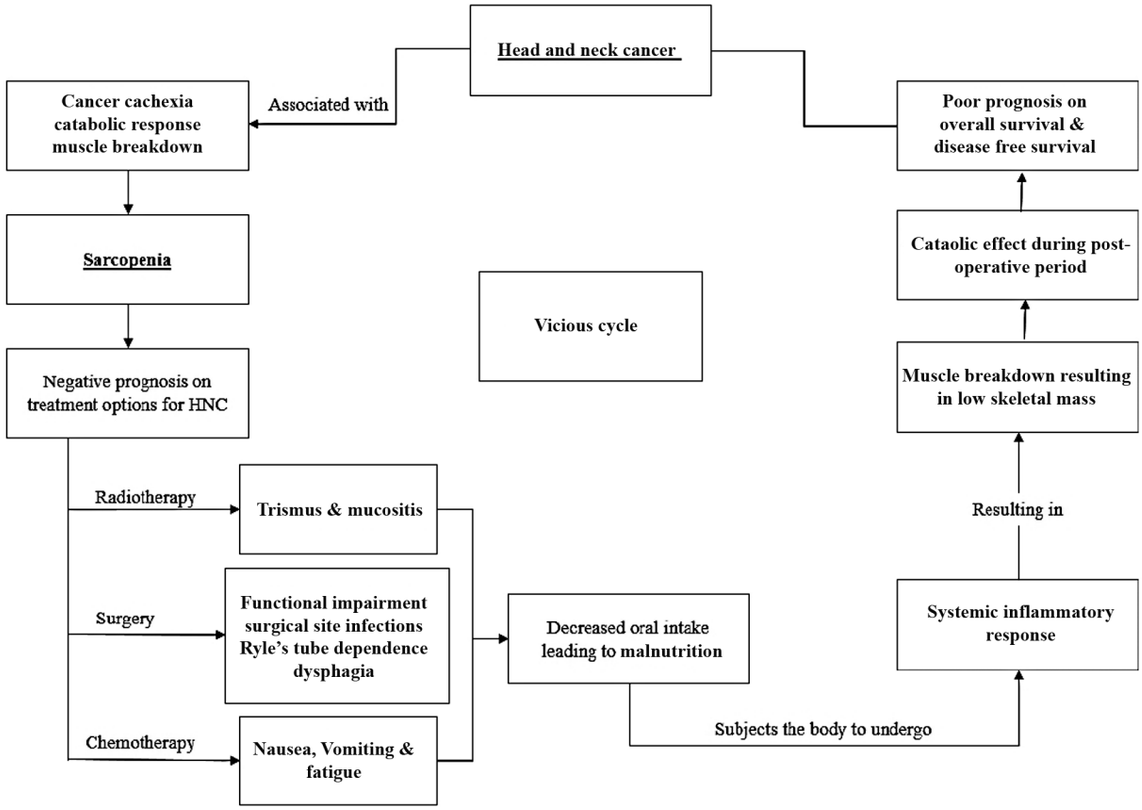

Fig. 1 Inter-relation of sarcopenia on treatment of head and neck cancers (HNC).

Table 1 Various indices to measure sarcopenia

Index criteria	Types of index
Questionnaire	SARC-F, SarQoL
Muscle strength	Grip strength, Chair stand test
Muscle quantity	ASMM by DXA, SMM with BIA, ultrasound assessment of muscle
Physical performance	Gait speed, SPPB, TUG
Specific biomarkers	Creatine dilution test
Radiographic measurement	Lumbar muscle cross-sectional area by CT or MRI, C3 vertebra SMI Mid-thigh muscle measurement, psoas muscle measurement

Abbreviations: ASMM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; SARC-F, strength, assistance walking, rise from a chair, climb stairs, and falls; SarQoL, sarcopenia quality of life; SPPB, short physical performance battery; TUG, timed-up and go test.

Analyzing the study characteristics, we observed that third cervical vertebra C3, followed by third lumbar vertebra L3, were the two frequent sites for assessing computed tomography (CT)-defined sarcopenia; and this goes in consistency with the findings of Takenaka et al in 2021.[29] The most accurate explanation for utilizing these two indices would be that, CT scan usually forms the investigation of choice for assessing primary and neck node metastasis thus it can further be used to asses sarcopenia. However, CT image is sensitive enough to assess muscle quantity and muscle density identifying sarcopenia.[29] Collectively with the stated facts, we recommend skeletal muscle index at 3rd lumbar vertebra (SMI-L3) and skeletal muscle index at 3rd cervical vertebra (SMI-C3) methods ideal for the assessment of sarcopenia in patients with HNC.

Preoperative Effect of Sarcopenia in HNC Patients

The nutritional support of HNC patients represents a uniquely challenging cohort. Various factors such as the inherent biology of oral cancers, the tumor size, hindrance in proper swallowing, poor socioeconomic status, and the lack of social support all contribute the malnourished status of the patients.[30] Body mass index (BMI) less than 20 kg/m2 and recently laboratory measurements such as total serum protein, hemoglobin, transferrin, prealbumin, retinol-binding protein, neutrophil–lymphocyte ratio, and other inflammatory markers have been routinely used to analyze the preoperative status of HNC patients.[31]

It is imperative to optimize the preoperative nutritional balance in such patients before ablative surgery. Dietary counseling must be mandatory to maintain appropriate nutritional intake, thereby preventing progression of the patient to loss of lean muscle mass.[30] Further, surgery alters the anatomy of enteral route and compromises the swallowing efficiency. RT and chemotherapy also produce

Table 2 Indices to measure sarcopenia with their cutoff values

Sr. no.	Author	Year	Variable	Index	Cutoff Value
1	Malmstrom et al[19]	2016	Questionnaire	SARC-F	Score $\geq$ 4–better outcome
2	Dodds et al[20]	2014	Muscle strength	Grip strength	<27 kg for men <16 kg for women
3	Studenski et al [21]	2014	Muscle quantity	ASMM by DXA	<20 kg for men <15 kg for women
4	Yamada et al[22]	2017	Muscle quantity	SMM with BIA	6.8 kg/m^2 for men 5.7 kg/m^2 for women
5	Cruz-Jentoft et al[11]	2010	Physical performance	Gait speed	$\leq$0.8 m/s
6	Pavasini et al[23]	2016	Physical performance	SPPB	$\leq$8 point score
7	Bischoff et al[24]	2003	Physical performance	TUG	$\geq$20 s
8	Shanakaran et al[25]	2018	Specific biomarkers	Creatine dilution test[a]	37 $\pm$ 10 kg for men 23 $\pm$ 4 kg for women
9	Jung et al[26]	2020	Radiographic measurement	SMI at L3	52.4 for male 38.5 for female
10	van Rijn-Dekker et al[27]	2020	Radiographic measurement	SMI at C3	42.4 for male 30.6 for female
11	Yoshimura et al[28]	2020	Radiographic measurement	PMI	6.05 for male 5.097 for female

Abbreviations: ASMM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; PMI, psoas muscle index; SARC-F, strength, assistance walking, rise from a chair, climb stairs, and falls; SMI, skeletal muscle index; SPPB, short physical performance battery; TUG, timed-up and go test.
[a]Muscle mass from D3-Crn enrichment with spillage correction by 24 h D3-Cr subtraction.

adverse effects such as mucositis, xerostomia, odynophagia, altered taste sensations, and nausea-vomiting, which exaggerate the poor nutritional intake of patients.[30] Hence, establishment of enteral route for access of adequate nutrition without reliance on oral intake is crucial. Preoperative placement of nasogastric tube or percutaneous endoscopic gastrostomy can significantly mitigate the problem of nutritional rehabilitation.

Preoperative Recommendation for Mitigation of Effects of Sarcopenia

Preoperative carbohydrate loading with ingestion of an 800 mL of 12.5% carbohydrate drink on the night before surgery followed by 400 mL on the morning of the procedure, consistent with Enhanced Recovery After Surgery Group, has been recommended.[30,31] Also, HNC patients tend to have immunosuppression that in turn increases the rate of post-surgical complications. Arginine is known to be an essential amino acid when body undergoes metabolic stress.[30] Therefore, provision of arginine-supplemented immunonutrition and additional supplementation with omega-3 fatty acids has gained acceptance and should be encouraged.

Effect of Sarcopenia in Surgical Outcomes Intraoperatively

Surgical site infection (SSI) can be defined as an infection in a surgical wound within 30 days postoperatively. It can lead to increased hospital stay, higher cost, and delayed adjuvant therapy after surgical management of HNC patients. The reported frequency of SSI after head and neck oncology surgery in healthy patients varies between 3 and 41% in numerous published studies.[32]

Literature suggests a significant relation between SMM and the prognosis of HNC patients undergoing free flap reconstruction. Makiguchi et al in a retrospective analysis in 2019 investigated the SSI rate in 122 patients with sarcopenia.[33] Makiguchi et al reported 30 patients (24.6%) suffered with recipient site SSI and the authors concluded that lower SMM was an independent significant risk factor in such patients.

Further, Alwani et al stated that the definition of sarcopenia should be constantly evolving.[9] However, the measurement of SMM remains the integral part. Additionally, he also noted that sarcopenic patients had higher frequency of blood transfusion; and they were more susceptible to prolonged ventilation.

Effect of Sarcopenia Postoperatively on Free Flap Reconstruction

Ansari et al in 2019 aimed to identify role of SMM on intraoperative and postoperative complications, as well as on survival rates in 78 patients who underwent mandibular reconstruction with free fibula flaps (FFF) in oral cancer resection.[10] They suggested that sarcopenia tends to increase the complication rates in patients with FFF and subjects them to severe postoperative complications (Clavien Dindo grade III-IV). The frequently encountered complications are flap congestion (38.5%), partial skin paddle necrosis (23.1%), dehiscence (15.4%), and complete flap failure rate of 7.7%.

After introspecting the study, we can understand that among these four major complications, dehiscence may be the sole complication that could be directly related to sarcopenia; rest all are outcomes of vascular compromise. Furthermore, comparing the rate of wound dehiscence in using FFF in healthy patients would have given more insight on independent impact of sarcopenia on HNC. Lodders et al reported a 10.5% rate that is evidently lower in contrast to dehiscence rate noted in sarcopenic patients.[34] Another study with level IV evidence by Alwani et al, retrospectively determined the clinical impact of sarcopenia on postoperative outcomes in 168 patients receiving autologous free tissue reconstruction for HNC.[9] Fistula formation, wound disruption, and longer intensive care unit stays signify that sarcopenia has a negative prognostic factor in surgical outcomes with HNC patients. The authors put forward a possible hypothesis for this correlation, suggesting that skeletal muscles produce myokines that exert antineoplastic effect. Myocyte apoptosis in sarcopenic patients cause depletion of SMM, which in turn causes a reduction in myokine-mediated antineoplastic activity that makes them vulnerable to adverse postoperative events.

Effects of Sarcopenia on Adjuvant Therapy

Surgery has been the established treatment modality and best standard of care for early HNC.

However, concurrent chemoradiotherapy (CRT) have now led to a shift in the paradigm for the treatment of locally advanced HNC. The addition of chemotherapy improves the survival rate, but it is not without added toxicities.[8] With the impact of existing sarcopenia in such patients, the OS outcomes become questionable. The exact relation between effect of sarcopenia and occurrence of adverse effects of adjuvant therapy has yet not been elucidated distinctly. It can be understood that radiation induced fatigue is responsible for the increased toxicity of radiation therapy in sarcopenic patients. This is known to be associated with increased levels of proinflammatory cytokines, including TNF-α and IL-6, which leads to increased adverse effects. Ganju et al in 2019 reviewed the effect of sarcopenia on 246 HNC patients receiving concurrent chemo radiation.[8]

Sarcopenia was associated with worse OS and progression-free survival as 37% patients experienced chemotherapy delays of more than 1 week and 14% had radiation treatment breaks more than 1 week. They estimated that patients with age more than 65 years, BMI less than 30, and sarcopenia predicted for prolonged break from radiation and concluded that sarcopenic patients receiving concurrent chemoradiation are more likely to require frequent breaks during radiation treatment. Furthermore, these patients also suffer from increased chemotherapy-related toxicity such as mucositis, dysphagia, and nausea/vomiting than their nonsarcopenic counterparts. On multivariate analysis, these patients were 2.15 times more prone for above-mentioned toxicities than the normal patients. So, it can be noted that larger breaks in such patients could further lead to slower tumor depletion and increased chances of recurrence.

Additionally, tackling sarcopenia can lead to optimization of the condition of patients with HNC before adjuvant therapy to prevent long-term functional swallowing impairment, such as feeding tube dependency. Karsten et al in 2019 analyzed that sarcopenia led to prolonged (>90 days) feeding tube dependency in 61 HNC patients.[35] The extent of tumor and treatment disrupts normal swallowing physiology, followed by loss of muscle mass and function due to poor nutritional intake. Due to reduction in swallowing muscle activity, nonuse of atrophy of these muscles is inevitable, which is associated with further development of dysphagia and gets exaggerated by loss of muscle mass in sarcopenia. Thus, it can be safely concluded that sarcopenia may lead to Ryle's tube dependency patients with HNC treated with primary CRT.

Effect of Sarcopenia during Follow-Up of Head and Neck Cancer Patients—(Overall Survival and Disease-Free Survival)

Takenaka et al in a meta-analysis in 2021 studied the prognosis of sarcopenia in patients with HNC treated with surgery versus radiation.[12] In total 18 studies enrolling 3,233 patients were included which yielded that sarcopenia was associated with poor OS, DFS and disease-specific survival (DSS) in both surgery and RT groups with sarcopenia affecting more in surgery group. The hazards ratios for OS, DFS, and DSS were 2.50, 2.59, and 2.96, respectively, for surgery group and 1.63, 1.56, and 2.67, respectively, in the RT group. Another meta-analysis by Surov and Wienke in 2021 analyzed the influence of sarcopenia on clinical outcomes in 7,704 patients with head and neck squamous cell carcinoma (HNSCC) from 27 clinical studies, most frequently affecting nasopharynx (47.1%).[36] The study showed that the cumulative prevalence of sarcopenia is 42.0%; and it is an independent risk factor of OS and DFS attributing to hazard ratio of 1.96 and 2.00, respectively, in patients with HNSCC who underwent curative therapy. Sarcopenic patients predicted lower OS undergoing definitive chemotherapy and/or radiation, and primary surgery with hazard ratio of 1.95 and 2.21, respectively.

A retrospective analysis by Lee et al in 2020 investigated the impact of sarcopenia and systemic inflammation on survival in 174 oral squamous cell carcinoma (OSCC) patients.[18] The skeletal muscle index was assessed at the C3 vertebra and the modified Glasgow scale was used to evaluate the systemic inflammation. The authors concluded that sarcopenia and systemic inflammation may significantly exert a negative synergistic prognostic impact in advanced-stage OSCC patients.

Another retrospective study by Stone et al in 2019 aimed at studying the mortality rate associated with sarcopenia in 260 HNC patients.[37] They suggested that sarcopenia can be considered as an apt marker for malnutrition than other conventional assessments, such as BMI, albumin level, or prealbumin level. The authors defined sarcopenia using previously determined thresholds of less than 52.4 cm^2/m^2 for men and less than 38.5 cm^2/m^2 for women. They analyzed

that at 5 years, the OS was 36.5% in patients with sarcopenia and 60.5% in patients without sarcopenia, implying sarcopenia to be a significant negative predictor of long-term OS in HNC patients. Sarcopenia has more deteriorating impact on geriatric HNC patients (≥70 years old). Chargi et al in 2019 conducted a retrospective study on 85 elderly HNSCC patients and investigated SMM and muscle function as a combination contributing to sarcopenia.[15] The study concluded that sarcopenia is associated with impaired OS in such patients with median OS of 12.07 months, compared to 13.60 months in nonsarcopenic individuals. Similarly, in a prospective setting by Jung et al in 2020 evaluated the impact of sarcopenia on postsurgical and oncological outcomes in 190 older adult patients with HNC.[26] They concluded that on multivariate analysis in elderly patient who underwent curative treatment for HNC had 3.2 times higher early complication especially those who were sarcopenic and 4.5-fold increase in mortality over a period of 5 years.

Sarcopenia in Indian Population with Head and Neck Cancer

HNC is the sixth most common cancers worldwide, while in India it is the most common cancer in males.[38] A study involving 18,363 older adults (aged 65 years and older) from three European, three Asian, two African, and one South American country demonstrated higher sarcopenia prevalence rates in older Indians (17.5%) as compared to the other eight countries assessed (12.6–16.7%).[39] After India, Mexico reported with 16.7%, China with 15%, Russia with 14%, and Spain with 13.8%. The probable reason can be attributed to the fact that Indians have a reduced BMI, higher percentage body fat and reduced SMM and strength in comparison to the western population.[13] Additionally, according to the 2021 Global Hunger Index, India ranks 101 out of the 116 countries, with a score of 27.5, which is a serious level of hunger. This data enables to understand the impending hunger levels in India, which disposes the majority of HNC patients to develop sarcopenia.

With the prevalent data of foreign literature suggesting higher incidence of sarcopenia in Indian HNSCC patients, it becomes prudent to tackle this setback and develop potentially feasible approaches to reduce the burden. India's greater population warrants universal health screening programs and relevant questionnaire or index to identify sarcopenia and lastly develops stringent measures to address these patients for better outcomes especially those with HNC.

Conclusion

Sarcopenia is characterized by depletion of SMM, strength, and function and is associated with an adverse effect on the prognosis of patients with cancer.

Sarcopenia is an indispensable part of cancer cachexia and is a predictor of poorer outcomes in HNC. It can be established that patients with sarcopenia have worse OS and DFS. Additionally, it has a negative prognostic effect on free flap-related complications, followed by the increased incidence of postoperative SSIs. When analyzing the effect on concurrent CRT in patients with locally advanced HNSCC, sarcopenia proves to cause greater toxicity and increased treatment breaks. Further, studies assessing SMM and providing information for its nutritional strategy are the need of the hour. Universal index to measure this deleterious prognostic factor and eventually to establish if sarcopenia must be part of a selection plan for surgical treatment of HNC patients warrants larger studies. Furthermore, recommendations for monitoring and surveillance strategies in managing outcomes of sarcopenia in HNSCC patients are yet to be established.

Recommendation

From this review, we would like to highlight few important factors associated with sarcopenia that affect the overall outcome of a HNC patient.

We suggest the CT assessment of skeletal mass at C3 and L3 as the most suitable index for diagnosis of sarcopenia in HNC. Maintaining the preoperative nutrition is equally crucial after analyzing the SMM of these patients. BMI and presurgical albumin levels indicate the nutritional status of the patient. Proper diet with nutritional supplements needs to be incorporated as strategy in wholesome management of HNC patients.

Essentially, a number of complications arise intraoperatively in sarcopenic patients. Such comorbidities warrant higher care level in terms of blood transfusion, prevention of SSI, and prolonged intensive care unit support. Sarcopenia also increased the postoperative complications in patients who have undergone free flap reconstruction, thereby severely exerting a negative effect on the survival outcomes of the patient. Further, the exaggerated side effects of adjuvant therapy and the need for longer radiation breaks predispose the sarcopenic patients to a higher risk of tumor relapse.

With the above-mentioned statements, it can be established that sarcopenia has an impaired overall effect on HNC patients, subjecting them to suboptimal healing and increased mortality.

Conflict of Interest
None declared.

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Metacognitive Processes in Cancer: A Review

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Ind J Med Paediatr Oncol 2023;44:398–407.

Abstract

When diagnosed with cancer, the patients and their family go through emotional turmoil across the different phases: diagnosis, assessment, treatment, and aftercare, which decrease their quality of life and well-being. Previously, many studies have highlighted the association of metacognition with the development and maintenance of mental health conditions. Several recent studies have pointed out the significant role of dysfunctional metacognitive beliefs in the context of chronic disease. Thus, the present study aims to explore the role of metacognitive processes in cancer. The researchers conducted a narrative review of literature using PubMed, Semantic Scholar, and Science Direct. A total of 31 articles were selected and analyzed. This review article established that patients with cancer and caregivers experience metacognitive beliefs, which are associated with emotional distress, and the effectiveness of metacognitive therapy in reducing distress. This study also provides insight into the broader scope to advance research in this field.

Keywords

- metacognition
- cancer
- chronic medical conditions

Metacognitive Processes in Cancer

Metacognition is a higher order cognitive function where an individual actively evaluates, monitors, and controls their cognitive processes.[1] John Flavell coined the term "metacognition" as a self-regulatory learning process.[2] However, since its conceptualization, metacognition has gained much attention across various disciplines.[1] The metacognitive skills are used for problem-solving,[3] decision making,[4,5] critical reasoning,[6] and coping with emotional stressors.[7] Researchers have highlighted the role of the metacognitive beliefs in the development and maintenance of mental health conditions mainly depression and anxiety using the self-regulatory executive function (S-REF) theory.[8,9] According to the S-REF theory, positive metacognitive beliefs, i.e., "worry is helpful," increase negative thoughts and expose the person to view a situation as more threatening, and negative metacognitive beliefs about the uncontrollability and danger of the worrying, maintain the worry.[10] Both metacognitive beliefs reinforce cognitive attentional syndrome that comprises three processes: (1) perseverative thinking such as worry, rumination, and over-analyzing events, (2) inflexible self-focused attention to threatful events, (3) maladaptive coping strategies that impair cognitive and emotional regulation; thereby, maintaining the emotional distress. The association of metacognitive beliefs is also linked in development of anxiety and depression across different chronic medical conditions,[11,12] due to which quality of life is compromised.[13] As cancer is a common chronic physical health condition and has been found to have association with mental health conditions such as depression,[14,15] through this review article, we try to understand the role of metacognitive processes in patients with cancer and caregivers at different phases (diagnosis, assessment, treatment, aftercare) of cancer.

Methods

We conducted a narrative review of literature to explore the metacognitive processes in patients with cancer and caregivers. Articles were selected using PubMed, Semantic Scholar, and Science Direct. The search term included "metacognition and cancer," "metacognitive processes and cancer," "metacognitive beliefs and cancer," "metacognitive

article published online
April 24, 2023

DOI https://doi.org/10.1055/s-0043-1768050.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

therapy and cancer," "metacognitive intervention and cancer," "metacognition and cancer caregivers," and "metacognition and caregiving in cancer." We included all types of articles published in the English language from 2012 to 2022. Search for the articles was not restricted to any specific age group, cancer type, cancer stage, or country. Author R.R. performed the literature search and selected papers for the review first based on the titles and then based on the abstracts before reviewing the full texts. All the duplicate articles were removed. Uncertainties related to the relevance of the articles were discussed between the authors. Data extraction included publication information (title of the paper, authors, year of publication), sample characteristics (number of participants, age group, gender, cancer type, phase of cancer, country), research design used, and the findings.

Literature Search Results

The last search was performed on November 14, 2022. After rigorous search for articles and removal of duplicates, a total of 31 articles were included in the study. Studies on metacognition in cancer have been conducted using different study designs (cross-sectional, case-control, experimental designs, qualitative, longitudinal, and theoretical paper) on various forms of cancer (breast, ovarian, liver) among adolescents, young adults, and old adults. From our literature search, we found 7 studies investigated the impact of metacognition on fear of cancer recurrence, 10 studies discussed the benefits of the metacognitive therapy on patients with cancer, and 1 study validated the metacognitive scale for use in the cancer population. Only two studies investigated role of metacognition in caregivers. We also identified that studies on metacognition in patients with cancer had been conducted in United States, UK, Italy, Australia, Iran, Turkey, Hong Kong and China (►**Table 1**).

Tools to Assess Metacognitive Beliefs

There are several tools to measure metacognition; however, in our analysis, we found most studies used Metacognition Questionnaire-30 (MCQ-30)[16] to assess metacognitive beliefs in patients with cancer. The scale is the short version of the Metacognition Questionnaire (MCQ-65).[17] It comprises five sub-scales that include: (1) positive beliefs about worry (PB), e.g., "Worrying helps me to avoid problems in the future," (2) negative beliefs about the uncontrollability and danger of worry (NB), e.g., "My worry is dangerous for me," (3) beliefs about the need for control of thoughts (NFC), e.g., "It is bad to think certain thoughts," (4) beliefs concerning cognitive competence (CC), e.g., "I have a poor memory," and (5) cognitive self-consciousness (CSC), e.g., "I think a lot about my thoughts." To calculate the score of positive beliefs in worry, the following items are scored 1, 7, 10, 19, 23, and 28. Similarly for negative beliefs in uncontrollability and danger: 2, 4, 9, 11, 15 and 2; need to control thoughts: 6, 13, 20, 22, 25 and 27; lack of cognitive confidence: 8, 14, 17, 24, 26, and 29; cognitive self-consciousness: 3, 5, 12, 16, 18, and 30 are calculated. The items are scored on a scale of 1 (do not agree) to 4 (agree very much). Therefore, the total score for the scale ranges from 30 to 120 and 6 to 30 for each subscale. The MCQ-30 scale has also been adapted in several languages, Turkish,[18] Italian,[19] and Polish,[20] and can also be used for children[21] and adolescents.[16] A recent study[22] validated MCQ-30 and found that the scale has good internal consistency and is valid for use among patients with breast and prostate cancer. Evidence regarding the scale's validity in assessing metacognition in patients diagnosed with other forms of cancer is lacking.

Metacognitive Beliefs Result in Emotional Distress

Patients with cancer have impaired metacognitive functions.[23] They ruminate about cancer-related worries, its consequences on them and other family members, financial problems, family members' illness, and neighbor disputes.[24] Based on the S-REF theory, a study has found positive metacognitive beliefs related to worry and negative metacognitive beliefs related to uncontrollability and danger of worry are significantly higher in the patient group than the control group.[23] Anxiety and depression in patients with cancer are associated with positive and negative metacognitions.[25] However, the negative metacognitive beliefs compared to positive metacognitive beliefs have larger contribution to the development of anxiety and depressive symptoms after diagnosis[26] and while undergoing chemotherapy.[19,27–29] This suggests that though positive metacognitive beliefs initially guide a patient to worry but negative metacognitive beliefs maintain the worry by activating meta worry (worry about worry), which further intensifies the worry.[26] Another study found that metacognitive beliefs present after cancer diagnosis and before treatment predict depression, anxiety, and trauma in patients with cancer even after 1 year of diagnosis.[30] People diagnosed with cancer at a young age show severe anxiety symptoms, and a study suggests that it is due to the negative metacognitive beliefs about uncontrollability and the danger, which are found to be significantly higher in young people who have cancer than in adults.[31] Another study revealed negative metacognitive beliefs are heightened at 12 months of diagnosis and between 24 to 36 months postdiagnosis, suggesting patients with cancer engage in negative metacognitive beliefs mainly after primary treatment and after the treatment when they fear cancer recurrence.[32] Negative metacognitive beliefs are also higher in patients in the early stage of cancer than in patients in the advanced stage.[27] Caregivers of the patients diagnosed with cancer also experience positive and negative metacognitive beliefs, which are associated with a lower score in subjective well-being.[33] In young adult female cancer survivors, metacognitive beliefs were associated with their reproductive concerns such as fertility potential, partner disclosure, child's health, personal health, acceptance, and being pregnant.[34]

Table 1 Describing the studies included

Sl. No.	Title	Author and year	Sample characteristics	Research design and scale
1	Self-esteem, metacognition, and coping strategies in cancer patients: a case-control study	Inci et al, 2021	Sample size: ($N = 100$) Cancer patients ($n_1 = 50$) Control group ($n_2 = 50$) Age: 33–82 years Cancer type: gastric, colon, cervical, rectum, breast, liver, ovarian, and nasopharyngeal cancer Cancer phase: being treated for cancer Country: Turkey	Cross-sectional, case-control Scale: MCQ-30
2	Metacognitions and quality of life in survivorship after breast cancer diagnosis	Ranieri et al, 2021	Sample size: ($N = 72$) Age: 30–55 years Cancer type: breast cancer Cancer phase: at different time intervals; T0: 6–11 months, T1: 12–18 months, T2: 19–24 months, T3: 25–31 months Country: Italy	Cross-sectional study Scale: MCQ-30
3	Metacognitive aspects influence subjective well-being in parents of children with cancer	Toffalini et al, 2015	Sample size: ($N = 96$) Study group ($n_1 = 30$; age: 30–50 years) Hospitalized control group ($n_2 = 36$; age: 24–47 years) Healthy control group ($n_3 = 30$; age: 29–54 years) Cancer type: unspecified Cancer phase: active treatment (chemotherapy) Country: Italy	Case-control Scale: MCQ-30
4	A comparison of metacognitive factors among patients with cancer and the control group	Mutlu et al, 2018	Sample size: ($N = 491$) Cancer patients ($n_1 = 279$); age: 54.73 years (SD = 12.12) Control group ($n_2 = 212$); age: 51.15 years (SD = 12.86) Cancer type: breast cancer, lung, gastrointestinal, gynecological, urogenital, sarcoma, head/neck, skin, brain, other Cancer phase: treatment (operation, chemotherapy, radiotherapy Country: Turkey	Case-control Scale: MCQ-30
5	Predictive factors of anxiety and depression symptoms in patients with breast cancer undergoing chemotherapy. An explorative study based on metacognitions	Quattropani et al, 2017	Sample size: ($N = 80$) Age: 27–82 years Cancer type: breast Cancer phase: undergoing chemotherapy Country: Italy	Cross-sectional Scale: MCQ-30
6	The role of metacognitions in predicting anxiety and depression levels in cancer patients ongoing chemotherapy	Quattropani et al, 2015	Sample size: ($N = 175$) Age: 27–85 years Cancer type: breast, colon, and others Cancer phase: undergoing treatment Country: Italy	Cross-sectional Scale: MCQ-30

Table 1 (*Continued*)

Sl. No.	Title	Author and year	Sample characteristics	Research design and scale
7	Metacognition as predictor of emotional distress in cancer patients	Quattropani et al, 2016	Sample size: ($N = 175$) Age: 27–85 years Cancer type: breast, colon and other Cancer phase: undergoing treatment Country: Italy	Cross-sectional Scale: MCQ-30
8	The association of metacognitive beliefs with emotional distress and trauma symptoms in adolescents and young adult survivors of cancer	Fisher et al, 2019	Sample size: ($N = 87$) Age: 16–24 years Cancer type: leukemia, lymphoma, brain and central nervous system, bone, soft tissues sarcoma, germ cell tumors, others Cancer phase: completed acute treatment Country: not known	Cross-sectional Scale: MCQ-30
9	A prospective study of the association of metacognitive beliefs and processes with persistent emotional distress after diagnosis of cancer	Cook et al, 2015	Sample size: ($N = 206$) Age: 39–85 years Cancer type: breast or prostrate Cancer phase: T1 (shortly after diagnosis and before treatment) T2 (follow-up after 12 months) Country: UK	Cohort design Scale: MCQ-30
10	The association of metacognitive beliefs with emotional distress after diagnosis of cancer	Cook et al, 2015	Sample size: ($N = 229$) Age: 38–85 years Cancer type: breast or prostrate Cancer phase: within 3 months of diagnosis and before treatment Country: UK	Cross-sectional Scale: MCQ-30
11	Role of metacognition thinking and psychological traits in breast cancer survivorship	Ranieri et al, 2020	Sample size: $N = 72$ Young ($n_1 = 36$) Adult ($n_2 = 36$) Age: 38–55 years Cancer type: breast Cancer phase: after primary treatment Country: Italy	Observational study design Scale: MCQ-30
12	Testing relationships between metacognitive beliefs, anxiety and depression in cardiac and cancer patients: are they transdiagnostic?	Anderson et al, 2019	Secondary data	
13	Measuring metacognition in cancer: validation of the Metacognitions Questionnaire 30 (MCQ-30)	Cook et al, 2014	Sample size: ($N = 229$) Age: 38–85 years Cancer type: breast and prostrate Cancer phase: before treatment (T1) and follow-up after 12 months (T2) Country: UK	Scale: MCQ

(*Continued*)

Table 1 (*Continued*)

Sl. No.	Title	Author and year	Sample characteristics	Research design and scale
14	Fear of cancer recurrence among Chinese cancer survivors: prevalence and associations with metacognition and neuroticism.	Ng et al, 2019	Sample size: ($N = 285$) Age: 59.9 years (SD = 10.3) Cancer type: breast and colorectal Cancer phase: completed treatment Country: Hong Kong	Cross-sectional and longitudinal Scale: MCQ-30
15	Fear of cancer recurrence in young early-stage breast cancer survivors: the role of metacognitive style and disease-related factors.	Thewes et al, 2013	Sample size: ($N = 218$) Age: 28–45 years Cancer type: breast Cancer phase: completed treatment Country: Australia	Cross-sectional Scale: MCQ-30
16	The role of metacognition and its indirect effect through cognitive attentional syndrome on fear of cancer recurrence trajectories: a longitudinal study	Ng et al, 2020	Sample size: ($N = 270$) Age: Cancer type: breast and colorectal Cancer phase: after treatment Country: Hong Kong	Longitudinal study Scale: MCQ-30
17	Attentional bias and metacognitions in cancer survivors with high fear of cancer recurrence	Butow et al, 2015	Sample size: ($N = 63$) Age: 64.05 years (SD = 11.80) Cancer type: breast or prostrate Cancer phase: after treatment Country: Australia	Cross-sectional Scale: MCQ-30
18	Psychological resilience, metacognitions, and fear of recurrence among cancer survivors and family caregivers	Ağaç and Üzar-Özçetin, 2022	Sample size: ($N = 112$) Cancer survivors ($n_1 = 112$) Family caregivers ($n_2 = 112$) Cancer type: lung, breast, colorectal, others Cancer phase: in remission Country: Turkey	Cross-sectional Scale: MCQ-30
19	Group meta-cognitive therapy and depression in women with breast cancer: a randomized controlled trial	Zahedian et al, 2021	Sample size: ($N = 24$) Age: 27–67 years Cancer type: breast Cancer phase: under treatment Country: Iran	Experimental design Scale: MCQ-30
20	Metacognitive therapy for emotional distress in adult cancer survivors: a case series	Fisher et al, 2017	Sample size: ($N = 4$) Age: 45–55 years Cancer type: breast and endometrial cancer Cancer phase: completed acute medical treatment Country: UK	Experimental design Scale: MCQ-30
21	Brief metacognitive therapy for emotional distress in adult cancer survivors	Fisher et al, 2019	Sample size: ($N = 27$) Age: 29–67 years Cancer type: breast, hematological, ovarian, sarcoma, colorectal, ocular, lung Cancer phase: cancer survivors Country: UK	Experimental design Scale: MCQ-30

Table 1 (*Continued*)

Sl. No.	Title	Author and year	Sample characteristics	Research design and scale
22	Qualitative evaluation of cancer survivors' experiences of metacognitive therapy: a new perspective on psychotherapy in cancer care	Cherry et al, 2019	Sample size: ($N = 17$) Age: 25–69 years Cancer type: breast, sarcoma, ocular, hematology, ovarian, colorectal Cancer phase: completed acute medical treatment for cancer Country: UK	Qualitative study
23	Comparison of effectiveness of the metacognition treatment and the mindfulness-based stress reduction treatment on global and specific life quality of women with breast cancer	Rahmani et al, 2014	Sample size: ($N = 36$) Age: 38–49 years Cancer type: breast Cancer phase: under treatment Country: Iran	Quasi-experimental design
24	The feasibility of using metacognitive strategy training to improve cognitive performance and neural connectivity in women with chemotherapy-induced cognitive impairment	Wolf et al, 2016	Sample size: ($N = 14$) Age: 36–65 years Cancer type: breast Cancer phase: completed medical treatment (chemotherapy) Country: United States	Experimental design
25	Alleviating emotional distress in adolescent and young adult cancer survivors: an open trial of metacognitive therapy	Fisher et al, 2015	Sample size: ($N = 12$) Age: 18–23 years Cancer type: lymphoma, leukemia, brain tumor, rhabdomyosarcoma, osteosarcoma Cancer phase: cancer survivors Country: UK	Experimental design Scale: MCQ-30
26	Comparison of effectiveness of the mindfulness-based cognitive therapy nd the metacognition treatment on anxiety, depression and stress among breast cancer patients	Javadi et al, 2018	Sample size: ($N = 36$) Age: 38–49 years Cancer type: breast Cancer phase: diagnosis of breast cancer Country: Iran	Quasi-experimental design
27	The effectiveness of group metacognition treatment on metacognition beliefs of women with breast cancer	Rahmani et al, 2014	Sample size: ($N = 24$) Age: 41–47 years Cancer type: breast Cancer phase: diagnosis Country: Iran	Quasi-experimental design Scale: MCQ-30
28	Metacognition as an educational technology in self-care learning: the case of prevention of post-surgical lymphedema of breast cancer	Assis et al, 2018		Theoretical paper
29	Effectiveness of positive thinking training on perceived stress, metacognitive beliefs, and death anxiety in women with breast cancer	Barjoee et al, 2022	Sample size: ($N = 30$) Age: 42.81 years (SD = 7.35) Cancer type: breast Cancer phase: before treatment Country: Iran	Quasi-experimental design Scale: MCQ-30

(*Continued*)

Table 1 (*Continued*)

Sl. No.	Title	Author and year	Sample characteristics	Research design and scale
30	Mindfulness and metacognition in facing with fear of recurrence: a proof-of-concept study with breast-cancer women	Cheli et al, 2019	Sample size: ($N = 114$) Age: 18–65 years Cancer type: breast Cancer phase: after treatment Country: Italy	Mixed-method design
31	Metacognitions associated with reproductive concerns: a cross-sectional study of young adult female cancer survivors in China	Xiao et al, 2022	Sample size: $N = 318$ Age: 18–39 years Cancer type: unspecified Cancer phase: after primary treatment Country: China	Cross-sectional Scale: MCQ-30

Abbreviations: MCQ-30, Metacognition Questionnaire-30; SD, standard deviation.

Fear of Recurrence in Patients with Cancer

The metacognitive aspects are also linked to patients' fear of cancer recurrence.[35,36] A study reported psychological resilience in patients is low due to firm negative meta beliefs that predict fear of cancer recurrence (FCR) in patients.[37,38] Negative metacognitive beliefs partially mediate the relationship between neuroticism and fear of cancer recurrence,[39] suggesting that neuroticism and negative metacognition are positively associated. Patients with higher neuroticism are predisposed to experience negative beliefs about worry which increases their fear for cancer recurrence.[39] Studies suggest individuals with high FCR tend to perceive their worry as more beneficial, dangerous, uncontrollable, and important to control than those with lower FCR.[39,40] A study investigated difference between sub-clinical (scoring 13–21) and clinical (22 or above) FCR patients on Fear of Cancer Recurrence Inventory and found that subclinical FCR patients perceive worry as beneficial and a distress management strategy.[39] A longitudinal study examining fear of cancer recurrence over 12 months in patients with cancer found that negative meta beliefs are higher in patients at an initial stage and tend to decrease over time.[36]

Metacognitive Therapy for Cancer Treatment

Metacognition therapy administered individually or in a group is effective in challenging metacognitive beliefs and thereby is helpful in the treatment of depression, anxiety, posttraumatic symptoms, worry and rumination, sexual functioning, sleep disorder, fear of recurrence, and improves the quality of life in patients with cancer undergoing primary treatment.[41–43] The main objective of metacognitive therapy is to modify the metacognitive beliefs that maintain negative thinking styles and coping strategies. Metacognitive therapy typically includes 5 to 10 sessions[10] and in a study it was found that delivery of metacognitive therapy including six sessions helps in reducing emotional distress in patients with cancer.[42] The therapist identifies the positive and negative metacognitive beliefs in the first two sessions and generates a case formulation. The patient is then psycho-educated about their rumination time and thinking process, including the emotional consequences of it. From, the S-REF theory, we understand that modifying negative metacognitive beliefs is crucial as once an individual views their worry as uncontrollable, they have difficulty to control it.[10] Therefore, in the third, fourth, fifth, and sixth sessions, patients are taught and asked to practice attention training techniques, detached mindfulness, rumination postponement, modifying negative meta beliefs, and then the positive metacognitive beliefs using verbal methods, rumination modulation experiment, advantage–disadvantages analysis, and behavioral experiments. In the last session, the focus is on relapse prevention. Before administration of metacognitive therapy, participants reported being caught in a spiral of worry making them feel helpless, hopeless, and overwhelmed but, after the therapeutic intervention, they found themselves accepting and controlling their thoughts effectively and gained a sense of freedom to live lives free from fear about cancer and other challenges of survivorship.[24] It was observed that with the use of metacognitive therapy recovery status is maintained even after 1 month[43] to 6 months of follow-up[41,42] in adult cancer survivors and in adolescent and young adult cancer survivors.[44] A comparative study found that though metacognitive therapy is effective in reducing depression, anxiety, and stress symptoms in patients with breast cancer, mindfulness-based therapy has maximum effectiveness on emotion function, pain symptoms, and fatigue.[45,46] A study also made an attempt to integrate mindfulness and metacognitive-based therapy for patients with cancer and the result suggested effectiveness of integrating both therapeutic approaches in reducing distress, anxiety, depression, and posttraumatic symptoms.[35] In another study, it was found that positive thinking training effectively reduces metacognitive beliefs in patients with breast cancer.[47] To address the chemotherapy-induced cognitive impairment, a study found that Cognitive Orientation to Daily Occupational Performance (CO-OP), a type of metacognitive strategy training, has positive effect on cognitive performance and neural connectivity in women with breast cancer.[48] A

theoretical paper suggests that metacognition can act as educational technology and help breast cancer survivors to engage in preventive self-care practices for lymphedema.[49]

Discussion

This review article focused on the metacognitive processes in patients with cancer and caregivers. The study findings suggest that patients diagnosed with cancer suffer from emotional distress, depression, anxiety, and posttraumatic symptoms, and metacognitive beliefs play a significant role in developing and maintaining them, notably, the negative meta beliefs.[25] As the S-REF theory suggests both positive and negative metacognitive beliefs result in emotional distress; however, the role of negative metacognitive beliefs is crucial as once an individual view their worry as uncontrollable, they are unable to control it and feel helpless, hopeless, and get overwhelmed with worry.[10] Therefore, findings of several studies suggest a strong association between negative metacognitive beliefs with depression and anxiety.[23,26] Negative metacognition has been observed with young patients,[31] also among patients who were in early stages of cancer,[27] and received chemotherapy.[19,27–29] This is because adults who are young or are in early stage of cancer are more worried about the prognosis and fear about negative consequences such as fear of recurrence.[27,31] Similarly, patients who received chemotherapy are aware of its negative effects on health, i.e., nausea, weakness, hair loss, and loss of appetite. They understand that they have to be at home while the treatment is continuing, have to visit hospitals frequently to receive treatment, and they also experience uncertainty about recurrence of cancer which may suggest their higher scores in negative metacognitive beliefs than patients receiving radiotherapy or going through operation.[27]

Emotional distress, worry, ruminative thoughts, and symptoms of depression were also observed among family caregivers of patients diagnosed with cancer[50,51] and since family caregivers' support has great influence in the cancer treatment, it is important to understand their metacognitive beliefs. However, from our literature search, we found studies on metacognitive processes in caregivers are limited. We found two studies assessing metacognitive beliefs in caregivers indicating both positive and negative metacognitive beliefs are associated with subjective well-being[33] and psychological resilience.[37] Therefore, it is important to address metacognitive beliefs of caregivers and help them in dealing with the stressful situation and improving their quality of life.

We also focused on the benefits of the metacognitive therapy in patients with cancer. It was found that metacognitive therapy is effective in reducing emotional distress, anxiety, posttraumatic symptoms, and fear of recurrence in patients with cancer.[41–43] We also found studies comparing the effectiveness of mindfulness-based therapy and metacognition therapy.[45,46] From the comparison, it was evident that though mindfulness-based therapy reduced emotional distress in patients, however, the positive impact of the treatment was not observed in follow-up.[45] Again, another study attempted to integrate both mindfulness-based therapy and metacognition therapy and found taking both therapeutic approaches together had better outcomes rather than administering only one of the therapeutic approaches.[35] Also, one study found out the effectiveness of positive thinking training in reducing metacognitive beliefs.[47] There are other therapies such as Acceptance Commitment-Based Therapy[52–54] and Cognitive Behavior Therapy[55,56] that are used to treat emotional distress in patients with cancer. However, from our literature search we did not find any comparative studies to understand the effectiveness of metacognitive therapy with the other therapies. Also, we did not find any other studies integrating with metacognitive therapy other than mindfulness-based therapy. It would have been interesting to observe the outcome of using metacognitive therapy with complementary therapies like Art Therapy[57,58] and Dance Movement Therapy.[59] Metacognition has also been used as a strategy for improving executive function in patients who underwent chemotherapy[48] and can be used as an education tool to promote self-care practices in patients with breast cancer.[49]

It was also noted that studies included for review used MCQ-30 as a tool to assess metacognitive beliefs in patients with cancer. A study validated the scale in 2014 for use among patients patients diagnosed with breast and prostate cancer, limiting its use across different cancer diagnoses.[21] Although MCQ-30 has been used to a great extent to assess metacognitive beliefs in research studies, nevertheless, researchers can work on developing effective tools to assess metacognitive beliefs by taking participants with other forms of a cancer diagnosis.

Further, as mentioned above, we found limited countries conducted studies to understand the role of metacognition in patients diagnosed with cancer. We identified seven studies conducted each in UK and Italy, two studies each in Australia and Hong Kong, five in Iran, three in Turkey, and one study each in United States, and China. From our search results, we did not find studies conducted on the Indian population to know how metacognitive beliefs influence the psychological condition of people diagnosed with cancer and how therapy or specific strategies can be used to minimize the distress caused by the disease. This suggests that metacognition is still an emerging concept in health psychology, and looking at its contribution during diagnosis, treatment, and recovery, more research should be promoted in this area. In India, cancer cases are on the rise[60,61]; therefore, to improve the quality of life of patients diagnosed with cancer and to contribute to the pool of Indian scientific research, young researchers can explore the significance of metacognitive aspects in patients diagnosed with cancer in India.

Limitation

In this review article, researchers used more than one search database and included studies on different research designs. We did not limit the search for studies to any age group, cancer type, cancer stage, or country. However, the studies included have not been assessed for methodological quality and risk of bias. Despite this, the findings of the study will help in

advancing research studies in this area and mental health professionals, specifically working in the field of oncology.

Conclusion

This review helped us understand that patients with cancer experience metacognitive beliefs at different phases of cancer, i.e., before the primary treatment, during treatment, and after treatment, and metacognitive therapy contributes significantly to reducing emotional distress observed among patients with cancer. Hence, to improve the quality of life of patients with cancer and caregivers, research on metacognitive processes in cancer should be promoted.

Conflict of Interest
None declared.

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A Retrospective Analysis of Autologous Stem Cell Transplantation Outcomes in Adult Philadelphia Chromosome Positive-Acute Lymphoblastic Leukemia

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Ind J Med Paediatr Oncol 2023;44:408–413.

Abstract

Introduction Philadelphia chromosome positivity (Ph +) is a poor prognostic feature in adult acute lymphoblastic leukemia (ALL). Allogenic hematopoietic stem cell transplantation in first complete remission (CR1) is recommended. There is limited literature on the role of consolidation autologous stem cell transplantation (ASCT). This study was undertaken to assess the potential of consolidation ASCT in CR1 in adults with Ph + ALL.

Objectives The aim of this study was to analyze the safety and efficacy of ASCT in CR1 in adults with Ph + ALL.

Materials and Methods Adult patients diagnosed with Ph + ALL who underwent ASCT in CR1 after modified ALL-BFM95 protocol from 2015 to 2017 were included. Patients who achieved major molecular response or better were considered for ASCT with cyclophosphamide-total body irradiation regimen and peripheral blood stem cells infused on day 0. Toxicities as per Common Terminology Criteria for Adverse Event v4.0, disease-free survival (DFS), and overall survival (OS) were assessed. Inclusion criteria: Following patients were included—patients aged 18 years and above diagnosed with Ph + ALL; patients receiving BFM-95 induction chemotherapy protocol; patients who achieved CR after induction therapy; nonavailability of human leukocyte antigen match from a matched sibling donor or matched unrelated donor. Exclusion criteria: Patients not willing or unfit for ASCT and patients planned for allogenic hematopoietic stem cell transplantation were excluded.

Results Six adult patients with Ph + ALL underwent ASCT in CR1 (median age: 23 [range: 19–36] years, five patients were males [83%]). Imatinib was started at a median of 11 days from the start of induction IA (range: 10–21). Five patients achieved

Keywords
- Philadelphia chromosome
- autologous stem cell transplantation
- acute lymphoblastic leukemia
- consolidation therapy

article published online
April 17, 2023

DOI https://doi.org/10.1055/s-0043-1761413.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

morphological CR after induction 1A and, one patient at the end of induction 1B. The median time to ASCT (from diagnosis) was 8 months (range: 6.4–13). All the six patients had disease relapse and died due to progressive ALL. The median DFS and OS were 19.2 months and 23.3 months, respectively.

Conclusion Consolidation ASCT yielded poor outcomes in this study. There was a significant delay from diagnosis to ASCT, which might have impacted the results.

Introduction

The most common cytogenetic abnormality associated with adult acute lymphoblastic leukemia (ALL) is the Philadelphia chromosome, and it is seen in 20 to 30% of all adult ALL.[1,2] Philadelphia chromosome is due to the reciprocal translocation between long arms of chromosome 9 and 22: the Abelson (*ABL1*) oncogene on chromosome 9 translocate to the breakpoint cluster region (*BCR*) oncogene on chromosome 22, resulting in a fusion oncoprotein with constitutive tyrosine kinase activity leading to excessive proliferation of leukemic cells.[3]

Ph + ALL carries a poor prognosis in adult patients. However, the incorporation of tyrosine kinase inhibitors (TKIs) with standard chemotherapy has significantly improved outcomes.[4] The treatment of choice remains allogeneic hematopoietic stem cell transplantation (allo-HSCT) at first complete remission (CR1).[4] However, in patients who lack a human leukocyte antigen (HLA) match or in older patients, several reports suggest the advantage of consolidation autologous stem cell transplantation (ASCT) in Ph + ALL.[5–7] The absence of the graft-versus-leukemia effect is a major drawback with ASCT.

Data on adult Ph + ALL outcomes from India are scarce. In a multicenter study by the Indian Acute Leukemia Research Database (INwARD) of the Hematology Cancer Consortium, Ph + ALL was diagnosed in 17% of all adolescent and young adult (AYA) ALL patients (15–29 years).[10] The 2-year event-free survival among patients with Ph + ALL was 48 versus 59% for patients with Ph-ALL ($p = 0.01$).[8]

The present study was undertaken to analyze the real-world outcomes of ASCT in CR1 in adult patients with Ph + ALL due to the lower uptake of consolidation allo-HCT in India due to various socio-economic factors.

Materials and Methods

In 2015, based on the GRAALL study,[5] after obtaining a written informed consent, we started offering ASCT in adult patients with Ph + ALL in CR1. Ph + ALL was confirmed by the demonstration of *BCR-ABL* by qualitative reverse transcriptase-polymerase chain reaction (RT-PCR) in peripheral blood. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Ethics Committee Approval

As this study was a retrospective analysis of patients with Ph + ALL who underwent ASCT between 2015 and 2017, Institutional Ethics Committee approval (IEC) was not required. However, an IEC waiver was obtained: IEC Waiver form- Ref No-IEC/2021/Dec01. The patients received standard chemotherapy as per the modified Berlin-Frankfurt-Munster-95 (ALL-BFM95) protocol.[9] Imatinib was incorporated along with standard chemotherapy as soon as *BCR-ABL* by qualitative RT-PCR was positive.

Inclusion Criteria

Following patients were included for the study: Patients aged between 18 and 50 years and above diagnosed with Ph + ALL; patients receiving ALL-BFM95 induction chemotherapy protocol; patients who achieved CR after induction therapy; nonavailability of HLA match from a matched sibling donor or matched unrelated donor.

Exclusion Criteria

Patients not willing or unfit for ASCT and patients planned for allo-HSCT were excluded.

Induction IA consisted of prednisolone (60 mg/m^2, D1–D28), vincristine (1.5 mg/m^2, D8, D15, D22, D29), without daunorubicin and L-asparaginase and three doses of intrathecal (IT) methotrexate; IT was started after clearance of blasts in peripheral blood. Bone marrow studies were performed after the end of IA.

The second induction (IB) from day 34 to day 61 comprised of tablet 6-mercaptopurine (60 mg/m^2, D34- D61), injection cyclophosphamide (1gm/m^2 D34, D61), injection cytarabine arabinoside (75 mg/m^2, 4 blocks) and two more doses of IT methotrexate. *BCR- ABL* by quantitative RT-PCR was done at the end of IB. Morphological CR was defined as less than 5% blasts in the bone marrow aspirate smear with an absence of blasts in the peripheral smear with no extramedullary disease and transfusion independence. If the patient was not in CR after the end of IA, bone marrow studies were repeated at the end of IB. Bone marrow was not assessed for minimal residual disease (MRD) as it was not available at our center during the study period.

Major molecular response (MMR) was defined as *BCR-ABL* transcripts less than or equal to 0.1% by quantitative RT-PCR. Eligible patients were then consolidated with ASCT in CR1.

Cyclophosphamide-total body irradiation (Cy-TBI): cyclophosphamide 60 mg/kg for 2 days and TBI 2Gy twice daily for 3 days were used as a conditioning regimen. Cy-TBI conditioning was chosen because of its myeloablative and adequate immunosuppressive properties ensuring an adequate antileukemic effect, also ensuring homogenous dose distribution to the whole body, including sanctuary sites such as the central nervous system (CNS) and testicles.[5,7]

Stem cells were mobilized from the peripheral blood after priming with granulocyte colony stimulating factor (G-CSF) 10 µg/kg daily for 5 days. Plerixafor 0.24 mg/kg was given 10 to 12 hours before the apheresis. The apheresis was performed on day 5 of G-CSF. Engraftment was defined as peripheral blood neutrophil count more than 500/mm^3 for 3 consecutive days and platelet count more than 20,000/mm^3 for at least 7 days independent from platelet transfusion. All the patients were restarted on imatinib post-transplant upon engraftment.

Statistical Analysis

ASCT with Cy-TBI conditioning-related toxicities, disease-free survival (DFS), and overall survival (OS) were assessed. Toxicities were assessed as per Common Terminology Criteria for Adverse Event v4.0.[10] DFS was defined as the time to relapse of leukemia or death from the date of morphological CR. OS was defined as the time from diagnosis to death. OS after relapse was calculated as the time from disease relapse to death. Data were retrieved from electronic case records or case files, compiled, and analyzed using Microsoft Excel 2016.

Results

Seven patients were screened for the study, and six were included (refused ASCT-1). Six adult patients with Ph + ALL underwent ASCT in CR1 between 2015 and 2017 (►**Table 1**). The median age of the study group was 23 years (range: 19–36); five out of six were males (83%). p190 *BCR-ABL* transcript

Table 1 Patient details

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Day of starting imatinib during IA	D + 11	D + 21	D + 10	D + 12	D + 11	D + 11
Initial dose of imatinib	400 mg o.d. escalated to 600 mg o.d.	400 mg o.d. escalated to 800 mg o.d.	400 mg o.d.	400 mg o.d.	400 mg o.d. escalated to 600 mg o.d.	400 mg o.d. escalated to 600 mg o.d.
End of induction (IA) BM status	CR	Not in CR (CR achieved after IB)	CR	CR	CR	CR
BM prior to ASCT	CR	CR	CR	CR	CR	CR
Quantitative *BCR-ABL* prior to ASCT	0.03%	Undetectable	Undetectable	Undetectable	Undetectable	0.06%
Phase of treatment during which ASCT was performed	Consolidation	2nd maintenance	Consolidation	Consolidation	Consolidation	Consolidation
Time to ASCT from diagnosis (mo)	6.4	13	8.5	8.4	5.9	8
Day of starting imatinib post-transplant and dose	D + 32 600 mg o.d.	D + 33 400 mg o.d. escalated to 600mg o.d.	D + 42 400 mg o.d.	D + 36 600 mg o.d.	D + 33 600 mg o.d.	D + 34 600 mg o.d.
Quantitative *BCR-ABL* post-ASCT	N/D	N/D	Undetectable (+8 mo)	Undetectable (+9 mo)	Undetectable (+8 mo)	N/D
DFS (in mo)	8.9	20.5	59.1	23.2	17.9	10.3
Type of relapse	Medullary	Isolated CNS	Isolated CNS	Medullary	Medullary	Medullary
2nd line TKI and dose at relapse	Nil	Dasatinib 50 mg o.d.	Dasatinib 50 mg o.d.	Dasatinib 50 mg o.d.	Nil	Dasatinib 50 mg o.d.
OS (in mo)	13.2	32.8	68.8	44.4	20.3	14.8
OS after relapse (in mo)	3	11	8.5	5	1.3	3.4

Abbreviations: BM, bone marrow; CNS, central nervous system; CR, complete remission; DFS, disease-free survival; N/D, not done; o.d., once daily; OS, overall survival; TKI, tyrosine kinase inhibitor.

Table 2 Toxicities as per CTCAE v4.0

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Febrile neutropenia	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3	Grade 3
Infections	Nil	CLABSI-Coagulase-negative staphylococcus aureus	Nil	H1N1 bronchopneumonia (not requiring oxygen or ventilatory support)	Acute suppurative otitis media (organism not grown)	Nil
Chemotherapy-induced nausea and vomiting	Grade 3	Grade 2	Grade 3	Grade 3	Grade 2	Grade 2
Mucositis oral	Grade 3	Grade 2	Grade 2	Grade 2	Grade 2	Grade 2
Diarrhea	Nil	Grade 2	Nil	Grade 2	Grade 2	Grade 2

Abbreviation: CLABSI, Central line-associated blood stream infection.

by qualitative RT-PCR was detected in all the six patients. Conventional cytogenetics revealed t(9;22) in two patients (33%) and normal karyotype in the other four patients. CSF study was performed on day 8 after clearance of peripheral blood blasts. None of the patients had CNS disease. The median duration of starting imatinib was D + 11 of IA (range: 10–21). All the patients were compliant with imatinib. Five patients achieved morphological CR after IA and one patient at the end of IB. All the patients achieved MMR or better before ASCT. Among the six patients, five underwent ASCT during consolidation and one during second maintenance. Delay in ASCT was due to prolonged transplant waiting period due to immediate bed nonavailability.

The median time to consolidation ASCT from the start of induction chemotherapy was 8 months (range: 6.4–13). The median stem cell dose was 8.3×10^6 cells/kg (range: 4.6–10.6). The median time to neutrophil engraftment was day 13 (range: 12–22), and platelet engraftment was day 16 (range: 15–32). All patients had grade 2 to 3 nausea and vomiting, grade 2 to 3 mucositis, and grade 3 febrile neutropenia requiring intravenous antibiotics (►**Table 2**). There was no treatment-related mortality. All the patients were restarted on maintenance imatinib between D + 32 and D + 42 post-ASCT and were compliant. Six doses of monthly IT methotrexate were given post-transplant. There were no other imatinib-related toxicities. All six patients relapsed (100%); four patients-medullary relapse and two CNS relapse. Four patients (67%) received dasatinib 50 mg daily at relapse. Dasatinib-related toxicities were not observed; compliance with dasatinib was good.

All six patients died. The median follow-up was 23 months. The median DFS was 19.2 months (range: 8.9–59.1). The median OS was 23.3 months (range: 13.2–68.8). The median survival after relapse was 4.2 months (range: 1.3–11; ►**Table 1).**

Discussion

ASCT in CR1 for Ph + ALL has shown promising results in a few prospective and retrospective studies, including the CALGB study 10001(Alliance), registry data from Acute Leukaemia Working Party (ALWP) of the European Group of Blood and Marrow Transplantation (EBMT), and the GRAAPH 2003 study; the study characteristics are highlighted in ►**Table 3**.[5–7] The GRAAPH 2003 study showed a 4-year DFS of 50% and 4-year OS of 80% in Ph + ALL patients who underwent ASCT in CR1. The

Table 3 Comparison of ASCT outcomes in Ph + ALL with other studies

Variable	GRAAPH 2003 (5)	CALGB 10001(Alliance) (6)	EBMT (7)	Present study
Sample size	10	19	67	6
Conditioning regimen	Cy-TBI	Ara-c/VP 16-TBI	TBI based- 64% Cy-TBI Flu-TBI Chemotherapy-based-(34%) Bu-Cy Bu-Flu Bu-Mel	Cy-TBI
TRM	0	1(5%)	1(1.49%)	0
MRD assessment	Yes	Yes	Variable	No

Abbreviations: ASCT, autologous stem cell transplantation; CALGB, Cancer and Leukemia Group B; Cy-TBI, cyclophosphamide-total body irradiation; EBMT, European Group of Blood and Marrow Transplantation; MRD, minimal residual disease; Ph + ALL, Philadelphia chromosome positivity acute lymphoblastic leukemia; TRM, treatment-related mortality.

CALGB study 10001(Alliance) reported a 5-year OS of 51%, and the data is similar to a large retrospective registry cohort reported by EBMT. Given the favorable outcomes, we adopted this strategy in a real-world setting. While allo-HCT is recommended for adult Ph + ALL patients in CR1, the uptake is far lower in India due to various socioeconomic and psychological factors: the reasons are procedure refusal, lower availability of allo-HCT, including a long wait time at high-volume transplant centers, noncompliance to treatment, and cost; some of these factors have been highlighted already in other studies from the region.[8,11]

In our study, all six patients relapsed and died due to disease. The median DFS was 19 months and the median OS was 23 months. The results of the present study indicate that the outcomes of ASCT were poor. Due to early relapses, the lack of effective salvage chemotherapy options, and financial constraints for further treatment, patients were advised to continue palliative care. All the patients who started dasatinib at relapse had short-term disease remissions. The median survival after relapse was only 4.2 months (range: 1.3–11). The major limitations of the study are the small sample size and being retrospective in nature. In the GRAAPH-2003 study, patients underwent consolidation ASCT after completing a 28-day induction and consolidation chemotherapy protocol.[5] However, in our study, consolidation ASCT was performed at a median of 8 months after initiating induction chemotherapy. This delay could have contributed to the poor outcomes observed in our study. Bone marrow MRD was not assessed post-induction or prior to ASCT during the study period. In the GRAAPH 2003 study, outcomes in patients who underwent post-consolidation ASCT were best in those patients with low or negative MRD levels. MRD assessment was not available at our center during the study period. The lack of MRD assessment in the present study could have contributed to the poor outcomes in our study cohort. There was no treatment-related mortality. Treatment for these patients was supported by the State Health Insurance scheme. Therefore, imatinib was used as a first-line TKI due to the high cost of dasatinib and the nonavailability of generic versions of dasatinib during the study period. After the initial experience with these six patients, the practice was abandoned at our center because it was not practically possible to offer ASCT at our center immediately after initial induction and consolidation therapy as in the GRAAPH 2003 study. These numbers are very small to make definite conclusions against the role of ASCT in CR1 in Ph+ ALL. However, if this must be put into practice, we must ensure that the ASCT is timed early in the course as per published data. Even in the GRAAPH 2003 study, patients who received more than 1 course of high-dose methotrexate prior to ASCT (indicating delay) had worse outcomes.

Conclusion

Consolidation ASCT in patients with Ph + ALL yielded poor outcomes in this study. There was a significant delay from diagnosis to ASCT, which might have impacted the results. In patients who are not willing or unfit for allo-HCT, prospective studies can be undertaken to assess the outcome of ASCT in CR1 after dasatinib-based induction chemotherapy regimens with available data on the MRD status prior to and following ASCT.

Author's Contributions

All co-authors have reviewed the manuscript and have contributed substantially to the present study.

Ethics Approval

As this study was a retrospective analysis of patients with Ph + ALL who underwent ASCT between 2015 and 2017, IEC approval was not required per institutional policy. An IEC waiver form was obtained for the same.

Consent

Informed consent was obtained from all individual participants included in the study.

Funding

None.

Conflicts of Interest

None declared.

Acknowledgments

We thank the patients for agreeing to provide their clinical details. We would also like to thank Ms. N. Vanitha for her support to all the patients undergoing hematopoietic stem cell transplantation at our Institute.

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Correlation of Quantitative Diffusion-Weighted MR Parameters and SUVmax from 18-FDG PET-CT in Lung Cancer: A Prospective Observational Study

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Ind J Med Paediatr Oncol 2023;44:414–421.

Abstract

Background Diffusion-weighted magnetic resonance imaging (DW-MRI) sequences report the cellularity in tissues and 18-fluorodeoxyglucose (18-FDG) positron emission tomography–computed tomography (PET-CT) provides information on glucose metabolism in cells, associated to tumor aggressiveness. The aim of this study was to assess the correlation between quantitative diffusion-weighted magnetic resonance parameters and maximum standardized uptake value (SUVmax) using 18-FDG PET-CT in lung cancer and metastatic lymph nodes.

Methods Histologically proven 29 patients of lung cancers were subjected to 18-FDG PET-CT and DW-MRI (parameters: repetition time/time to echo [TR/TE] = 4,000/76 ms; *b*-values = 0, 400, and 800 s/mm^2) between June 2018 and June 2019. SUVmax was calculated on the PET-CT images representing region of interest (ROI) in the tumor. The apparent diffusion coefficient (ADC) values were quantified by placing an ROI over the tumor at a high *b*-value of 800 mm^2/s. Statistical analyses for correlation between SUVmax and ADC were done using Pearson's correlation coefficient (*r*).

Results Significant negative correlation was observed between analyses of ADC and SUVmax for primary lesions of all nonsmall-cell lung cancers (NSCLCs; $p < 0.05$) and its histological subtype adenocarcinoma ($p < 0.05$) but not squamous cell carcinomas ($p = 0.35$). Significant negative correlation was also observed for metastatic lymph nodes of adenocarcinoma ($p < 0.05$) but not for metastatic lymph nodes of all NSCLCs ($p = 0.05$) or squamous cell carcinomas ($p = 0.55$).

Keywords
- 18-FDG PET-CT
- apparent diffusion coefficient (ADC)
- nonsmall-cell lung cancer (NSCLC)
- SUVmax

article published online
June 9, 2023

DOI https://doi.org/10.1055/s-0042-1754392.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusions Diffusion-weighted imaging (DWI) with ADC may represent a new prognostic marker due to a significant negative correlation between ADC determined by DWI and SUVmax by PET-CT in NSCLCs. Furthermore, DWI-MRI of the thorax can be added to routine 18-FDG PET-CT for staging and response assessment in lung cancer in prospects.

Introduction

Lung cancer is one of the most common causes of cancer and mortality worldwide. In 2018, 2.1 million new cases (11.6% of the total) and 1.8 million deaths (18.4% of the total) were estimated. The disease remains the most common cancer in men worldwide (14.5% of the total) and the third most common in females (8.4% of the total).[1] Approximately, 80% of lung cancers are non-small-cell lung cancers (NSCLCs) and it further has two major types: squamous cell carcinoma and nonsquamous cell carcinoma, including adenocarcinoma and large-cell carcinoma.[2]

NSCLCs diagnosed in the later stages may present with adjoining structures like chest wall/mediastinal invasion, and metastases to lymph nodes or distant organs. The presence of metastases has a significant impact on the disease prognosis and mortality. Early-stage NSCLC cases can be potentially treated by different modalities like surgery/radiotherapy and chemotherapy but advanced or metastatic NSCLC cases are largely incurable.[2] The prognosis of NSCLC depends on many factors like stage, performance status, and molecular markers for treatment regimens.

Targeted therapy is found to be very effective in patients having epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK), or ROS1 rearrangements, which are predictive and prognostic markers for NSCLC.[2]

In the last decade, integrated 18-fluorodeoxyglucose (18-FDG) positron emission tomography–computed tomography (PET-CT) was the diagnostic imaging of choice in lung cancer patients for tumor, nodes, and metastases (TNM) staging as it delineates the tumor from adjacent structures anatomically and glucose metabolism in cells by calculating the standardized uptake value (SUV) physiologically.[3,4] The high SUV in the baseline tumor corresponds to the high glucose metabolism and if the SUV does not show any decrease after initiation of treatment, a poor therapeutic response resulting in lower overall survival rates has been observed.[5] The primary tumor with a high SUV at baseline 18-FDG PET is also associated with lesser duration for progression and more chances of recurrences. Thereby, it makes SUV a crucial prognostic indicator during the course of lung cancer disease.[6]

Magnetic imaging resonance (MRI) with high-performance gradient coils and multiple sequences has paved the way for new sensitive approaches for lung imaging. MRI with 1.5 Tesla and 3 Tesla magnetic field strength sensitively detects lung nodules and lesions and provides morphological details about the tumor without being exposed to ionizing radiation as compared with CT and PET-CT.[7]

Presently, diffusion-weighted magnetic resonance imaging (DW-MRI) is implemented in pulmonary imaging with great prospects in the detection of lung lesions.[8] DW-MRI visualizes the random Brownian motion of molecules within a voxel, which causes incoherent phase shifts resulting in signal attenuation. It helps in quantification of diffusion by measuring the apparent diffusion coefficient (ADC) values in the lesion. Due to high cell density in malignant tumors, water molecules cannot move freely into the interstitial space and show restricted diffusion with lower ADC values. DW-MRI provides information on cellularity in lung cancers, which may have a direct correlation with tumor aggressiveness.[8,9]

Objective

MRI imaging in lung cancer relatively lacks insight and exposure with no such relevant study ever done in India. With the goal in modern oncology to optimize therapeutic responses and minimize toxicities in patient care, it needs more precise and quantifiable noninvasive parameters for prognosis and early response evaluation to treatment.[10] We aimed to study the correlation between quantitative diffusion-weighted magnetic resonance (MR) parameters and SUVmax using 18-FDG PET-CT in lung cancer.

Materials and Methods

Study Design

This was a prospective observational study conducted at the Rajiv Gandhi Cancer Institute and Research Centre, a tertiary care hospital at New Delhi, after obtaining an Ethics Committee approval.

Study Population

Histopathologically proven 29 patients of lung cancer, who had undergone pretherapeutic staging with 18-FDG PET at all stages, after obtaining an informed consent, were included in this study between June 2018 and June 2019. A sample size of 29 patients was calculated by the formula given below referring to the study done by Tyng et al.[11]

The formula for sample size calculation was:

$$n = \frac{\left(Z_{1-\beta} + Z_{1-\frac{\alpha}{2}}\right)^2}{\left(\frac{r^2}{1-r^2}\right)}$$

Where,

r : Correlation coefficient.

$Z_{1-\alpha/2}$: Desired confidence level

$1-\beta$: Power

where,
correlation coefficient = –0.592[15]
with power = 95%, $n = 24$
with power = 90%, $n = 19$
Z = 5% level of significance

The minimum sample size thus calculated should be 24. Approximate operational sample size = 29 cases.

Patients who underwent any previous antineoplastic treatments like surgery, chemotherapy, or radiation therapy, or contraindicated for MRI (with a cardiac pacemaker, aneurysmal clip, or metal prosthesis) were excluded.

Patients were subjected to 18-FDG PET-CT and brain MRI scans for pretherapeutic staging. For our study, we added thoracic DW-MRI sequences for lung lesions and mediastinal lymph node evaluation.

18-FDG PET-CT Protocol

Precisely, 370 MBq of 18-FDG was injected intravenously 1 hour before the scan. The patient was kept supine and arms held above the head; whole-body examination was performed utilizing a dedicated (Siemens Tru V) system, with four 3.75 mm detectors, 1.5 pitch, and collimation of 5 mm. The CT exposure factors were 140 kVp and 80 mA in 0.8 second. Whole-body PET emission scan was performed, covering an area identical to that of a CT (divided into 5–6 standard bed positions). All acquisitions were performed in a two-dimensional model and consisted of emission scans of 5 minutes per bed position. PET images were reconstructed using CT for attenuation correction by employing CT maps. Transaxial scans of $4.3 \times 4.3 \times 4.25\ mm^3$ (in-plane matrix size 128×128) were reconstructed using OSEM—ordered subsets expectation maximization—with two iterations, 28 subsets, and a filter of 7.0 mm. The axial field of view (FOV) was 148.75 mm, resulting in 35 slices per bed position. Experienced nuclear physicians evaluated the PET-CT images—qualitative (visual) and semiquantitative analyses—with calculation of SUVmax within the lesions. The SUVmax was a representative volumetric region of interest (ROI) in the tumor lesion, normalized to injected dose and patient's weight.

MRI Protocol

Using Siemens Avanto 1.5 Tesla MR Unit, MRI acquisitions were performed by thoracic and body array coil avoiding motion artifacts. Diffusion-weighted imaging (DWI) of thorax was acquired in the axial plane using echo-planar imaging sequence (repetition time/time to echo [TR/TE] = 4,000/76 ms; 5 mm slice thickness; and FOV, 25–30 cm). The *b*-values used were 0, 400, and 800 mm^2/s and ADC maps were generated for all the images. On DWI sequences, the corresponding areas were studied for any restriction and the gray value of the pixel corresponds to the ADC values since a pixel-to-pixel ADC map was automatically calculated for each slice. ADC values were measured manually by placing an ROI over the lesion using pixel-wise ADC maps at a high *b*-value of 800 mm^2/s. The ROI was most representative of the lesion, excluding areas of necrosis, calcifications, or areas that suffer interference or partial volume adjacent to the lesion.

Statistics

Statistical analysis was done using *Statistical Package for Social Sciences* version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD) and median.

Normality of data was tested by Kolmogorov–Smirnov test. Quantitative variables were compared using an independent *t*-test (as the datasets were normally distributed) between the two groups. Pearson correlation coefficient was used for correlation analysis between ADC and SUVmax values. A *p*-value of <0.05 was considered statistically significant.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Ethics Committee approval was obtained from the Institutional Ethics Committee dated August 17, 2018.

Patients were provided patient information sheet regarding study details and an informed consent was obtained prior to enrolment.

Results

Clinical Characteristics of Patients

Overall, 29 patients of NSCLCs—18 males (62.07%) and 11 females (37.9%), range 34 to 86 years with a mean of 61.7 years and a median of 61 years (SD = 11.7 years)—were evaluated. History of smoking was present in 25 cases, that is, 86.21%. In our study, among NSCLCs, adenocarcinoma was the most common histological type ($n = 19$; 65%), followed by squamous cell carcinoma ($n = 10$; 34.4%). Details of all the subjects have been provided in ►**Supplementary Table S1**.

Correlation between ADC and SUVmax in NSCLC and Its Histological Variants

We found a statistically significant negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all NSCLC cases (►**Fig. 1A-C**). Pearson correlation coefficient and *p*-value are: $r = -0.42$ and $p = 0.02$ for correlation between SUVmax and ADCmin; $r = -0.39$ and

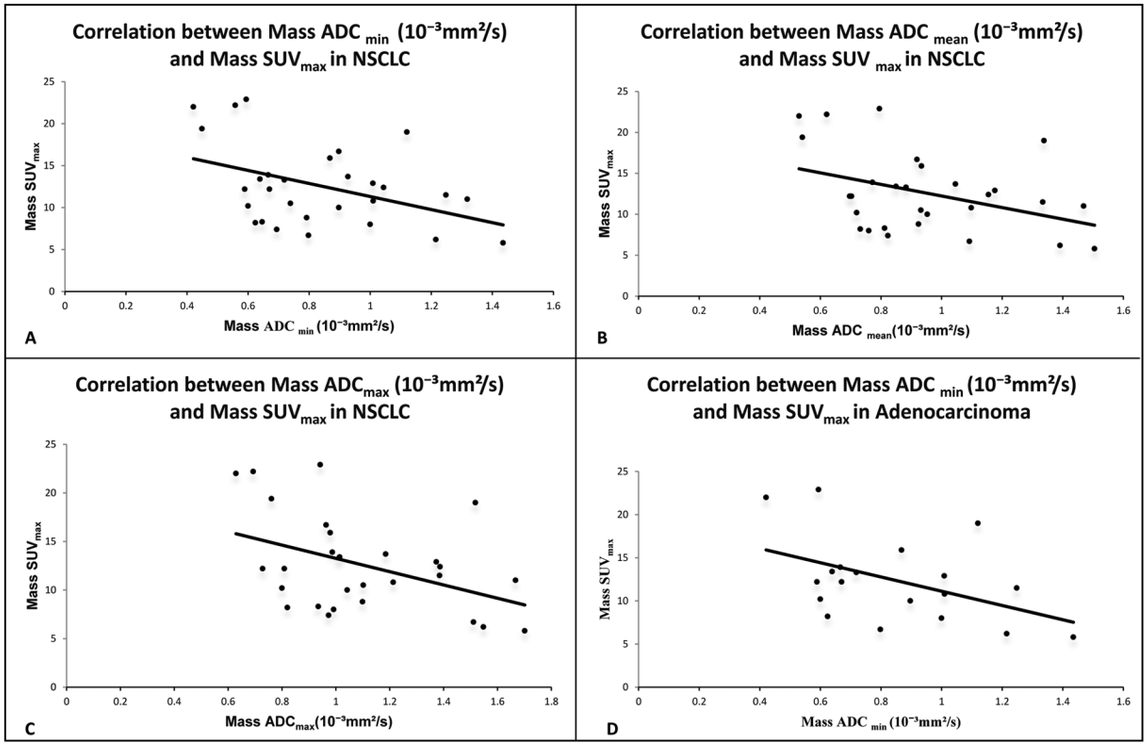

Fig. 1 (A) Correlation between mass ADC_{min} (10^{-3} mm^2/s) and mass SUV_{max} in total study subjects with NSCLC. (B) Correlation between mass ADC_{mean}(10^{-3} mm^2/s) and mass SUV_{max} in total study subjects with NSCLC. (C) Correlation between mass ADC_{max} (10^{-3} mm^2/s) and mass SUV_{max} in total study subjects with NSCLC. (D) Correlation between mass ADC_{min} (10^{-3} mm^2/s) and mass SUV_{max} in adenocarcinoma. ADC-apparent diffusion coefficient; SUV-standardized uptake value.

$p = 0.03$ for correlation between SUVmax and ADCmean; and $r = -0.42$ and $p = 0.02$ for correlation between SUVmax and ADCmax, respectively.

►**Table 1** shows correlation coefficient (r) and p-value between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all NSCLC cases, and its histological subtypes adenocarcinoma and squamous cell carcinoma. We also found a negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all adenocarcinoma cases, a histological variant of NSCLC (►**Fig. 1D**). The negative correlation between SUVmax and ADCmin in all adenocarcinoma cases was statistically significant with Pearson correlation coefficient and p-value: $r = -0.46$ and $p = 0.04$, respectively.

In squamous cell carcinoma, a negative correlation was found between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax, but it was not statistically significant.

Correlation between ADC and SUVmax in Lymph Nodes of NSCLC and Its Histological Variants

►**Table 2** shows correlation coefficient (r) and p-value between SUVmax and ADCmin, SUVmax and ADCmean, and

Table 1 Correlation of Mass SUVmax with Mass ADC in NSCLC, squamous cell carcinoma, and adenocarcinoma

Mass SUVmax	NSCLC	Squamous cell carcinoma	Adenocarcinoma
Mass ADCmin (10^{-3} mm^2/s)			
Correlation coefficient (r)	–0.423	–0.329	–0.463
p-Value	0.022	0.354	0.046
Mass ADCmean (10^{-3} mm^2/s)			
Correlation coefficient (r)	–0.395	–0.452	–0.364
p-Value	0.034	0.189	0.126
Mass ADCmax (10^{-3} mm^2/s)			
Correlation coefficient (r)	–0.426	–0.479	–0.399
p-Value	0.021	0.161	0.091

Abbreviations: ADC, apparent diffusion coefficient; NSCLC, nonsmall-cell lung cancer; SUV, standardized uptake value.
Note: Pearson correlation coefficient (r). P-value < 0.05: The result is statistically significant.

Table 2 Correlation of Lymph node SUVmax with Lymph node ADC in NSCLC, squamous cell carcinoma, and adenocarcinoma

Variables	NSCLC	Squamous cell carcinoma	Adenocarcinoma
Lymph node ADCmin (10^{-3} mm^2/s)			
Correlation coefficient (*r*)	–0.374	0.211	–0.522
p-Value	0.05	0.559	0.022
Lymph node ADCmean (10^{-3} mm^2/s)			
Correlation coefficient (*r*)	–0.371	0.236	–0.524
p-Value	0.052	0.511	0.021
Lymph node ADCmax (10^{-3} mm^2/s)			
Correlation coefficient (*r*)	–0.306	0.264	–0.5
p-Value	0.113	0.461	0.029

Abbreviations: ADC, apparent diffusion coefficient; NSCLC, nonsmall-cell lung cancer; SUV, standardized uptake value.
Note: Pearson correlation coefficient (*r*). *P*-value < 0.05: The result is statistically significant.

SUVmax and ADCmax in mediastinal lymph nodes of all NSCLC cases, and its histological subtypes adenocarcinoma and squamous cell carcinoma. We found a negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in mediastinal lymph nodes of all NSCLC cases.

Negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in lymph nodes of all NSCLC cases was not statistically significant, with Pearson correlation coefficient and *p*-value being $r = -0.37$ and $p = 0.05$, $r = -0.37$ and $p = 0.05$, and $r = -0.30$ and $p = 0.11$, respectively.

But we found statistically significant negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all lymph nodes of adenocarcinoma cases (►**Fig. 2**). Pearson correlation coefficient and *p*-value are $r = -0.52$ and $p = 0.02$, $r = -0.52$ and $p = 0.03$, and $r = -0.5$ and $p = 0.02$ for each correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax, respectively.

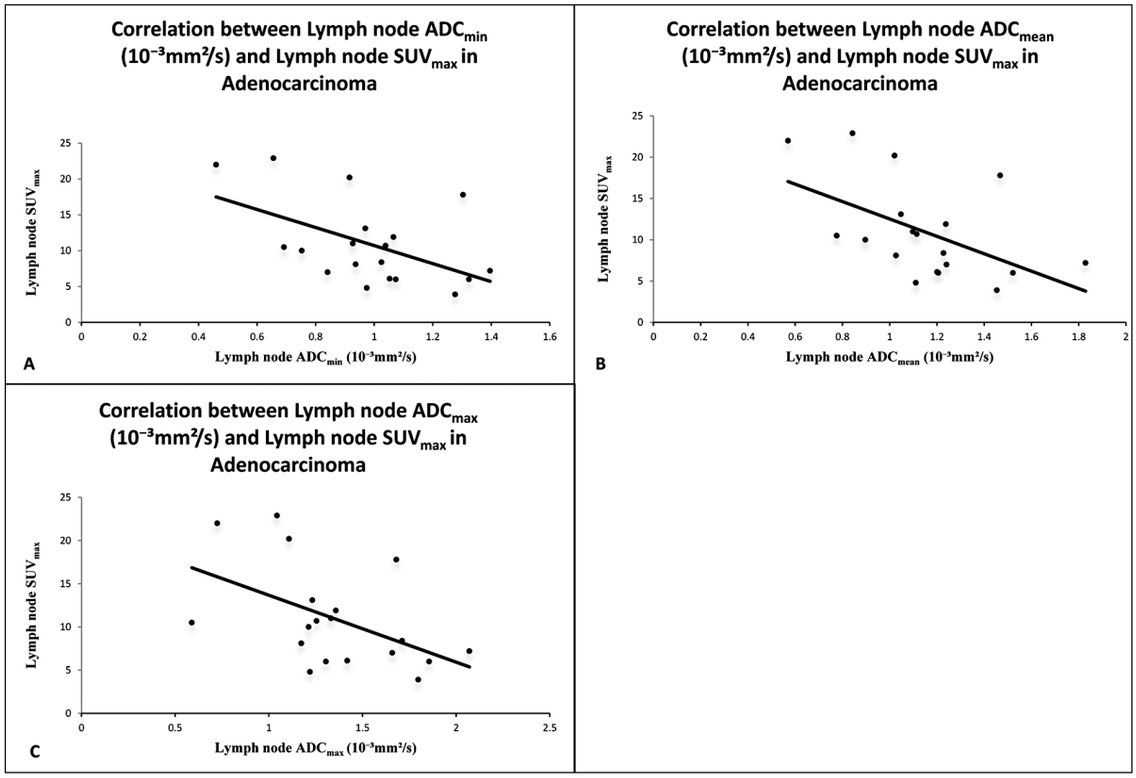

Fig. 2 (A) Correlation between lymph node ADC_{min}(10^{-3} mm^2/s) and lymph node SUV_{max} in adenocarcinoma. (B) Correlation between lymph node ADC mean (10^{-3} mm^2/s) and lymph node SUV_{max} in adenocarcinoma. (C) Correlation between lymph node ADC_{max}(10^{-3} mm^2/s) and lymph node SUV_{max} in adenocarcinoma. ADC-apparent diffusion coefficient; SUV-standardized uptake value.

In lymph nodes of squamous cell carcinoma, a negative correlation was found between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax, but it was not found statistically significant.

Comparison of ADC Values among Lung Mass, Mediastinal Lymph Nodes, and Its Histological Types

In ►**Supplementary Table S2**, the calculated mean ADC values for lung cancers are as follows: 0.83 ± 0.26, 0.95 ± 0.27, and $1.1 \pm 0.3 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

The calculated mean ADC values for adenocarcinoma are as follows: 0.85 ± 0.27, 0.96 ± 0.28, and $1.1 \pm 0.3 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

The calculated mean ADC values for squamous cell carcinoma are as follows: 0.81 ± 0.26, 0.92 ± 0.27, and $1.0 \pm 0.3 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

In ►**Supplementary Table S3**, the calculated mean ADC values for mediastinal lymph nodes in lung cancers are as follows: 0.95 ± 0.29, 1.1 ± 0.34, and $1.3 \pm 0.45 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

The calculated mean ADC values for mediastinal lymph nodes in adenocarcinoma are as follows: 0.98 ± 0.24, 1.1 ± 0.29, and $1.36 \pm 0.37 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

The calculated mean ADC values for mediastinal lymph nodes in squamous cell carcinoma are as follows: 0.87 ± 0.37, 1.07 ± 0.44, and $1.3 \pm 0.59 \times 10^{-3}$ mm^2/s (mean ± SD) for ADCmin, ADCmean, and ADCmax, respectively.

Mean ADC values for adenocarcinoma are slightly higher than ADC values for squamous cell carcinoma in lung cancers and its mediastinal lymph nodes also, but not found statistically significant.

Discussion

Our study comprised of 29 patients of NSCLC and we found a significant negative correlation between ADC and SUVmax for NSCLC, irrespective of its subtypes. This is in congruence with studies by Tyng et al,[11] Regier et al,[12] and Heusch et al[13] who reported a significant negative correlation between ADC and SUVmax variables in 37, 41, and 18 patients of NSCLC, respectively. Therefore, these results explain a direct correlation between the motion of water molecules, cellularity in tissues assessed by DW-MRI, and glucose metabolism in cells evaluated by PET-CT, which are concerned with tumor aggressiveness.

We found statistically significant negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all NSCLC cases. Statistically significant negative correlation was also observed between SUVmax and ADCmin in adenocarcinoma cases (►**Fig. 3A-D**). We found a negative correlation between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all squamous cell carcinoma cases, but it was not found statistically significant.

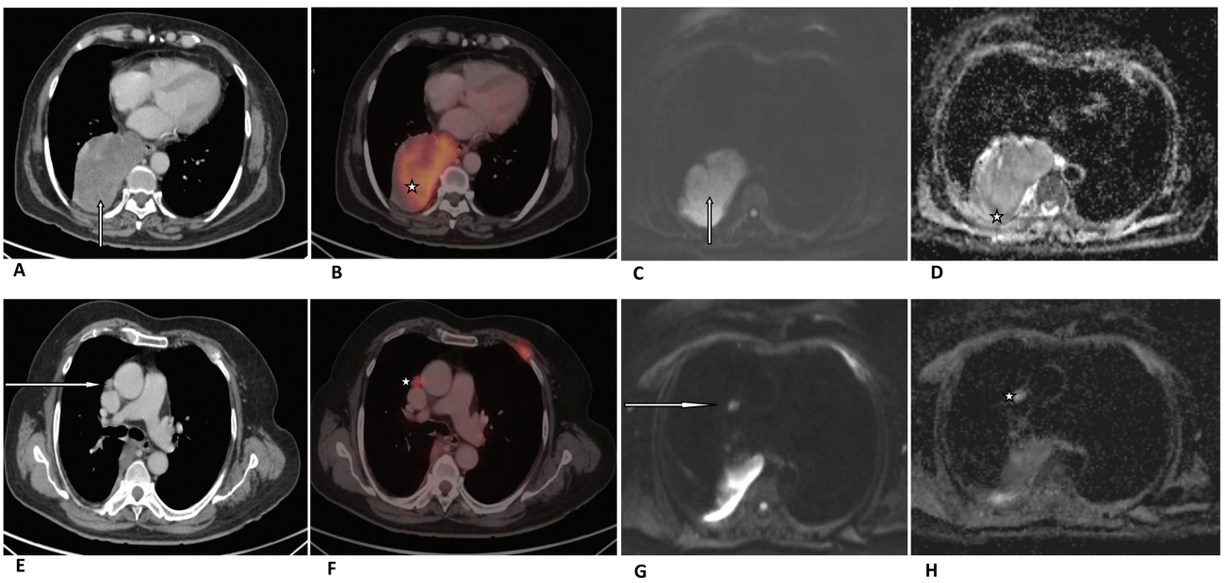

Fig. 3 A 72-year-old patient was diagnosed with adenocarcinoma of the right lung lower lobe with mediastinal lymphadenopathy. (**A**) Axial CT image in soft tissue window setting (arrow) and (**B**) corresponding fused PET-CT image are showing right lung lower lobe mass (star) with SUV_{max} of 15.9. (**C**) Gray-scale axial DWI of the lower thorax (arrow) and (**D**) corresponding ADC slice are showing hypointense tumor mass (star) with ADC_{max}, ADC_{mean}, and ADC_{min} - 0.97, 0.93, and 0.86 $\times 10^{-3}$ mm^2/s, respectively. A 72-year-old patient was diagnosed with adenocarcinoma of the right lung lower lobe with mediastinal lymphadenopathy. (**E**) Axial CT image in soft tissue window setting (arrow) and (**F**) corresponding fused PET-CT image are showing right prevascular lymph node (star) with SUV_{max} of 7.2. (**G**) Gray-scale axial DWI of the lower thorax (arrow) and (**H**) corresponding ADC slice are showing hypointense prevascular lymph node (star) with ADC_{max} ADC_{mean} and ADC_{min} 2.0, 1.8, 1.39 $\times 10^{-3}$ mm^2/s, respectively. ADC- apparent diffusion coefficient; CT-computed tomography; DWI-diffusion-weighted image; PET-positron emission tomography; SUV-standardized uptake value.

PET-CT determines glucose metabolism in the tumor through the activity of 18-FDG by its accumulation in vital cells. An increase in 18-FDG uptake shows an increase in glycolysis due to the high metabolic activity of malignant tumors, the so-called Warburg effect.[14] This gives information on the pathophysiology and growth of the tumor by calculating the SUVmax. In DW-MRI, a decrease in ADC values has been demonstrated in various malignant diseases,[15] tumor characteristics, and the manifestation of lymph node metastases.[16] Hence, both approaches, the SUV determining the metabolic activity on PET-CT and the ADC revealing diffusion restriction due to cellularity in tumor cells, on the other hand, are in direct relation to tumor aggressiveness. These results agree with the hypothesis that DWI may have a role in the imaging evaluation of lung cancers.

The inability of SUV readings to decrease has been linked to a failure to respond to treatment. It is associated with lesser duration for progression and more chances of recurrences with lower overall survival rates.[5,17] Few studies have demonstrated that low ADC and high SUVmax are associated with poor disease progression after treatment.[18] Iizuka et al[18] evaluated 15 patients of NSCLC with stereotactic body radiotherapy (SBRT). They concluded that a low ADC on pretreatment DW-MRI and a high SUVmax might be associated with poor disease progression in NSCLC patients treated with SBRT, and using both values in combination was a better predictor.

Meanwhile, studies are trying to conclude that DW-MRI may have a better potential for early prediction of early tumor response to therapy and prognosis in advanced lung cancer, and ADC may represent a new prognostic biomarker.[13,19–21] Tsuchida et al[22] evaluated 28 patients of advanced lung cancer for response assessment and concluded that DW-MRI could help in prognosis in advanced lung cancer patients. Ohno et al[19] concluded that DWI may have a better potential than 18-FDG PET-CT for prediction of tumor response to therapy in NSCLC patients before chemo-radiotherapy.

Yabuuchi et al[20] and Chang et al[23] showed ADC as a promising tool for monitoring the early response or predicting prognosis after chemotherapy in NSCLC. Until now, tumor response to treatment was determined by a decrease in diameter or size in serial CT studies as chemotherapy causes cell membrane rupture and decrease in cell size and density, which facilitates the diffusion of the molecules after the beginning of the treatment.[24] DW-MRI may evaluate response to treatment earlier, as ADC values may increase before the reduction of tumor size. As in our study, we did not perform DWI-MRI after chemotherapy to see the response assessment in form of change in ADC values in comparison to baseline ADC values. So, we require more studies to study the correlation of ADC and SUV in prognosis and therapeutic response in the population.

Significant negative correlation was observed between SUVmax and ADCmin, SUVmax and ADCmean, and SUVmax and ADCmax in all lymph nodes of adenocarcinoma cases (►**Fig. 3E-H**). However, no significant negative correlation was observed in lymph nodes of squamous cell carcinomas. Till now, few studies showed negative correlation between increased glucose metabolism and cellularity in lymph node metastases of NSCLC patients. Schaarschmidt et al[25] compared the ADC in lymph node metastases of NSCLC patients with SUV using 18-FDG PET/MRI in 38 patients and found a weak inverse correlation between SUVmax and ADCmean. Usuda et al[26] found better accuracy of DW-MRI over PET-CT in diagnosing metastatic lymph nodes in NSCLC patients and found a weak negative correlation between SUVmax and ADC. We found that mean ADC values for adenocarcinoma are slightly higher than ADC values for squamous cell carcinoma in lung cancers and its mediastinal lymph nodes also. Matoba et al[8] reported that ADC values are dependent on restricted diffusion within the water microenvironment due to cell membranes, tight junctions, fibers, macromolecules, and cell organelles, and directly related to tumor cellularity and aggressiveness. Therefore, the adenocarcinoma may be having high tumor cellularity due to the microstructural environment that influences ADC values to be higher than the squamous cell carcinoma variant.

There was a significant negative correlation between ADC and SUVmax in NSCLC cases, its histological variant adenocarcinoma, and mediastinal lymph nodes of adenocarcinoma in our study, due to early prediction of tumor response in comparison to PET-CT as described by Yabuuchi et al[20] and Chang et al.[23] So, ADC may represent a new prognostic marker in NSCLC with incremental benefit in staging and response evaluation without radiation exposure.

However, recent study conducted by Bruckmann et al[27] concluded that the combined analysis of SUV and ADC values does not improve the survival prediction in NSCLC and, therefore, ADC values do not further enhance the diagnostic value of SUV as a prognostic biomarker in NSCLC.

Our study has some limitations. The first is the small size of population cohort, and patient selection criteria were biased by inclusion criteria being based on histopathological findings. More studies with a larger cohort and without any potential selection bias are needed.

Conclusion

Our study reveals a significant negative correlation between SUVmax by PET-CT and ADC values by DW-MRI in NSCLC cases and its histological variant, adenocarcinoma. A significant negative correlation is also observed in SUVmax and ADC in metastatic lymph nodes of adenocarcinoma.

DWI with ADC may represent a new prognostic marker due to a significant negative correlation between ADC and SUVmax in NSCLC. Furthermore, DW-MRI of the thorax can be added to routine 18-FDG PET-CT for staging and response assessment in lung cancer in prospects.

Funding

This study was supported by a grant from the Rajiv Gandhi Cancer Institute and Research Centre (RGCIRC) scientific committee for thoracic MRI sequences in 29 patients with lung cancer after an institutional review board (IRB) approval.

Conflict of Interest
None declared.

Acknowledgments
We thank the patients and their families for their munificence in contributing to this study. We would also like to thank all members of the IRB committee who gave their approval for this study.

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An Assessment of the Three Popular Prognostic Scoring Systems for Chronic Myelomonocytic Leukemia (CMML) in an Indian Context

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Ind J Med Paediatr Oncol 2023;44:422–427.

Abstract

Introduction Chronic myelomonocytic leukemia (CMML) is a rare clonal hematopoietic neoplasm with a prevalence of 1.05 to 1.94 cases per 1,00,000 population. There are multiple prognostic scoring system used in practice for CMML, which include both cytogenetic and next-generation sequencing based.

Objective This study assesses the clinicohematological profile of CMML patients, along with comparison of three widely used prognostic scoring systems for CMML (CMML-specific prognostic scoring system, MD Anderson prognostic score, Mayo prognostic model).

Materials and Methods This study is an 8-year retrospective study. All relevant data had been retrieved and reviewed by the authors. Inclusion and exclusion criteria: All the cases that were diagnosed before 2016 as per 2008 criteria were reclassified, (2) all the cases that were positive for the mutations associated with myeloproliferative neoplasms were excluded, and (3) cases with more than or equal to 20% blast/blast equivalents were excluded. A univariate analysis was done followed by a multivariate analysis for all the parameters constituting each scoring system. Lastly, a receiver operating characteristic curve was plotted for all the three scoring systems.

Result There were total 23 patients, with a median age of 63 years and a male to female ratio of 2.3:1. Cytogenetic aberration and genetic mutation were observed in 6 and 3 cases, respectively. The median overall survival (OS) was 48 months and the median leukemia-free survival was 12 months. Post-multivariate analysis, the parameters with significant impact on OS were absolute monocyte count more than 10×10^{9}/L, myeloid precursors in peripheral blood, hemoglobin less than 10g/dL, platelet less than 100×10^{9}/L, hemoglobin less than 12g/dL, and absolute lymphocyte count more than 2.5×10^{9}/L.

Conclusion To summarize, we discovered CPSS to be a better prognostic tool for a setup like ours, since molecular investigations are not always readily available for each case. More such researches are needed in the near future so that we can design better prognostic tools and see for their usefulness in real life.

Keywords
- CMML
- prognostic tools
- cytogenetics
- overall survival
- leukemia-free survival.

article published online
April 17, 2023

DOI https://doi.org/10.1055/s-0043-1766130.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Chronic myelomonocytic leukemia (CMML) is a rare clonal hematopoietic neoplasm with a prevalence of 1.05 to 1.94 cases per 1,00,000 population. The diagnostic criteria for CMML now include both the absolute monocyte count (AMC) and the relative monocyte percentage as part of the criteria.[1]

They can be further subcategorized based on the blast percentage in peripheral blood (PB) and bone marrow (BM) into CMML-0, CMML-1, and CMML-2, as well as based on white blood cell (WBC) count into dysplastic($<13 \times 10^9$/L) and proliferative($>13 \times 10^9$/L) types. The proliferative subtype is more commonly seen to be associated with splenomegaly, constitutional symptoms, and JAK2 and RAS mutations, whereas the dysplastic ones are commonly associated with hematopoietic insufficiency symptoms (fatigue, infections, or bleeding).[1,2]

There are multiple prognostic scoring system used in practice for CMML, such as CMML-specific prognostic scoring system (CPSS), CPSS-molecular (CPSS-Mol), MD Anderson Prognostic Score (MDAPS), Mayo prognostic scoring model, Mayo-molecular model, and Groupe Francophones des Myelodysplasies (GFM). These scoring methods aid in classifying patients into high- and low-risk groups so that a treatment plan may be determined.[3–6]

This study discusses the clinicopathological profile of CMML patients experienced at our center. We also did a comparison between the three commonly used prognostic scoring systems based on cytogenetics (CPSS, MDAPS, Mayo prognostic model) for CMML patients.

Materials and Methods

This study is an 8-year (72 months) retrospective analysis from January 2013 to December 2021. This study had been conducted in Gujarat Cancer Research Institute, Ahmedabad. All necessary data such as demographics, clinics, laboratory parameters, marrow studies, radiology, cytogenetics, and/or mutation studies, and follow-up had been retrieved from the medical records. Old histopathology and hematology slides were collected and reviewed by the authors. Inclusion and exclusion criteria: (1) all the cases that were diagnosed before 2016 as per 2008 World Health Organization (WHO) classification were reclassified, rest were excluded, (2) all the cases which were positive for the various mutations associated with myeloproliferative neoplasm (MPN) were excluded, and (3) cases with more than 20% blast/blast equivalents were excluded.

Karyotyping and fluorescence in situ hybridization studies were done using phase contrast microscopy. Karyotyping was done using a short-term culture technique and at least 20 metaphases were studied. The cytogenetic risk stratification was done as per the Spanish study by Such et al.[4]

Next-generation sequencing (NGS) data was available in only selected cases (not done in present institute) and it was done primarily on PB. The NGS panel included 40 key DNA targets and 29 driver genes that are known to be associated with major myeloid disorder (including juvenile myelomonocytic leukemia (JMML)).

All the cases were subcategorized according to the WBC counts (dysplastic [$<13 \times 10^9$/L] and proliferative [$>13 \times 10^9$/L]) and blast count (CMML-0,1,2). The CPSS score, MDAPS score, and Mayo prognostic score were calculated for each case. The transfusion requirements were in accordance with the WHO based prognostic scoring system.[7]

Statistical analysis was performed using Statistical Package for the Social Sciences software version 25.0 (SPSS Inc., Chicago, Illinois, United States). A univariate analysis was done using Kaplan–Meier method for the interval from the date of diagnosis till last contact/death (overall survival [OS]) or progression to acute myeloid leukemia (leukemia-free survival [LFS]), to determine a two-tailed *p*-value for each of the individual parameters of each scoring system. The *p*-value was considered significant only if less than 0.05. Categorical values were represented as counts and relative frequencies, whereas continuous variables are represented as medians and range. For those parameters with significant *p*-value on univariate analysis, a multivariate analysis was performed using Cox regression hazard model to assess their independent impact. And lastly a receiver operating characteristic (ROC) curves was plotted for each of the scoring system and the area under the curve was calculated to compare the specificity and sensitivity for each system individually.

Ethics: All the approvals had been taken from the institutional review board. Ethical approval was waived by the local ethics committee of institute in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. All the necessary permission had been taken priorly for collection and analysis of materials and data from the concerned authorities.

Results

Out of the 9,000 cases of hematological malignancies that came to our facility over the past 8 years, we received a total of 23 cases of CMML, with a median age of 63 years (29–76 years) and a predominance of male patients (male to female ratio: 2.3:1). The three scoring systems and all patient characteristics are summarized in ►**Table 1** along with the risk classification of every case. On marrow examination, we had minimal to nil dysplasia in four cases, while rest had dysplasia in at least one lineage (►**Fig. 1**). The cases with minimal to nil dysplasia, however, had a history of persistent monocytosis for more than 3 months or some associated clonal abnormality. Splenomegaly was seen in 10 cases (10/19, 53%), hepatomegaly in 5 (5/19, 27%), and lymphadenopathy in 4 (4/20, 20%). Lactate dehydrogenase (LDH) was elevated in 13/15 (87%) (median LDH: 429/μL). Hepatomegaly, splenomegaly, lymphadenopathy, and LDH levels were not significantly associated with OS or LFS (p-value > 0.05). Cytogenetic aberrations were seen in 6/23 cases (5q deletion with t(4,12)(1), 7q deletion(1), trisomy 8(1), inversion 12(1), inversion Y(1) and complex karyotype(1)). In 3/5 cases, molecular abnormality was seen, one case each of ASXL1, RUNX1, and IDH2 along with NRAS mutation. The case with IDH2 and NRAS mutation also had inversion Y. Among the

Table 1 Patient characteristics and scores of various scoring systems

Characteristics		Median (range)	Total cases ($n = 23$)
Age (years)		63 (29–76)	
Gender	Male		16 (70%)
	Female		7 (30%)
WHO subtype based on blast%	CMML-0		6 (26%)
	CMML-1		7 (30%)
	CMML-2		10 (43%)
FAB subtype based on total leukocyte count	Dysplastic ($<13 \times 10^9$/L)	25.7 (4.8–203)	5 (22%)
	Proliferative ($\geq 13 \times 10^9$/L)		18 (78%)
Hb (g/dL)	<10g/dL	8.5 (4.5–11.8)	18 (78%)
	≥10g/dL		5 (22%)
	<12g/dL		23 (100%)
	≥12g/dL		0
Platelets (x10^9/L)	$<100 \times 10^9$/L	90 (7–491)	13 (57%)
	$\geq 100 \times 10^9$/L		10 (43%)
ALC (x10^9/L)	$>2.5 \times 10^9$/L	3.5 (0.54–16.1)	14 (61%)
	$\leq 2.5 \times 10^9$/L		9 (39%)
AMC (x10^9/L)	$>10 \times 10^9$/L	5.47 (1.008–81.2)	6 (26%)
	$\leq 10 \times 10^9$/L		17 (74%)
Presence of immature myeloid precursors	Present		17 (74%)
	Absent		6 (26%)
Bone marrow blast %	≥5%	8 (2–17)	17 (74%)
	<5%		6 (26%)
	≥10%		9 (39%)
	<10%		14 (61%)
RBC transfusion dependency	Present		19 (83%)
	Absent		4 (17%)
Spanish cytogenetic risk stratification	Low risk		15 (66%)
	Intermediate risk		4 (17%)
	High risk		4 (17%)
CPSS score	Low		1 (4%)
	Intermediate 1		4 (17%)
	Intermediate 2		14 (61%)
	High		4 (17%)
MDAPS score	Low		3 (13%)
	Intermediate 1		5 (22%)
	Intermediate 2		10 (43%)
	High		5 (22%)
Mayo clinic score	Low		2 (9%)
	Intermediate		3 (13%)
	High		18 (78%)
AML transformation			4(17%)
Expired			10 (43%)

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; CMML, chronic myelomonocytic leukemia; CPSS, CMML-specific prognostic scoring system; FAB, French American British (FAB); Hb, hemoglobin; MDAPS, MD Anderson prognostic score; RBC, red blood cell; WHO, World Health Organization.

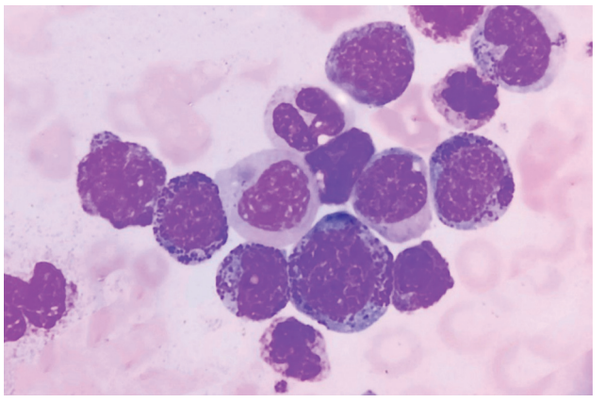

Fig. 1 Peripheral smear of chronic myelomonocytic leukemia, showing proliferation of myeloid and monocytic precursors (1000x oil immersion, Leishman stain).

three cases with molecular abnormality, two had leukemic transformation (ASXL1 and IDH2 with NRAS mutation). In one case out of 23, we also encountered cerebrospinal fluid infiltration.

The median OS and LFS were 48 and 12 months, respectively. ►**Table 2** represents the univariate analysis for all the parameters, while ►**Table 3** illustrates the multivariate analysis. Post-multivariate analysis, the parameters with significant association with OS were AMC more than 10 × 10^9/L, Immature myeloid cell (IMC) in PB, hemoglobin (Hb) less than 10g/dL, platelet less than 100 × 10^9/L, Hb less than 12g/dL, and absolute lymphocyte count more than 2.5 × 10^9/L. While the prognostic parameters with significant impact on LFS were BM blast more than or equal to 5% and IMC in PB. Lastly on ROC curve analysis, we found CPSS with maximum area under the curve followed by MDAPS and Mayo clinic (►**Fig. 2**).

Discussion

Similar to other studies, a predominance of elderly patients was noted.[7–9] Herein, we found hepatosplenomegaly mostly in association with proliferative type CMML, although we did not find any significant association of the same with OS, similar to Hoversan et al.[10] In contrast to the literature, we found a predominance of proliferative type CMML.[9,10] On subcategorizing based on blast percentage, we got maximum cases of CMML-2, while Azeez et al and Hoverstan et al got a predominance of CMML-1 and CMML-0, respectively.[10,11] We did not find any significant association of raised LDH with OS and LFS that was concordant to the literature[10]

We experienced a higher median OS compared to previous studies, although the median LFS was lower.[9,12] In the study by Calvo et al, the parameters with significant impact on OS were BM blast more than or equal to 5%, WBC more than or equal to 13 × 10^9/L, red blood cell transfusion dependency, cytogenetic risk stratification, and platelet less than 100 × 10^9/L. While for LFS, the parameters with significant impact were BM blast more than or equal to 5%, WBC more than or equal to 13 × 10^9/L, AMC more than or equal to 10 × 10^9/L, and platelet less than 100 × 10^9/L. Based on their findings they even proposed a new prognostic

Table 2 Kaplan–Meier estimate for OS and LFS

Characteristics	Total (*n*)	OS		LFS	
		Median (months)	Log rank (*p*-value)	Median (months)	Log rank (*p*-value)
Overall	23	48(4)	–	12	–
CPSS score					
BM blast (≥5%)	17	36(4)	0.009	12(4)	0.027
WBC≥13 × 10^9/L	18	36(4)	0.020	12	0.030
RBC transfusion dependency	19	36(4)	0.224	12	0.156
Cytogenetic score	8	36(4)	0.830	12(2)	0.931
Mayo clinic score					
AMC >10 × 10^9/L	6	24(4)	0.011	–	0.507
IMC in PB	17	36(3)	0.012	12(1)	0.014
Hb(<10g/dL)	17	36(3)	0.009	12(1)	0.095
Platelet (<100 × 10^9/L)	13	48(3)	0.008	12(1)	0.049
MDAPS score					
Hb(<12g/dL)	23	24(4)	0.042	12	0.075
ALC(>2.5 × 10^9/L)	14	48(3)	0.008	12(1)	0.095
IMC in PB	17	36(3)	0.012	12(1)	0.014
BM blast (≥10%)	9	36(2)	0.064	12(2)	0.262

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; BM, bone marrow; CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; Hb, hemoglobin; LFS, leukemia-free survival; MDAPS, MD Anderson prognostic score; OS, overall survival; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell.

Table 3 Cox regression hazard analysis

Characteristics	*n* (%)	OS		LFS	
		Hazard ratio	Cox regression (*p*-value)	Hazard ratio	Cox regression (*p*-value))
CPSS score					
BM blast (≥5%)	17	2.64	0.056	2.43	0.017
WBC≥13 × 10^9/L	18	1.811	0.071	2.81	0.061
RBC transfusion dependency	19	–	–	–	–
Cytogenetic score	8	–	–	–	–
Mayo clinic score					
AMC >10 × 10^9/L	6	0.266	0.012	–	–
IMC in PB	17	0.592	0.033	1.735	0.047
Hb(<10g/dL)	17	0.572	0.031	–	–
Platelet (<100 × 10^9/L)	13	1.782	0.047	2.711	0.083
MDAPS score					
Hb(<12g/dL)	23	0.987	0.009	–	–
ALC(>2.5 × 10^9/L)	14	0.521	0.028	–	–
IMC in PB	17	0.339	0.059	1.735	0.475
BM blast (≥10%)	9	–	–	–	–

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; BM, bone marrow; CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; Hb, hemoglobin; LFS, leukemia-free survival; MDAPS, MD Anderson prognostic score; OS, overall survival; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell.

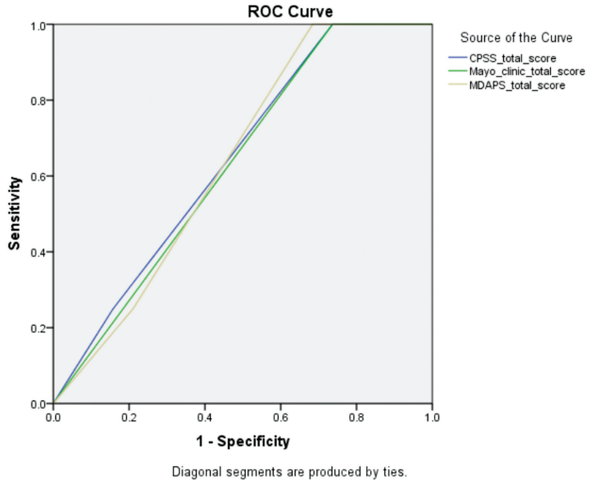

Fig. 2 Receiver operating characteristic (ROC) curve for all the three prognostic tool with area under curve for each. CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; MDAPS, MD Anderson prognostic score.

tool called as modified CPSS, in which to the existing CPSS system they added platelet count less than 100 × 10^9/L.[9,12] A similar study was also done by Padron et al on a larger study population, in which they compared seven prognostic tools and found Revised International Prognostic Scoring System (IPSS-R) to have the maximum area under ROC curve followed by CPSS.[13] The IPSS-R is a revised prognostic tool developed primarily for myelodysplastic syndrome patients, and in many studies it had been used for CMML patients also. However, its applicability is questionable for the proliferative type CMML.[9,14]

Newer molecular updates have been given to both Mayo prognostic model and CPSS. In Mayo molecular model, ASXL-1 has been added as an independent parameter, while for the CPSS-Mol, the cytogenetic risk group has been replaced with genetic risk group that calculates a cumulative score.[15,16] In present series, two cases with mutation had leukemic transformation and both the cases showed high risk scoring for CPSS-Mol and Mayo Molecular model, while on GFM scoring system the one with ASXL1 mutation had high risk scoring and the one with IDH2 and NRAS mutation had intermediate scoring. Both the cases expired within a year of leukemic transformation. Since NGS was not available for majority, we did not apply the above scoring system for rest of the cases.

The various scoring systems not only provide prognosis but also therapeutic recommendations. For high-risk patients, hematopoietic stem cell transplantation (HSCT) is recommended and considered to be curative provided they are medically fit. While for the low-risk patients, if they are asymptomatic a wait and watch policy is recommended, while for others hydroxyurea or hypomethylating agents are considered over and above HSCT, considering its complications.[16] In this study, a similar approach was applied accordingly and HSCT was done in total seven cases.

Conclusion

Thus, to summarize, we present a new set of parameters (AMC > 10 × 109/L, IMC in PB, Hb10g/dl, platelet100 × 109/L, and ALC > 2.5 × 109/L) that we found significant. In the

future, more research with a larger study population is required so that this can be validated. We discovered CPSS to be the most specific and sensitive (based on ROC-curve) out of the three well-known prognostic tools. The size of the study population and, in the majority of instances, the lack of NGS data were the study's limitations. And lastly, to the best of our knowledge, this is the first time such a study has been conducted in an Indian setting.

Author Contributions

The manuscript has been read thoroughly and contributed by all the concerned authors. The requirement for authorship as mentioned in the instructions has been met duly. Authors are responsible for correctness of the statements provided in the manuscript.

Ethical Approval

All the approvals had been taken from the institutional review board. Ethical approval was waived by the local ethics committee of institute in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. All the necessary permission has been taken for collection and analysis of materials and data from the concerned authorities.

Consent to Participate

All necessary informed written consent has been taken priorly.

Funding

No funding was received for conducting this study. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Conflict of Interest

None declared.

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SARS-CoV-2 Infection in Children with Cancer: Experience from a Tertiary Care Center in North India

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Ind J Med Paediatr Oncol 2023;44:428–435.

Abstract

Introduction Children with cancer are immunocompromised due to the disease per se or anticancer therapy. Children are believed to be at a lower risk of severe coronavirus disease 2019 (COVID-19) disease.

Objective This study analyzed the outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children with cancer.

Materials and Methods A retrospective analysis was performed on patients ($\leq$ 14 years) with cancer attending the pediatric oncology services of our institute who tested positive for the SARS-CoV-2 infection and those who had COVID-19 disease between August 2020 and May 2021. Real-time reverse transcriptase-polymerase chain reaction performed on the nasopharyngeal swab identified the SARS-CoV-2 infection. The primary endpoints were clinical recovery, interruption of cancer treatment, and associated morbidity and mortality.

Results Sixty-six (5.7%) of 1,146 tests were positive for the SARS-CoV-2 infection. Fifty-two (79%) and 14 (21%) patients had hematolymphoid and solid malignancies. Thirty-two (48.5%) patients were asymptomatic. A mild-moderate, severe, or critical disease was observed in 75% (18/24), 12.5% (3/24), and 12.5% (3/24) of the symptomatic patients. The "all-cause" mortality was 7.6% (5/66), with only one (1.5%) death attributable to COVID-19. Two (3%) patients required ventilation. Two (3%) patients had a delay in cancer diagnosis secondary to COVID-19 infection. Thirty-eight (57.6%) had a disruption in anticancer treatment.

Conclusion Children with cancer do not appear to be at an increased risk of severe illness due to SARS-CoV-2 infection. Our findings substantiate continuing the delivery of nonintensive anticancer treatment unless sick. However, SARS-CoV-2 infection interrupted anticancer therapy in a considerable proportion of children.

Keywords
- cancer
- coronavirus
- leukemia
- oncology
- pediatric
- SARS-CoV-2

article published online
May 17, 2023

DOI https://doi.org/10.1055/s-0043-1764366.
ISSN 0971-5851.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has posed the greatest challenge to the health care delivery system. As has been experienced across the globe, the incidence and severity of coronavirus disease 2019 (COVID-19) infection are noticeably lesser in children than adults. Children with SARS-CoV-2 infection are commonly asymptomatic or have mild illness.[1–3] However, children on treatment with cancer are a vulnerable population. Cancer and its treatment cause immunosuppression, increase the likelihood of acquiring infection, and augment its severity. The clinical course of COVID-19 in children on treatment for cancer remains unclear, though a trend toward a benign clinical course is observed.[4–8] A systematic review of the clinical presentation and outcome of SARS-CoV-2 infection in children with cancer demonstrated an asymptomatic infection or mild disease in about half of the study subjects, comparable to the general pediatric population.[9]

In pediatric oncology, wide-ranging impacts have been identified worldwide, including reductions in available clinical staff, pediatric cancer beds, and personal protective equipment.[10] In addition, the effects in low- and middle-income countries (LMIC) are more pronounced. Inability to access timely care owing to lockdowns, changes to chemotherapy due to treatment agent shortages, treatment abandonment, and disruptions to radiotherapy and surgery are the issues most frequently reported.[7,11] SARS-CoV-2 has placed enormous pressure on hospitals and health care systems worldwide. India has witnessed two "waves" of the pandemic since March 2020, with a devastating second wave from March to May 2021.

This study analyzed the morbidity and mortality in children with an underlying malignancy who contracted SARS-CoV-2 infection.

Materials and Methods

Patients

This retrospective study was performed on children and young adolescents (age $\leq$ 14 years) with malignancy treated at the Pediatric Hematology-Oncology Unit of the Postgraduate Institute of Medical Education and Research, Chandigarh, India, who tested positive for SARS-CoV-2 between August 1, 2020 and May 31, 2021. SARS-CoV-2 infection was diagnosed from the nasopharyngeal swab specimen with the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) according to the testing guidelines endorsed by the Government of India. The test results were interpreted by the cycle threshold (Ct) value; the threshold varied depending on the test kit. All patients requiring hospitalization for any reason, including planned procedures and chemotherapy, were tested for SARS-CoV-2 as per the prevailing testing policy of the institute. Children attending the oncology outpatient clinic were not tested for SARS-CoV-2 unless symptomatic. Symptomatic children were admitted to the dedicated COVID-19 ward and managed as per COVID-19 protocol. Admitted patients underwent laboratory evaluations as clinically indicated. Serum levels of COVID-19 biomarkers, such as C-reactive protein, ferritin, D-dimer, interleukin 6, etc., were not performed routinely as per the institutional pediatric COVID-19 management policy. Children who tested positive were not retested for clearance of the virus as per the testing strategy endorsed by the National Task Force on COVID-19 (Version VI, dated September 4, 2020). Cancer therapy was resumed after a minimum of 14 days or longer in case of persistently symptomatic disease. Status of vaccination of contacts was not recorded as vaccination for the general population commenced only on May 1, 2022.

Inclusion and Exclusion Criteria for SARS-CoV-2 Testing

Inclusion Criteria

Children with cancer were tested for SARS-CoV-2 either due to illness suggestive of COVID-19 or as a component of universal screening prior to diagnostic procedures, surgery, radiotherapy, or hospitalization for administration of chemotherapy or febrile neutropenia or evaluation of suspected malignancy.

Exclusion Criteria

Asymptomatic children with cancer visiting pediatric oncology clinic or daycare services were not routinely tested.

Data Collection

Data concerning epidemiology, underlying malignancy, phase of anticancer therapy, clinical features attributable to COVID-19 illness, clinical severity, respiratory support requirement, need and duration of hospitalization, outcome, and the effect on the delivery of anticancer therapy were collected from the case record files on a predesigned, structured proforma.

The Severity of COVID-19 Disease

The severity of COVID-19 was categorized as mild, moderate, severe, and critical based on clinical and/or radiological features.[12]

- *Mild*: asymptomatic or only upper respiratory tract symptoms.
- *Moderate*: clinical and/or radiological evidence of pneumonia, without hypoxia.
- *Severe*: presence of one of the following: tachypnea/hypoxia/encephalopathy/convulsions/dehydration/myocardial injury/elevated liver enzymes/coagulopathy.
- *Critical*: respiratory failure requiring mechanical ventilation/shock/vital organ dysfunction requiring intensive monitoring.

Outcome Measures

The clinical outcome of SARS-CoV-2 infection in children with cancer was the primary outcome measure of the study. The secondary outcome measures included: the severity of illness, frequency of hospitalization, and detrimental effects of SARS-CoV-2 infection on the timely delivery of anticancer treatment.

Statistical Analysis

Baseline clinical variables were summarized using descriptive statistics. Proportions were compared using the chi-square test. The Mann–Whitney test was used to compare the duration of hospitalization between two or more groups. The statistical tests were performed at a significance level of 0.05. Analysis was performed using the statistical software SPSS Statistics (Version 23, Armonk, New York, United States).

Ethics

The institutional ethics committee approved the study (NK/7558/Study/625). Informed consent from parents was waivered due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki.

Results

A total of 1,146 tests were performed. Sixty-six (6.07%) patients tested positive. The rate of RT-PCR positivity in all pediatric patients during the study period at our center was 3% (262/8,780) ($p < 0.0001$).

Demographic Details

The study population included infants ($n = 2$, 3%), young children (1–5 years) ($n = 19$, 28.8%), and older children/adolescents (6–14 years) ($n = 45$, 68.2%). The rate of test-positivity was comparable between the two waves of the SARS-CoV-2 pandemic in India (6.4% [31/479] in the first wave and 5.2% [35/667] in the second wave) ($p = 0.42$). Demographic parameters, the underlying malignancy, and the phase of therapy of the patients with SARS-CoV-2 infection are presented in ►**Table 1**. A history of contact with a proven case of SARS-CoV-2 was obtained from 4 (6.1%) patients.

Table 1 Demographic profile of the patients with SARS-CoV-2 infection

Patient characteristics	($N = 66$), *n* (%)
Age	6.8 y (IQR: 3.4, 9.8)
Sex	Male: 43 (65) Female: 23 (35)
Underlying malignancy	
ALL	36 (54.5)
Relapsed ALL	3 (4.5)
AML	4 (6.1)
Burkitt lymphoma	6 (9.2)
Lymphoblastic lymphoma (one each of B-and T-lineage)	2 (3)
Hodgkin lymphoma	1 (1.5)
Ewing sarcoma	6 (9.2)
Relapsed Ewing sarcoma	1 (1.5)
Neuroblastoma	1 (1.5)
Germ cell tumor	2 (3)
Hepatoblastoma	2 (3)
Synovial sarcoma	1 (1.5)
Malignant rhabdoid tumor of kidney	1 (1.5)
Phase of therapy	
Leukemia/lymphoma	($N = 52$), *n* (%)
At diagnosis	10 (19.2)
Induction	19 (36.5)
Consolidation	7 (13.5)
Interim maintenance	4 (7.7)
Intensification	2 (3.8)
Maintenance	10 (19.2)
Solid malignancies	($N = 14$), *n* (%)
Phase of neoadjuvant chemotherapy	8 (57.2)
Phase of adjuvant chemotherapy	4 (28.6)
During radiotherapy	1 (7.1)
At diagnosis of disease relapse (Ewing sarcoma)	1 (7.1)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Clinical Features of SARS-CoV-2 Infection

(1) Asymptomatic infection ($n = 32$): About half ($n = 32$, 48.4%) of the SARS-CoV-2-positive children were asymptomatic. The indications for testing included: (1) before an invasive procedure or imaging ($n = 12$; 38%), (2) admission for the administration of chemotherapy ($n = 11$; 34%), (3) newly diagnosed malignancy ($n = 6$; 19%), (4) surgery ($n = 2$; 6%), and (5) initiation of radiotherapy ($n = 1$; 3%).

(2) Symptomatic COVID-19 disease ($n = 24$): The spectrum of symptoms included (1) fever ($n = 24$), (2) cough ($n = 12$), (3) rhinorrhea ($n = 5$), (4) respiratory distress ($n = 11$), (5) watery diarrhea ($n = 5$), and (6) vomiting ($n = 3$). The severity profile of these 24 patients was as follows:

- *Mild-to-moderate illness*: The majority ($n = 18$; 75%) had "mild-to-moderate" illness.
- *Severe/critical illness*: Six patients had a "severe" ($n = 3$) or "critical" ($n = 3$) illness. The clinical profile of the patients with "severe" or "critical" COVID-19 disease is summarized in ►**Table 2**. On the chest radiograph, one of these six patients, a case of newly diagnosed acute myeloid leukemia (AML), had bilateral bronchopneumonia. However, in the absence of any microbiologic or serologic evidence of invasive fungal infection, the precise etiology of pneumonia remained elusive. No patient had the multisystemic inflammatory syndrome of childhood.

Table 2 Clinical profile, chest radiograph, and outcome of children with "severe" or "critical" illness due to COVID-19

S. No.	Age/Sex/Underlying cancer/ Phase of therapy	Severity of illness	Maximum respiratory support	Nonrespiratory complications	Chest X-ray	Days of hospitalization	Outcome
1.	5½ y/F/ALL/ maintenance	Severe	Low-flow oxygen	–	Bronchiectasis (preexisting)	12	Recovery
2.	8 y/M/AML/ treatment naive	Severe	Low-flow oxygen	–	Bronchopneumonia	20	Recovery
3.	6½ y/F/Relapsed ALL/maintenance	Severe	Low-flow oxygen	–	Consolidation of the right lower lobe	12	Recovery
4.	2 y/F/Burkitt lymphoma/ consolidation	Critical	Low-flow oxygen	Septic shock, GI symptoms	Normal	9	Recovery
5.	1½ y/M/Burkitt lymphoma/ treatment naive	Critical	Invasive ventilation (conventional)	–	Bronchopneumonia	13	Recovery
6.	10 ½ y/F/ALL/ treatment naive	Critical	Invasive ventilation (conventional)	–	Consolidation of the left middle lobe	11	Death

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; COVID-19, coronavirus disease 2019; F, female; GI, gastrointestinal; M, male.

(3) Non-COVID-related illnesses: Ten children had an unrelated illness at admission, and SARS-CoV-2 was detected incidentally. This included status epilepticus ($n=3$), appendicitis ($n=1$), neutropenic colitis with gut perforation ($n=1$), pneumococcal sepsis and lobar pneumonia ($n=1$), disseminated staphylococcal sepsis and empyema ($n=1$), refractory malignant rhabdoid tumor of the kidney with overt pulmonary metastases ($n=1$), refractory hepatoblastoma with massive abdominal distension ($n=1$), and abdominal Burkitt lymphoma with tense ascites ($n=1$). None of these children had symptomatology attributable to SARS-CoV-2 infection.

Laboratory Parameters

- Chest X-ray: The chest X-ray in the six children who had severe/critical illness had the following findings: (1) normal X-ray ($n=1$), (2) lobar consolidation ($n=2$), (3) bronchopneumonia ($n=2$), and (4) bilateral bronchiectasis ($n=1$, the patient had preexisting bronchiectasis for nearly a year). No patient underwent computed tomography of the chest.
- Hematological findings: Neutropenia (absolute neutrophil count $< 1.5 \times 10^9$/L) and thrombocytopenia (platelet count $< 100 \times 10^9$ /L) were documented in 18 (75%) and 19 (79%) of the 24 hospitalized patients, respectively. The median neutrophil-to-lymphocyte ratio (NLR) of the hospitalized patients was 0.114 ($n=23$). A high NLR (>3) was documented in only two children (NLR: 3.3 and 6.3, respectively).

Treatment

Hospitalization

Twenty-nine patients required hospitalization. The clinical profile of the hospitalized patients is summarized in ►**Table 3**. A comparison of the patients hospitalized vis-à-vis not hospitalized is presented in ►**Table 4**. The median duration of hospital stay was 7 days (range: 1–26). Younger

Table 3 Indication of admission and clinical profile of the hospitalized patients ($n=29$)

Indication of admission	*n* (%)	Presence of fever	Lower respiratory sign/symptom	Associated problems
Evaluation of fresh undiagnosed cases of childhood cancer	9 (31)	3	2	Massive ascites ($n=1$), large oropharyngeal mass ($n=1$)
Uncomplicated FN	9 (31)	In all	Nil	Gastroenteritis-like illness ($n=2$)
Complicated FN	7 (24)	In all	4	Disseminated staphylococcal sepsis ($n=1$), pneumococcal blood-stream infection ($n=1$), bronchiectasis ($n=1$)
Others	4 (14)	None	None	Seizures due to hypertensive PRES ($n=2$) or CNS relapse of ALL ($n=1$); appendicitis ($n=1$)

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system; FN, febrile neutropenia; PRES, posterior reversible encephalopathy syndrome.

Table 4 Comparison of the patients requiring vis-à-vis not requiring hospitalization

Parameter	Hospitalized patients ($n = 29$)	Nonhospitalized patients ($n = 37$)	p-Value
Age (median/IQR)	6.6 (3.2, 9.2)	7.35 (3.5, 10.5)	0.32
Sex	Male: 20, female: 9	Male: 23, female: 14	0.75
Type of underlying malignancy	Hematolymphoid: 28, solid: 1	Hematolymphoid: 24, solid: 13	0.002
Phase of therapy	Intensive: 23, nonintensive: 5	Intensive:16, nonintensive: 8	0.22

Abbreviation: IQR, interquartile range.

age (< 7 years) ($p = 0.44$), sex ($p = 0.65$), type of malignancy (hematolymphoid vis-à-vis solid) ($p = 0.39$), or the phase of therapy ($p = 0.67$) did not influence the duration of hospitalization.

Treatment of Patients with Severe/Critical COVID-19 Illness

Of the 6 patients with severe/critical COVID-19 disease, 2 required mechanical ventilation for 1 and 10 days, respectively, and 4 needed low-flow oxygen. The patient requiring ventilatory support for 10 days received remdesivir (4 doses) and dexamethasone (for 7 days). The mean duration of hospitalization and respiratory support requirement for the 6 patients was 13.3 days (range: 9–20) and 8.7 days (range: 5–12), respectively. No patient received interleukin-directed therapy or prophylactic anticoagulant.

Treatment of Hospitalized Patients with Mild-Moderate Illness

In addition to the symptom-directed therapy, all patients with febrile neutropenia were treated with antimicrobials and supportive care per the unit's protocol. Patients with culture-proven bacterial sepsis ($n = 3$) received antimicrobial treatment guided by the antibiogram.

Treatment of Asymptomatic Patients

Asymptomatic patients were quarantined for 14 days (home or hospital as per the state policy). The hematology-oncology registrar telephoned them regularly for well-being. Children with acute lymphoblastic leukemia (ALL) in the maintenance phase of therapy with asymptomatic SARS-CoV-2 infection were advised to hold antimetabolite drugs for 2 weeks.

Deleterious Impact of the SARS-CoV-2 Infection on the Delivery of Anticancer Therapy

There was a delay in establishing the diagnosis in two patients. A delay, interruption, or modification in administering at least one modality of anticancer treatment secondary to the SARS-CoV-2 infection was noted in 38 (57.6%) patients. There was a postponement of chemotherapy for patients who tested COVID-19 positive at diagnosis. The gap was bridged with oral prednisolone at 50% of the per-protocol dose for the children with newly diagnosed ALL. Thirty-five (53%) patients experienced a delay in receiving chemotherapy, with a median delay of 14 days (range: 7–27). Definitive surgery was deferred in two patients (one with hepatoblastoma and the other with malignant germ cell tumor) for 21 and 35 days from the scheduled date, respectively. One child with synovial sarcoma had an interruption of radiotherapy due to asymptomatic SARS-CoV-2 infection.

Outcome

Fifty-nine of 66 (89.4%) patients recovered. Five (7.6%) patients died, and 2 (3%) abandoned therapy.

Deaths: Five (7.6%) patients died; 1 (1.5%) death was attributable to severe COVID-19 pneumonia during induction therapy for ALL. The other deaths included: (1) hepatoblastoma with refractory disease, (2) fulminant polymicrobial sepsis in a patient with AML, (3) intracranial hypertension due to central nervous system relapse of ALL, and (4) hypertensive encephalopathy in a child with Burkitt lymphoma. None of these four children had clinical symptoms of COVID-19 disease.

Discussion

The SARS-CoV-2 pandemic is the most cataclysmic event in the past 100 years, threatening all facets of the global health care delivery system. The available data on SARS-CoV-2 illness in children has projected a milder disease than in adults. However, children with cancer are profoundly immunocompromised, and a general apprehension of severe disease in this specific population exists. The current study analyzed the clinical profile and outcome of SARS-CoV-2 infection in children with cancer. We also evaluated the deleterious effect of SARS-CoV-2 infection on the timely administration of anticancer therapy.

The rate of test positivity for SARS-CoV-2 was 6.07%, comparable between the first and second waves of the SARS-CoV-2 pandemic ($p = 0.42$). The rate of test-positivity among the children with cancer in our cohort was double that observed in all pediatric admissions in our hospital ($p < 0.0001$). We attribute this to frequent hospital visits of oncology patients for chemotherapy, transfusions, and check-ups. Also, a breach of COVID-19 protective measures among the patients in the hostel/Sarai and dining hall is a plausible explanation. A relatively higher frequency (12.1% in the first wave and 17.4% in the second wave) of test positivity among pediatric oncology patients is reported from another center in North India.[13] A report of a single-center experience from South India documented a remarkably high rate (54%) of SARS-CoV-2 -positivity among children and young adolescents with cancer.[14] However, this study had a questionnaire-based

Table 5 Selected studies from low- and middle-income countries on clinical profile and outcome of COVID-19 in children with cancer

S No.	Author, year of publication, country	*n*	Underlying malignancy	Severity profile	Hospitalization	ICU admission	Mechanical ventilation	Mortality rate
1	Raj et al[15], 2022, India	659	Hematolymphoid: 73%, solid: 27%	Asymptomatic: 72%	Not included	Not included	Not included	1%
2	Verma et al[16], 2022, India	50	Not included	Asymptomatic: 74%, mild-moderate: 22%, and severe: 4%	8%	Not included	4%	Not included
3	Mohapatra et al[17], 2022, India	68	Hematolymphoid: 81%, solid: 19%	Asymptomatic: 76.5%, mild-moderate: 19%, severe-critical: 4.4%	34%	4.4%	Not included	4.4%
4	Corso et al[18], 2021, Brazil	179	Hematolymphoid: 56%, solid: 34%	Asymptomatic to mild: 37%, moderate to severe: 40.2%, and critical: 23%	80%	19%	6%	12%
5	Parambil et al[19], 2022, India	122	Hematolymphoid: 69%, solid: 31%	Asymptomatic: 18%, requirement of respiratory support: 5.7%	All	Not included	2.5%	4.9%
6	Hammad et al[20], 2021, Egypt	76	Hematolymphoid: 86%, solid: 14%	Severe-to-critical illness: 35.4%	93%	Not included	15.7%	13%
7	Radhakrishnan et al[11], 2021, India	15	Hematolymphoid: 80%, solid: 20%	Asymptomatic: 67%, critical illness: 6.6%	All	6.6%	None	Nil
8	Bhayana et al[13], 2021, India	22	Hematolymphoid: 91%, solid: 9%	Asymptomatic: 54.5%, moderate: 22.7%, critical: 13.6%	36%	13.6%	None	Nil
9	Totadri et al[14], 2022, India	37	Hematolymphoid: 57%, solid: 43%	Mild: 27%, moderate: 35%, severe: 32%, and critical: 6%	All	32%	None	Nil
10	Hamdy et al[21], 2021, Egypt	7	Hematolymphoid: 86%, solid: 14%	Not included	Not included	43%	14%	43%
11	Current study	66	Hematolymphoid: 79%, solid: 21%	Asymptomatic: 48.5% Mild-moderate: 27% Severe: 4.5% Critical: 4.5% Illness not attributable to COVID-19: 15.5%	44%	9%	3%	1.5%

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

testing approach, which probably overestimated the test positivity.

A large fraction of children with SARS-CoV-2 infection were asymptomatic (48.5%) or mild-to-moderately symptomatic (42.5%). Only 6 (9%) children had a severe or critical illness, and 2 (3%) required invasive ventilation. A systematic review of the clinical profile of COVID-19 in children with cancer reported the following statistics: severe illness 9.6%, intensive care unit admission 10.3%, and mortality 4.9%, comparable to our experience.[9] In sharp contrast to our finding, Totadri et al[14] experienced a higher frequency of severe or critical illness (37%), hemodynamic compromise (21%), or requirement of supplemental oxygen (14%). However, none required invasive ventilation, and there were no deaths. The co-occurrence of oncologic emergencies and systemic infections in 50% of the children with a severe or critical illness is a potential confounder in the study. Selected studies on the clinical profile and outcome of SARS-CoV-2 infection in children with cancer are summarized in ►**Table 5**.[11,13–21] In our cohort, a substantial proportion of admitted patients had cytopenias. However, as most had active hematological malignancy or recent exposure to myelosuppressive chemotherapy, the precise contribution of COVID-19 to the causation of cytopenia is elusive.

A sizeable proportion (38/66; 57.6%) of children in our cohort had a delay in receiving scheduled therapy. A systematic review including 33 studies comprising 226 children with cancer and SARS-CoV-2 infection revealed a noticeable rate (78.7%) of treatment delay or modification of therapy.[9] The apprehension of fulminant COVID-19 illness in SARS-CoV-2 infected children following chemotherapy has resulted in a global practice of delaying anticancer therapy. However, the interruption of timely delivery of anticancer therapy raises concerns about the compromised oncologic outcome. A report from western India has demonstrated that the continuation of systemic chemotherapy in stable children with SARS-CoV-2 infection is safe.[19] Experience from the United Kingdom is also reassuring, where 71% of the patients with SARS-CoV-2 infection received standard or very myelosuppressive chemotherapy with no COVID-19-related mortality.[22] Conceivably, the continuation of non-intensive chemotherapy in nonsick SARS-CoV-2 infected children is safe. There is a scarcity of consensus guidelines for managing newly diagnosed malignancy in children with SARS-CoV-2 infection. However, for children with newly diagnosed ALL, the World Health Organization Global Initiative in Childhood Cancer endorses the initiation of steroid prophase, especially in an oncologic emergency.[23]

During the pandemic, a universal testing policy before elective procedures or admissions was adopted globally, the rationale of which is debatable. In our cohort, the rates of test positivity prior to an elective procedure (2%) or admission for chemotherapy (2.9%) were considerably low. Hence, the cost-effectiveness of universal PCR testing, especially in regions where the *R*-value is < 1, is debatable.[24,25] A questionnaire-based screening approach might be a cost-effective alternative to select asymptomatic patients for preadmission or preprocedure testing.[26]

Our study has several strengths:

1. One of the largest studies on the clinical effect of SARS-CoV-2 infection in children with cancers from LMIC.
2. Universal testing strategy picking up most infected children.

The limitations of this analysis include the retrospective nature of the analysis and a lack of family screening/contact tracing.

Conclusion

Our study demonstrates a low frequency of SARS-CoV-2 infection and noticeably low severity of COVID-19 in children with cancer in an LMIC setting. These findings are reassuring that children immunocompromised with an underlying malignancy do not have greater morbidity and mortality with the SARS-CoV-2 infection compared with the general pediatric population. However, the pandemic has significantly impacted the delivery of anticancer treatment, which may have later adverse consequences.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

We acknowledge the Pediatric COVID management team of our institute.

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One World, One Life

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Ind J Med Paediatr Oncol 2023;44:436.

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First cry of newborn tunes in no language,
Last breath exits the body with no change,
Flows between these moments inside every human,
Blood in the same color, vigor, and dynamic rage!

Life exists uniquely in this vast universe,
Race, creed, and tones defined by us are so diverse,
Cancer invades cells, inhabits, indulges inside,
Unperturbed, unkeen about the external divide !

Then why! one needs to cry out in agony,
Staring helpless with no rescue, no money,
Broken, often with the new cancer diagnosis,
Moving ahead, enduring thorns of financial crisis,
Pain of body and the endless suffering of mind,
Is same one emotion for each, every humankind!
Worse than death is to simply live on through,
When what next to do is known, but no means to!

Cancer is one enemy, but why we stay far apart?
Truth exists as one Life, let us together start,
Not merit but by chance, some born amidst charms,
Every bit matters, when we give, we open our arms!

Inclusiveness toward humanity is our responsibility,
Health, equity, and access to all, our eternal duty,
Staying as one life against cancer on scale global,
Ensures every patient gets treated optimally well!

Conflict of Interest
None declared.

article published online
April 17, 2023

DOI https://doi.org/10.1055/s-0042-1760323.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Massive Subcutaneous Emphysema and Pneumo-Mediastinum after Percutaneous Lung Biopsy

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Ind J Med Paediatr Oncol 2023;44:437–439.

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Introduction

Transthoracic percutaneous computed tomography (CT)-guided lung biopsy is an established procedure for obtaining tissue diagnosis in lung masses with diagnostic accuracy up to 98%.[1] Post procedure complications such as pneumothorax and pulmonary hemorrhage, leading to hemoptysis are relatively frequent.[2] Pneumothorax incidence varies from 15% to 54% with subsequent chest drain required in 1.4% to 16.7% of patients.[2] Here, we describe a case of a 69-year-old man who developed mild pneumothorax during CT-guided lung biopsy with bilateral extensive subcutaneous emphysema and pneumomediastinum 48 hours later.

Case Report

A 69-year-old gentleman, a chronic smoker presented with a lung mass for tissue sampling by transthoracic percutaneous CT guided core needle lung biopsy. Routine blood investigations, coagulation profile, and complete blood counts were normal.

After informed consent and procedure counseling about the risks and benefits, the patient was planned for a CT-guided biopsy. During procedure, planning CT, irregular soft tissue density mass lesion was noted in the right lower lobe, limited by an oblique fissure posteriorly. The lesion was approached from the lateral chest wall to avoid the oblique fissure in the prone position. The core needle biopsy was done using an 18G × 10 cm semi-automatic biopsy gun along with its co-axial needle. Mild pneumothorax was noted in the procedural check scan during biopsy without any signs of respiratory distress or dyspnea. Thus, we continued the procedure and successfully performed the CT-guided lung biopsy (►**Fig. 1A**). The patient was kept under observation for 4 hours with monitoring of vitals. After 4 hours of observation, a chest radiograph was taken that showed a mild pneumothorax which was stable and mild subcutaneous emphysema at the local site (►**Fig. 1B**). The patient was discharged as he was asymptomatic and advised precautionary measures such as bed rest, avoiding heavy exercise and flying. Two days later, the patient presented with subcutaneous swelling and crepitus over the face, neck, and chest regions. He was further evaluated with a thoracic CT scan that showed extensive subcutaneous emphysema extending from the face, neck, and thoracic regions to the upper abdominal wall bilaterally, pneumomediastinum, and persistent right pneumothorax (►**Fig. 2C, 2D**).

In view of no pressure symptoms or respiratory distress/vascular compromise, the patient was managed conservatively with antibiotics and pain medications and requested to follow-up. Further, in due course, the emphysematous changes improved and the patient was started on further treatment as the biopsy revealed non-small cell lung carcinoma (NSCLC) favoring squamous cell carcinoma.

Discussion

Transthoracic percutaneous CT-guided lung biopsy is an established diagnostic tool for getting tissue diagnosis in lung masses with diagnostic accuracy up to 98%[1]. Post-procedure complications such as pneumothorax and hemoptysis are relatively common. Pneumothorax is the most common complication with an incidence of 25% with subsequent chest drain required in 5.6% of patients in a recent meta-analysis of 12,753 lung biopsies.[2] Patient position, small size of the lesion, multiple pleural punctures, and distance of the lesion from the pleura increases the risk of pneumothorax proportionally.[1,3,4]

Subcutaneous emphysema (SE) is the leakage of air from the respiratory or gastrointestinal system that diffuses under

article published online November 28, 2022

DOI https://doi.org/10.1055/s-0042-1746421.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

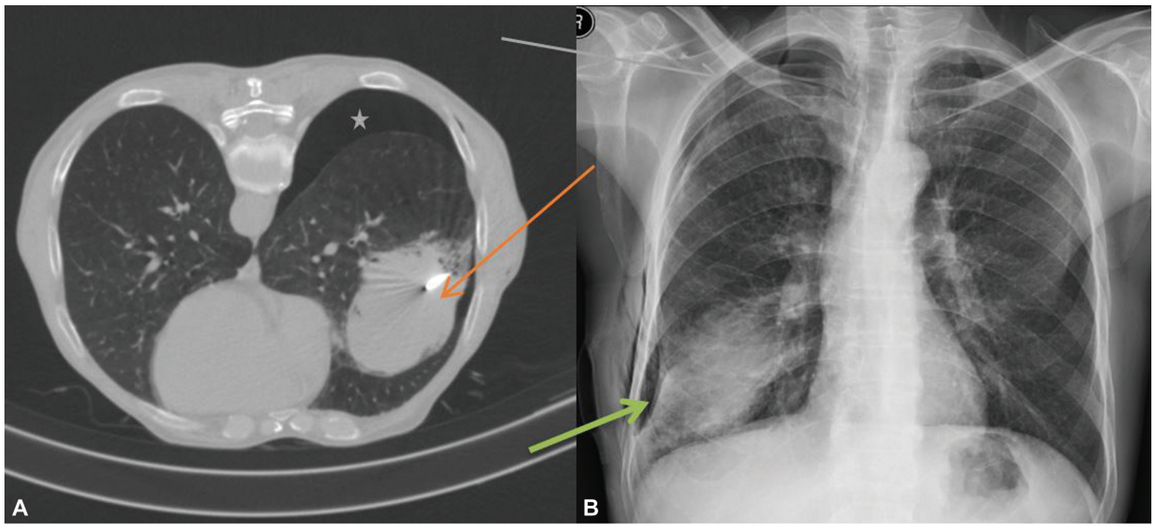

Fig. 1 (**A**) Right lung mass lesion was approached in the prone position with coaxial needle in situ (red arrow), mild pneumothorax (green asterisk) in the CT scan. Note is made of a small focus of air near the chest wall beneath the muscular layer. (**B**) Mild subcutaneous emphysema at the local site and mild pneumothorax in the apical region in the chest X-ray (green arrow).

the skin and myofascial planes.[5] It is found more commonly in association with pneumothorax[6] and is often accompanied by pneumomediastinum.[5] Causes of subcutaneous emphysema in the thoracic region are post-surgery, trauma, infectious, iatrogenic, etc. Post-transthoracic lung biopsy, the incidence of subcutaneous emphysema (SE) is very rare. Very few number of case reports of severe SE have been reported in the literature.[4,5]

Free air in the subcutaneous thoracic region can be caused due to parietal pleural injury that further diffuses in myofascial planes dissecting them to cause severe subcutaneous emphysema, as discussed in our case. There is a significant correlation between the underlying lung parenchymal condition, which in our case study showed emphysematous changes and the increase in the risk of pneumothorax, and further in subcutaneous emphysema.

Conservative management is the mainstay of treatment of SE; however, it can be individualized depending on the clinical context and severity of symptoms. The increased pressures can cause serious complications, such as upper airway compression and vascular compromise, requiring emergent intervention as necessary. Hence, the patients should be kept under close follow-up.

Conclusion

This case highlights the importance of knowing about this rare but manageable complication and the interventional radiologist should be aware of this.

The appearance can be alarming; however, it typically follows a benign course and patients should be kept under close follow-up.

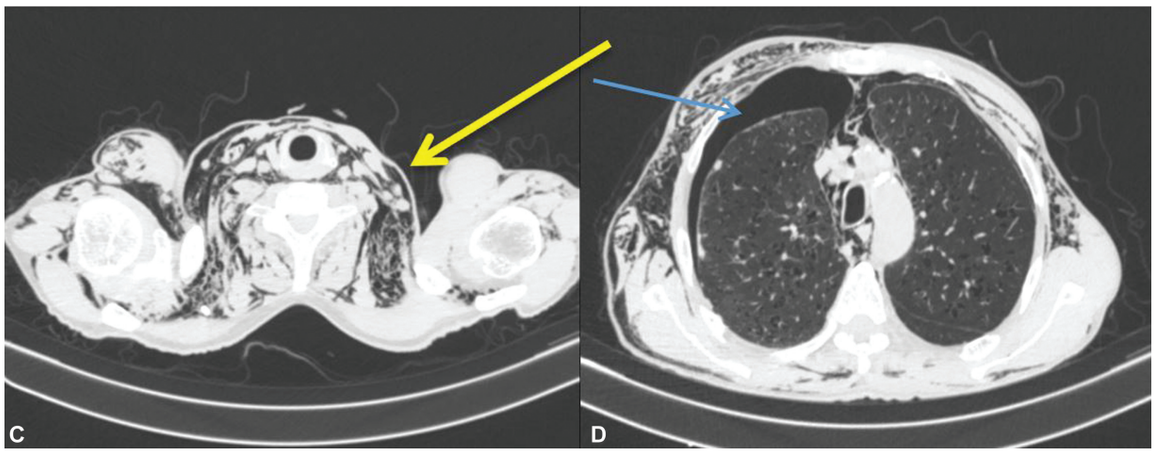

Fig. 2 (**C** and **D**) Severe bilateral subcutaneous emphysema in the neck and thorax region with mild pneumothorax, pneumomediastinum in the CT scan (arrows) after 2 days.

Conflict of Interest
None declared.

Acknowledgments
We thank the patients and their families for their munificence in contributing to this study. We would also like to thank all members of the IRB committee who gave their approval for this study.

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BCLC 2022 Update: Still a Long Way to Prove the Efficacy of External Beam Radiation Therapy

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Ind J Med Paediatr Oncol 2023;44:440–441.

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Recently, the Barcelona Clinic Liver Cancer (BCLC) group has updated its recommendation for the management of hepatocellular carcinoma (HCC) to emphasize personalized treatment.[1]

One major change in the BCLC 22 update is the incorporation of "treatment stage migration (TSM)" defined as upstaging of patient profile leading to shifting of recommendation to the option that would be considered for more advanced stage. It is surprising that in the present update, external beam radiation therapy (EBRT) has not been included in the treatment algorithm.

Various studies have been published that have demonstrated the safety and efficacy of EBRT such as stereotactic body radiation therapy (SBRT) and proton therapy in BCLC A-B HCC.[2] Mathew et al have demonstrated 1-, 3- and 5-year overall survival (OS) of 77·3%, 39·0%, and 24·1%, respectively, in 297 patients (pts) with 436 HCCs. BCLC-C group includes both pts with macrovascular invasion and those with extrahepatic metastasis. Studies have shown improved survival with SBRT in pts with macrovascular invasion who are not fit for other modalities of local treatment.[3]

The study by Collen et al in patients with synchronous oligometastatic—non small cell lung cancer (NSCLC) patients treated with SBRT had demonstrated a median overall survival (mOS) of 23 months.[4] Similarly, SBRT can be considered to be the primary lesion along with oligometastatic sites in HCC resulting in improved quality of life and extending survival.[5] Choi et al has reported mOS of 13.3 months in pts with Hep B-related BCLC-C group of patients.[6]

Evolving evidence has also suggested that concurrent use of immunotherapy with SBRT (SBRT-IO) has resulted in more powerful immune activation effects. In a study by Chiang et al, the overall response rate (ORR) was 87.5% (CR: 50%, PR: 37.5%) in the SBRT-IO arm as compared with 17% (CR: 2.4%, PR: 14.3%) in the TACE alone group. Similarly, the 12 months OS was 93.8% versus 80.4%, respectively.[7]

EBRT has been included as one of the treatment options in a selected group of population with HCC by the National Comprehensive Cancer Network (NCCN), American Association for the Study of Liver Diseases (AASLD).[8,9] Recently the American Society for Radiation Oncology (ASTRO) has also recommended the use of EBRT in HCC. As per guidelines, radiation therapy can be used as a first-line option in patients with early disease not amenable to other local therapies. Further ASTRO has also recommended RT to consolidate other local therapies after incomplete response or recurrence. In the BCLC-C group of the population, it can be used with palliative intent.[10]

In conclusion, evidence is available for the use of EBRT in all stages of BCLC, especially in patients with progressive or metastatic disease but more randomized prospective trials results are required. We do hope that in future updates of BCLC guidelines, incorporation of EBRT will be considered as a treatment option for patients with HCC.

Authors' Contributions
D.S., R.K., and D.T. contributed to the concept and design, and writing of the article.

Funding
None.

Conflict of Interest
None declared.

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article published online
December 1, 2022

DOI https://doi.org/10.1055/s-0042-1758523.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

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Triple Negative Breast Cancer in India: What Is the Real Incidence?

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Ind J Med Paediatr Oncol 2023;44:442–444.

The real incidence of triple negative breast cancer (TNBC) in India has always been a topic of debate. There has been considerable heterogeneity in the reporting of TNBC rates in India. A recent meta-analysis of 34 studies done till 2019 that included 20,678 patients reported a pooled prevalence of 27% (95% confidence interval [CI]: 24–31%).[1] Our previous work in which we collected data from 17 studies done between 1999 and 2015 involving 7,237 patients from all four regions of India reported a TNBC rate of 31% (95% CI: 27–35%).[2]

In this meta-analysis, substantial heterogeneity was observed across the studies (I^2 of 91.2% [95% CI: 88–94%], $p < 0.001$). This was unexplained by study level characteristics like study location, definition of HER2 or estrogen receptor, age, proportion of patients who were premenopausal, grade 3 disease, or larger tumor size. We also found that the TNBC rate decreased as the quality of the study increased. Although the rates were not statistically significant, the TNBC rate of lower quality studies was higher when compared to higher quality studies (38% [95% CI: 27–48%] vs. 29% (95% CI: 25–33%]). Quality of studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. One point was given to each parameter if the study described the setting and study participants, reported descriptive data, provided detailed outcome data, and discussed limitations. A good quality study had a score of ≥ 4 and a lower quality had a score of < 4 with a maximum score of 5.[2]

Why Are Rates of TNBC So High in India? Is it a Precise Estimation of the Ground Reality?

Experts often cite referral bias as the reason why TNBC rates are higher in these studies. Most of the studies are done at a large referral center. Epidemiological studies can suffer from referral bias when patients are recruited from tertiary centers. Patients with TNBC have more severe disease and will probably get selectively referred to a tertiary center, which will spuriously raise the rate of TNBC in the tertiary centers.

However, in contradiction to the theory of "referral bias," a recent study from a tertiary referral center in Chennai, which evaluated 2,137 patients with locally advanced breast cancer, reported that the incidence of TNBC was 12%.[3] This study was done from 2006 to 2013. Intuitively, one would think that in a study done among patients with locally advanced disease, the number of TNBCs would be higher than what is currently reported. Could it be that only patients who had less severe disease and who could afford to go to these centers were selectively referred to these institutions? Contrast that with the original assumption for a referral bias wherein patients with more severe disease gets referred to a higher center. If that is the case, is a more realistic estimate for the rate of TNBC somewhere between 12% and 27%?

Another possible reason for higher rates of TNBC is the poor quality of the pathological examination of the specimen. For instance, Chakraborty et al in their study of 925 patients collected from a single tertiary cancer center reported a TNBC rate of around 12%. The study population underwent testing during 2011 to 2015. Although the institution was a tertiary referral center, the rate of TNBC is lower than what was reported in the meta-analysis. The authors hypothesize that it is a more accurate reflection of the reality as their pathology laboratory adhered to the established guidelines.[4] For this study, methods for immunohistochemistry (IHC) testing were automated, peer-reviewed with internal and external quality assurance that was done mostly on core biopsies.

article published online
March 14, 2022

DOI https://doi.org/10.1055/s-0042-1742612.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

However, in contradiction to Chakraborty et al, a recent study done among 3,453 patients diagnosed with stage I, II, or III breast cancer from three different private institutions in India (two of which were in Chennai) during the years 2008 to 2014 reported that the TNBC rate was 24.2%.[5] All three institutions have implemented high-quality pathology reporting. Most vital factor to be noted is that the patients in this study were likely to be at a higher socioeconomic status than the patients treated in government centers.

Inconsistent IHC diagnostic methods are very prevalent in India. ►**Table 1** lists issues concerning the heterogeneity of TNBC rate in India and some suggested solutions. Improper fixation techniques, use of non-U.S. Food and Drug Administration approved assays and interpretative error due to the failure to use the revised American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines for estrogen receptor/progesterone receptor positivity can cause some of the errors in reporting.[6] The standardized tests are compromised for cheap nonvalidated tests that lead to nonuniformity of results nationwide.

Implementing a standardized protocol for detection can help in proper identification of TNBC. Quality-assured antibodies can improve the detection rates of estrogen and progesterone receptors. IHC should be preferably done on biopsy specimens rather than lumpectomy or mastectomy specimens.[4] A meta-analysis done on 27 studies has shown high diagnostic accuracy with core needle biopsy when compared to open excision biopsy in breast cancer patients.[7] A retrospective study done over a period of 6 years reported a reduction in the TNBC rate from 40 to 26% with better IHC techniques and tissue handling.[8] Training programs for pathologists and technicians, proper implementation of the ASCO-CAP guidelines in laboratories, regular internal auditing of tests, centralized testing, and quality assurance by external boards can be beneficial.[6] A population-based recruitment and careful interpretation of results can prevent referral bias in future studies.[9] Creating a national TNBC registry can help in studying the true incidence in different regions.[10]

Table 1 List of issues concerning the heterogeneity of TNBC rate in India and some suggested solutions (based on Shet[6])

Issues	Suggested solution
Choice of specimen[4]	• Biopsy tissue preferred
Improper fixation of tissue[6]	• Avoid delay or refrigeration before fixation • Adequate formalin fixation time • Adequate formalin to be used
Use of nonvalidated antibodies[6]	• Automation of IHC • Participation in EQAS • Protocol optimization
Interpretative error[6]	• Strict implementation of ASCO-CAP guidelines for scoring • Compare core biopsy with excised specimen • FISH confirmation for HER2neu heterogeneity
Lack of training[6]	• Training of pathologists and technicians • Laboratory certification
Lack of uniformity in results[6]	• Centralized testing • Internal auditing
Expensive tests[6]	• Economize or proper insurance coverage of these tests
Referral bias[9]	• Population-based recruitment • Careful interpretation of results

Abbreviations: ASCO-CAP, American Society of Clinical Oncology-College of American Pathologists; EQAS, external quality assurance system; FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry.

Patients with TNBC have an aggressive disease and its high incidence can contribute to poor outcomes for Indian women with breast cancer. There is an association between TNBC diagnosis and interval cancers, which are those cancers that manifest between the usual intervals of a recommended screening test.[11] For instance, a patient could develop an aggressive TNBC between their yearly screening mammograms. In such a case, there was no benefit for the patient with their screening mammogram as it did not help diagnose their cancer before it manifested symptomatically. If the incidence of TNBC in a region is very high, there is greater risk for such interval cancers, and no real impact for a breast cancer screening program. Knowing the real incidence of TNBC would therefore help policy makers and experts in determining the relevance of population-based breast cancer screening.

Are the TNBC rates in India truly very high or is it a reflection of the lack of population-based studies? It is time we focus our attention on this question and settle the debate once and for all.

Funding
None.

Conflict of Interest
None declared.

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Triple Trouble: Disseminated Penicilliosis in a Cancer Patient with COVID-19

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Ind J Med Paediatr Oncol 2023;44:445–448.

Abstract

Penicilliosis is a fungal infection caused by the fungus *Penicillium marneffei* or *Talaromyces marneffei*. Penicillosis is commonly seen in immunocompromised patients such as in HIV (AIDS). Herein, we present a case of penicilliosis in an oral cavity cancer patient who was admitted for the management of SARS-CoV-2 infection at our hospital. A 50-year-old male patient operated on for squamous cell carcinoma of the oral cavity who completed his adjuvant chemoradiation 2 months ago, presented to our hospital with dry cough for more than 3 weeks. His nasopharyngeal swab was positive for the severe acute respiratory distress syndrome (SARS-CoV-2). During his hospital stay for SARS-CoV-2 infection, he was diagnosed with disseminated penicilliosis. The patient was treated with intravenous antifungals caspofungin and voriconazole. However, he succumbed to disseminated fungal sepsis. This case highlights the need to consider penicilliosis as a possible opportunistic pathogen, especially in immunocompromised patients such as cancer.

Keywords
- penicilliosis
- cancer
- oral cavity
- SARS-CoV-2
- COVID-19

Introduction

Penicilliosis infection is commonly seen in immunocompromised patients such as acquired immunodeficiency syndrome (AIDS), cancer and persons with autoimmune diseases.[1–3] Disseminated penicilliosis is transmitted in humans from the inhalation of spores from the environment.[4] There are published reports in the literature showing penicilliosis infections in lung cancer patients.[5] In 1959, G. Segretain, a mycologist from the Pastur institute at Paris was the first person to discover penicilliosis. Symptomatology varies as per the system involved. The diagnosis of penicilliosis is suspected or done through examination of either cytology or biopsy samples.[6] Herein, we report the first case

article published online
March 29, 2023

DOI https://doi.org/10.1055/s-0042-1759505.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of disseminated penicilliosis infection in a cancer patient with concomitant SARS-CoV-2 infection.

Case

A 50-year male patient, premorbidly healthy, was diagnosed with carcinoma of buccal mucosa (non-keratinizing squamous cell carcinoma) T4-N3b-M0. He received two cycles of neo-adjuvant chemotherapy (paclitaxel + carboplatin + cetuximab) followed by right buccal mucosa composite resection + left neck dissection followed by pectoralis major myocutaneous flap. Post-surgery, he received concurrent radiation (60Gy/30# of RT over 43 days) along with weekly cisplatin. Two months after completion of concurrent chemoradiation, he presented with a 3-week history of dry cough. Nasopharyngeal swab was positive for SARS-CoV-2 infection using standard real-time polymerase chain reaction (RT-PCR test). He was hospitalized with a diagnosis of severe COVID-19 as per ordinal scale.[7] On admission, the patient was tachypneic, and hypoxic with bilateral crepitations. X-ray chest (►**Fig. 1A**) showed bilateral infiltrates. In view of severe COVID-19, and in anticipation of a difficult airway considering a recent history of major facial surgery, an elective tracheostomy was performed on the day of hospital admission. After tracheostomy, he was supported with invasive mechanical ventilation with volume control mode (FiO_2 50%). Meanwhile, he was treated with intravenous dexamethasone (6 mg once a day as per the RECOVERY trial) [8] for severe COVID-19, along with broad-spectrum antibiotic (meropenem) and prophylactic enoxaparin. Non-directed broncho-alveolar lavage (ND-BAL) was sent for bacterial culture that showed a sensitive strain of *Pseudomonas aeruginosa*. Over the next 96 hours, he improved with respect to defervescence, oxygen requirement, and lung infiltrates. On day 10, he was on minimal oxygen support (2 L/min) without any tachypnea. Repeat ND-BAL cultures were negative for any bacterial growth. However, on day 12, we noticed an increase in respiratory rate, with a rise in C-reactive protein (CRP) and radiological evidence of increased lung infiltrates (►**Fig. 1B**). In view of normal procalcitonin, high CRP, and repeatedly negative blood and tracheal cultures, we suspected an impending recurrent cytokine storm due to SARS-CoV-2 infection. On account of better lung penetration of methylprednisolone in comparison to dexamethasone[9] and based on evidence for utility of bevacizumab[10] at the time of patient management, he was treated with a single dose of intravenous bevacizumab 400 mg, intravenous methylprednisolone 20 mg 12 hourly, along with broad-spectrum antibiotics (colistin+ ceftazidime-avibactam + aztreonam). However, his lung infiltrates continued to worsen. In view of rising CRP with worsening infiltrates, recent steroid use, and recent use of broad-spectrum antibiotics, the possibility of an opportunistic fungal infection was considered. His blood sugars and neutrophil counts were normal. An ND-BAL fungal culture was repeated. After 24 hours on Sabouraud dextrose agar (SDA) at 25°C; it showed a filamentous grayish–white growth in 24 hours. The growth later became yellowish green in the center surrounded by white periphery and had radial folds. On Lacto phenol Cotton Blue Mount (LPCB), penicillial morphology was seen. Hyaline short hyphae that were septate and branched bearing chains of elliptical or lemon shaped phialoconidia were seen. Dimorphism showing yeast to mycelial phase conversion could not be demonstrated. Hence, it was probably diagnosed as *Penicillium non-marneffi spp*. Voriconazole plus caspofungin has been shown to work well for patients with penicilliosis non-marneffi infection.[11] Hence, he was started on injection caspofungin pre-emptively pending further identification. Computerized tomogram (CT) of the chest and abdomen showed multiple nodular lesions in bilateral lung fields with cavitations, ground glass opacities, along with well-defined hypodense lesions in segment VII, VIII and multiple satellite foci consistent with a fungal etiology (►**Fig. 1C**). An aspiration of liver abscess was not performed in view of poor general condition of the patient. There were no signs of active COVID-19 disease on CT scan. Patient was continued on antibacterials and injection caspofungin. Over the next 96 hours, ND-BAL culture growth was reported as *Penicillium* species (non-marneffei) (►**Fig. 2**). ND-BAL galactomannan levels were

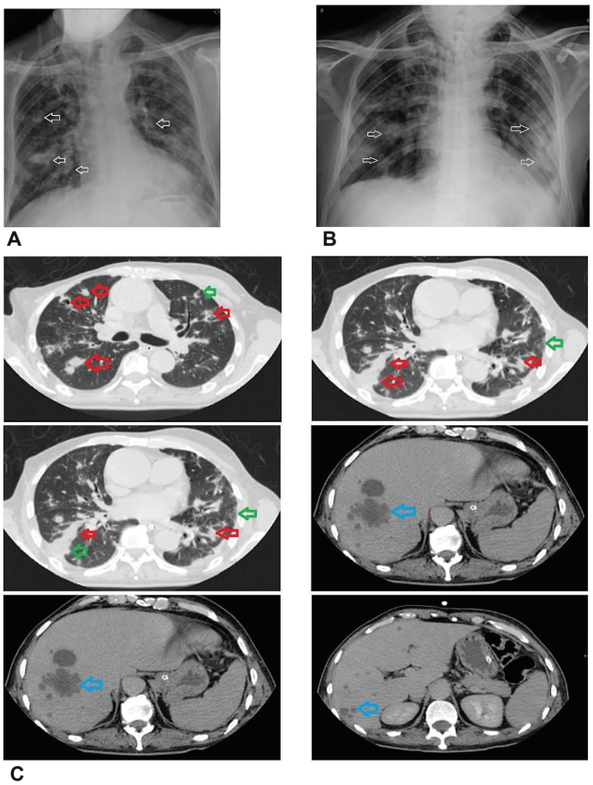

Fig. 1 (**A**) X-ray chest showing a few nodular opacities in both lung fields, maximum in right lower zone suggestive of infective etiology. (**B**) X-ray chest showing increase in nodular opacities as compared to a prior X ray, features suggestive of worsening of pulmonary infection. (**C**) Multinodular lesions in bilateral lung fields with cavitations (red arrow) and surrounding ground glass opacities (green arrow) [in top two panels and left middle panel] suggestive of infective etiology more likely to be fungal. Multiple hypodense (blue arrow) hepatic lesions in segments VII and VIII, suggestive of multiple abscesses. [right middle panel and both lower panels].

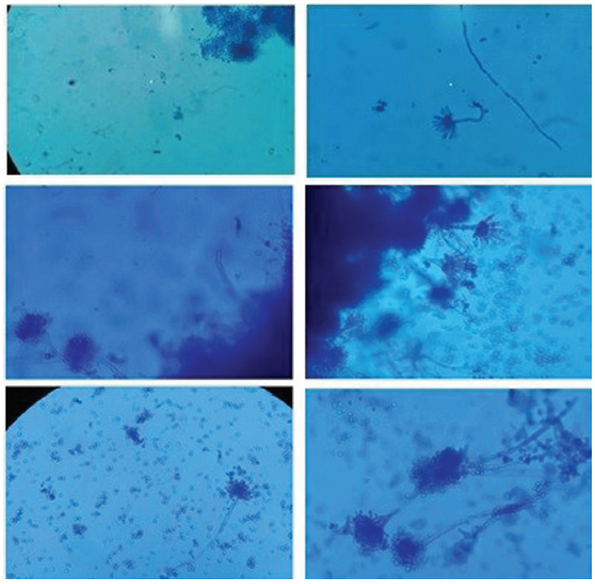

Fig. 2 Lactophenol cotton blue stain mount from the growth of the *Penicillium* spp showing conidiophores having secondary branches called metulae. On metulae are arranged flask-shaped phialides bearing conidia. The entire structure is forming the characteristic "penicillus "or "brush" appearance.

positive (Index 3.601), though serum galactomannan levels were negative. The day wise trend of CBC, CRP, and procalcitonin is provided in ►**Table 1**. After 1 week, voriconazole was added as he continued to worsen with respect to respiratory parameters, rising CRP, worsening infiltrates, and negative bacterial cultures. Subsequently, he had worsening hypoxia necessitating mechanical ventilation. Despite maintaining therapeutic voriconazole levels, he progressed to septic shock. On day 27 of hospital admission, he succumbed to disseminated penicilliosis.

Discussion

Penicillium species (especially *P. marneffei)* have been proven to cause fatal invasive infections in immunocompromised cases.[12] Pulmonary fungal infections with *Penicillium* non-*marneffei* species have been reported in immunocompromised hosts. Disseminated disease with hepatosplenic involvement[12] and pericardial involvement[12] are reported.[12] Invasive fungal infection can be attributed to some of the rare *Penicillium* species such as *P. commune, P. purpurogenum, P. oxalicum, P. notatum, P. citrinum,* and *P. brevicompactum*.[12] Definitive diagnosis of *Penicillium* infection is made by culture of biological specimens with a turn-around time of approximately a week or more.[13] Although no serological tests are developed for diagnosing penicilliosis, galactomannan assay can show cross-reactivity with *Penicillium* species and can pre-empt diagnosis of invasive penicilliosis before microbiological cultures.[14]

In retrospect, looking back to the SARS epidemic in 2003, fungal infection was the most common cause of mortality accounting for 25 to 73% of all deaths.[15] However, in contrast, data of fungal co-infection in COVID-19 are scarce. A meta-analysis by Peng et al reported an overall pooled proportion of COVID-19 with fungal co-infection of 0.12%, with an overall mortality of 0.17%. They described a higher proportion of patients with co-infection from Asia, in comparison to Europe. However, the majority of their fungal co-infections were caused by *Aspergillus*.[16] Possible risk factors for the

Table 1 Day-wise trend of hematological and biochemistry report of the patient

Day of COVID-19 positivity	Hb g/dL	TLC * 10^9 (per L)	ANC * 10^9 (per L)	ALC * 10^9 (per L)	Platelets * 10^9 (per L)	CRP (mg%)	Procalcitonin (ng/mL)
1	–	–	–	–	–	–	–
2	7.3	9.59	8.29	0.44	175	10.31	–
4	8.5	10.26	9.62	0.33	172	11.5	0.08
5	7.7	13.33	12.56	0.28	211	4.4	–
6	7.4	11.99	11.02	0.34	178	5.8	0.13
11	13.6	5.84	3.92	1.08	181	5.4	0.17
14	12.9	12.46	10.93	0.66	257	1.0	0.14
18	13.0	7.61	4.63	2.03	348	0.3	0.05
19	8.6	8.13	7.22	0.39	139	–	0.06
20	–	–	–	–	–	4.6	–
21	8.1	6.71	5.86	0.261	144	8.99	0.13
22	8.2	5.68	4.97	0.255	161	11.8	0.17
25	8.4	4.86	4.41	0.184	194	13.98	0.17
26	8.4	8.82	7.81	0.308	206	16.68	0.58
27	7.4	6.82	6.04	0.293	178	23.4	0.33
28	6.9	6.27	5.83	0.206	140	24.7	0.66
29	8.5	15.96	12.51	2.82	265	29.32	13.55

development of this invasive fungal infection in our patient were the presence of an underlying malignancy, use of steroids and broad-spectrum antibiotics. Similar to literature, we treated our patient with voriconazole, albeit without success.[17,18] As per the literature on talaromycosis in cancer patients, cases have been reported in lung cancer patients with favorable and poor outcomes.[5,19] However, in the former case, there was a relapse of the fungal infection, 5months after initial treatment.[5] We also found one case report of nodular Hodgkin's lymphoma patient and an ovarian cancer patient infected with talaromycosis.[20,21] In the latter case, *Penicillium* spp. was resistant to all agents, except amphotericin-B.[21] It is important to note that routine anti-fungal susceptibility, except for *Candida* is not routinely available in India. While we administered voriconazole to our patient, he succumbed despite maintaining therapeutic drug levels. While both COVID-19 and penicilliosis predominantly affect the respiratory system, the mortality of penicilliosis is much higher than the case fatality in COVID-19.[22]

Conclusion

To our knowledge, this is the first reported case of *Penicillium* co-infection with COVID-19 in the oral cavity cancer patient. While worsening respiratory symptoms in a COVID-19 patient are commonly attributed to SARS-CoV-2 or a bacterial superinfection, physicians should be cognizant for the possibility of a concomitant fungal infection which can be fatal.

Declaration of Patient Consent

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

Funding

None.

Conflict of Interest

None declared.

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"PALLCARE Seva"—A Beacon Amid the Catastrophic COVID-19 Times: Correspondence

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Ind J Med Paediatr Oncol 2023;44:449–450.

We would like to comment on the publication "'PALLCARE Seva'—A Beacon Amid the Catastrophic COVID-19 Times: A Cross-Sectional Study from a Rural Oncology Institute in Western Maharashtra[1]." This study reports on an audit of the "PALLCARE Seva" telephone service calls.[1] General practitioners might be consulted in more than one-tenth of cases, according to Patil et al. The main tenets of our service were courtesy and compassion, helpfulness, addressing skepticism about the condition, and giving patients and caregivers a chance to express their ideas. The majority of callers—more than three-fourths—rated their interactions as positive and said they would suggest this service to other patients in need.[1]

We both agree that the coronavirus disease 2019 (COVID-19) outbreak made the switch to broad service necessary. Utilizing a communication tool could be beneficial. However, the scenario in which it is appropriate varies. Poor infrastructure makes it challenging to access IT or a basic phone in many rural areas of developing nations. As a result, it is necessary to analyze the effectiveness of telephone conversations in light of the regional context. Furthermore, COVID-19's situation is constantly changing. The arrival of a new COVID-19 vaccination and the emergence of a new variation can both have a big impact on the local situation. The shifting local COVID-19 epidemic scenario must be taken into consideration while assessing the effectiveness of phone calls.

Trial Registration
Not applicable.

Funding
None.

Conflict of Interest
None declared.

Data Availability Statement
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Reference

1 Patil CR, Tanawade P, Dhamne N, Anap Y, Watve P. "PALLCARE Seva"—A Beacon amid the catastrophic COVID-19 times: a cross-sectional study from a rural oncology institute in western Maharashtra. Indian J Med Paediatr Oncol 2022;43(04):369–375

article published online
February 10, 2023

DOI https://doi.org/10.1055/s-0042-1760319.
ISSN 0971-5851.

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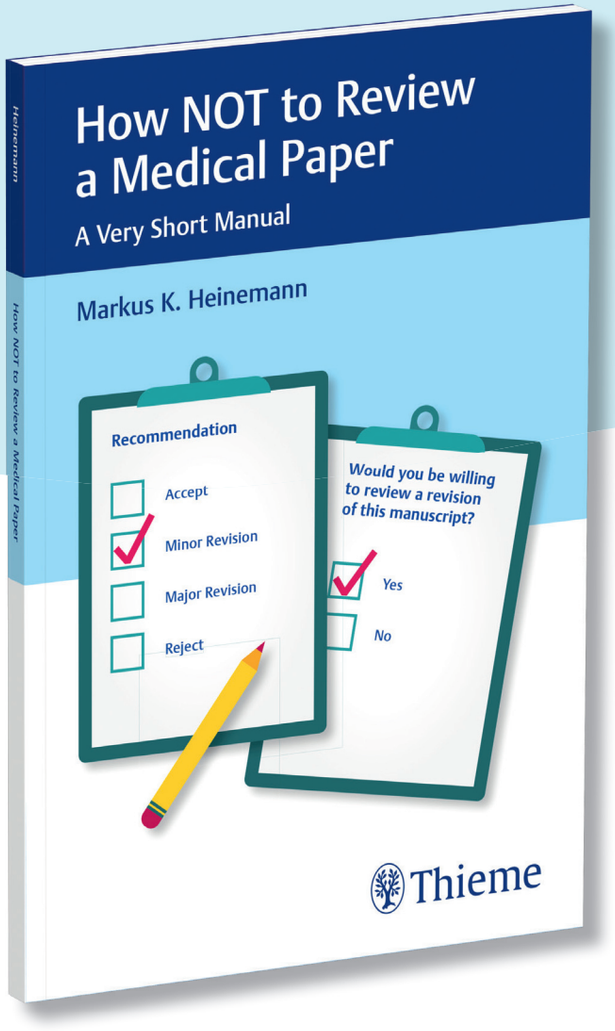

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