



# When Do Patients with Breast Cancer Seek Help from Psycho-oncology Services? A 3-Year Retrospective Study from India

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# **Abstract**

**Introduction** Breast cancer is the most frequent cancer among women. In the last few decades, the outcome of breast cancer has improved significantly in terms of survivorship and quality of life. However, it is crucial that alongside managing the disease, breast cancer services address and manage associated or co-occurring psychiatric illnesses such as acute stress reactions, procedural anxieties, adjustment issues, depression, and fear of recurrence, which leads to an overall better experience of the patient.

**Objective** There is a paucity of data on the patterns of psychiatric morbidity in patients with breast cancer who access psycho-oncology services in a naturalistic setup outside research studies from India. The current study focused on exploring this alongside reporting the common treatment methods adopted for this group of patients.

Materials and Methods Real-life data from electronic patient records were retrospectively reviewed for all patients with breast cancer accessing integrated psychooncology services in a tertiary care hospital in India over three 3 years (2018–2020). The various psychiatric morbidities were reported, along with associated cancer demographic data, disease characteristics, and treatment details.

**Results** Of all the breast cancer patients (n = 338) in the calendar years 2018 to 2020 reviewed by psycho-oncology services, the most common psychiatric diagnosis was depressive illness (n = 100, 29.6%), followed by adjustment disorders (n = 68, 20.1%) and anxiety (n = 66, 19.5%). There was a significant minority with serious enduring mental illnesses such as schizophrenia (n = 11, 3.3%) and bipolar disorders (n = 14,4.1%). On the other hand, 14.2% (n = 48) of the patients with breast cancer who attended Psycho-oncology outpatient department did not have any psychiatric syndrome. Around 16.3% of patients could be managed without a prescription for any medications and almost half of the patients needed only one psychotropic

# **Keywords**

- breast cancer
- ► India
- ► medical oncology
- psychiatry
- psycho-oncology
- psycho-oncology service

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medicine. Psychological interventions were used for 45.6% of patients.

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Conclusion Integrated psycho-oncology services in a cancer hospital catering to patients with breast cancer help in psychiatric assessment, diagnosis, and addressing the mental health needs of patients. The treatment offered needs to be nuanced and individualized and may require a combination of psychotropic medications and psychological techniques.

# Introduction

Breast cancer is presently the most diagnosed cancer and the fifth leading cause of death worldwide. In India, it is the most frequent cancer among women.<sup>2</sup> In the past three decades, remarkable advancements have been made in breast cancer treatments, especially in the areas of surgery, radiotherapy, targeted systemic therapies, genomics, and molecular biology that in turn has not only improved overall survival (including disease-free survival) but has also resulted in better management of the axilla, more acceptable cosmetic outcomes, and reduced treatment time and hospital visits.<sup>3</sup> Due to enhanced survivorship and better cosmesis, patients often face minimization of the subjective distress associated with the diagnosis. They often face comments as "it's only breast cancer" and that "there is nothing much to worry about."4 However, objective data show, despite the medical advances, rates of psychological morbidities is highest among patients with breast cancer as compared to all other cancers. 5 Breast cancer treatments, although ensuring longer survivorship, affect nearly all the key aspects of femininity including sexuality, physical identity, fertility, and the ability to breastfeed.<sup>4</sup> The diagnosed person or the survivor deals with a plethora of issues including a constant preoccupation about the relapse of cancer, body-image issues related to mastectomy, lymphoedema and hair loss, anticipated problems in companionship, sexual intimacy, reproduction, and parenting abilities, and even worries about passing the "cancer gene" to their grown-up children.<sup>3,6,7</sup> Many of these concerns can be chronic and patients may continue to have anxiety and depressive symptoms for years.<sup>8,9</sup> These symptoms are often colored by the patient's perception of the disease, their illness experience, and the coping resources of the person. Interestingly studies showed that the psychological symptoms are not associated with any biological prognostic factors like tumor size, histology, number of axillary lymph nodes involved, or other treatmentrelated factors, except for adjuvant chemotherapy which has been found to increase the risk for either or both anxiety and depression. The patient's concerns have a significant impact on the family members. The prevalence of anxiety and depression in family/caregivers is similar to that of breast cancer patients. 10 In India, caregiving is mostly performed by family members (both physical and psychological) and in most cases, family members do not feel the need or have the means to seek professional help.<sup>11</sup> Family caregivers of cancer patients often report significant anxiety or depressive symptoms and these symptoms persist during the initial months and years following the cancer diagnosis. 12 Therefore, there has been an increasing emphasis on the psychosocial care of breast cancer patients, survivors, and caregivers. A recent study conducted in India points out that both the patient and the caregiver seek structured counselling services for patient-caregiver dyads, improved doctor-caregiver communication, and routine practice of disclosure of cancer diagnosis.<sup>13</sup>

Psycho-oncology is a relatively recent area of specialization in India and not many cancer centers in India have a psycho-oncology service accessible to patients, although this is changing rapidly. One paper cites the lack of routine integration of psychosocial care in cancer settings.<sup>14</sup> Most psycho-oncology studies conducted in India usually point to the need for the development of psychosocial approaches for cancer that are suitable and acceptable to patients. In this article, we report the types of mental health issues faced by patients with breast cancer who were assessed by the psycho-oncology unit in a tertiary cancer hospital in eastern India over 3 years starting from January 2018 and ending in December 2020. The article also discusses a service delivery model that is suited to low- and middle-income country settings.

# **Objectives**

The main objective of the current study was to explore and describe the nature of psycho-oncological services accessed by patients with breast cancer in a specialist cancer center.

# **Materials and Methods**

# Study Design

The study follows a design of a retrospective case series for a period of 3 years based on a contemporaneous electronic medical record of psychiatric assessments documented for all the patients by the treating consultant psychiatrist after ethical clearance for the institutional review board.

# Setting

This study was conducted in a tertiary, philanthropic cancer care center serving eastern Indian states and neighboring South Asian countries like Bangladesh, Nepal, and Bhutan. Currently, the hospital has a capacity of 431 beds and caters to a large catchment area.

## **Psycho-oncology Services**

The study hospital has a well-functioning psycho-oncology service, developed since the very beginning of the hospital's inception and currently maintained by two consultant psychiatrists and clinical psychologists. The department has daily outpatient and in-patient services and works consistently and routinely for patients reaching out for psychological aid. The hospital's breast disease management protocol ensures optimal access for patients, who at times come with ailments in the context of their cancer diagnoses and at other times with a premorbid psychiatric illness that might affect cancer treatment itself.

#### **Duration of Service Assessed**

The duration of the study was for three calendar years, from January 1, 2018 to December 31, 2020.

## **Collection of Data**

The study hospital maintains an electronic health record system and the department of psycho-oncology maintained contemporaneous health records electronically. Data were collected from the existing health records. The electronic hospital management system provided the demographic and clinical data for the patient and was supplemented by manual documents of the hospital. Institutional ethics approval was obtained (EC/WV/TMC/49/20) for the study.

## **Analysis of Data**

All breast cancer patients who were assessed by the psychooncology department between 2018 to 2020 were included in the study. Simple descriptive statistics were used with frequencies to describe the patients accessing psycho-oncology services. The continuous variables (age and distance of the patient's home to the hospital) were checked for normality with the Shapiro-Wilk test and Q-Q plots and an appropriate measure of central tendency was used to describe the data. Since the results suggested that our data were not normally distributed, we proceeded to use the median and the interquartile range as descriptive parameters for the data.

#### **Ethics**

The present study was in accordance with the ethical standards of the institutional ethical committee, national guidance on research ethics, and the 1964 Helsinki Declaration and its later amendments. The study was approved by the institutional ethics committee of Tata Medical Center, Kolkata. In view of the retrospective nature of the study, a waiver of consent was obtained from the institutional ethics committee of Tata Medical Center, Kolkata. As per institutional policy (IEC Protocol Waiver No – EC/WV/TMC/49/20 on August 18, 2020).

# Results

A total of 2,448 patients were treated by the breast oncosurgery team between the years 2018 and 2020, out of which 338 patients reached out for psycho-oncology services (**Table 1**). Of 338 patients, 335 were females, while three of the patients were adult males with breast cancer. The age of the patient and the distance of the patient's home to the hospital were both continuous variables that were not normally distributed. The age of patients ranged from

**Table 1** Description of the data/sociodemographic details

Variable		n=338	%
Age (in years) at presentation		Median = 48.50 (IQR: 41–57) Maximum = 76 Minimum = 23	
Gender	Female	335	99.1
	Male	3	0.9
Marital status	Married	307	90.8
	Single	21	6.2
	Widow	10	3
Fund	Yes	47	13.9
	No	291	86.1
Occupation	Homemaker	286	84.6
	Business	4	1.2
	Government job	16	4.7
	Private job	6	1.8
	Other	22	6.5
	Retired	4	1.2
Distance (in kilometers)		Median = 56.30 (IQR: 20.20–229.48) Maximum = 1,583 Minimum = 1	

Abbreviation: IQR, interquartile range.

23 years to 76 years with a median age of 48.5 years (interquartile range [IQR]: 41–57). They were mostly homemakers (n = 286, 84.6%), followed by government employees (n = 16, 4.7%). Four patients ran personal businesses (n = 4, 4.7%)1.2%). The median distance between the hospital and their home was 56.3 km (IQR = 20.2-229.48 km) with the longest distance travelled by any patient being 1,583 km.

Of the 338 patients who accessed our service, 319 patients (94.4%) had a diagnosis of invasive ductal carcinoma, whereas 9 patients (2.7%) had invasive lobular carcinoma. Other carcinoma types (3% of all patients) included ductal carcinoma in situ, invasive mammary carcinoma, and carcinomas of no special type/mixed type (> Table 2). Among the patients who accessed psycho-oncology outpatient department, 171 (50.6%) patients were at stage 2 cancer, 110 (32.5%) patients had stage 3 cancer, and 45 (13.3%) patients were diagnosed to have stage 4 cancer. More than half of the patients (51.5%) patients underwent mastectomy, while 34.9% of patients underwent breast-conserving surgery. Among all the patients, 13.6% patients did not undergo any form of surgery as they had distant metastasis. Almost three-fourths of the patients (73.4%) did not have any distant metastasis. Most (88.8%) patients underwent some form of chemotherapy. More than three-fourths of all patients (83.1%) were given radiation therapy, while two-thirds of the patients (66.9%) received hormone therapy. More than half of all patients (190 or 56.20%) presented with some form of medical comorbidity; of them, 59 (17.45%) patients had at least two comorbidities and 26 (7.69%) had more than two comorbidities. Hypertension was the most common comorbidity reported in 123 (64.73%) patients, followed by diabetes in 68 (35.78%) patients and hypothyroidism/hyperthyroidism in 55 (28.94%) patients. Only 35 patients (10.35%) had both diabetes with hypertension.

Of all the breast cancer patients reviewed by psychooncology services, the most common psychiatric diagnosis was depressive illness (n = 100, 29.6%), followed by adjustment disorders (n = 68, 20.1%) and anxiety (n = 66, 19.5%); next were major psychiatric disorders such as schizophrenia (n = 11, 3.3%), bipolar disorders (n = 14, 4.1%), organic mood or psychotic disorders (n = 9, 2.7%), and neuro-cognitive disorders (n = 3, 0.9%) ( $\succ$  **Table 3**). Amongst the patients who were referred, 14.2% (n = 48) of the breast cancer patients did not have any psychiatric syndrome. There was no report of completed suicide amongst the patients diagnosed with breast cancer in the year for which the data were being analyzed. The number of treatment contacts with psycho-oncology services varied and ranged from a single contact to 24 separate contacts with mental health professionals, the median number of contacts being 2 (IQR = 1-4). The number of contacts was more (median 3.50, IQR = 1.75-9.25) for people with known severe enduring mental illness. Based on the median score, the entire sample of patients included in the study was divided into two groups (1-3 evaluations vs. > 3 evaluations by psychooncology). The chi-square test was used for exploring the association of those with and without severe mental illnesses (e.g., schizophrenia, bipolar disorder, etc.), the total number of evaluations by psycho-oncology (1-3 evaluations vs. >3 evaluations by psycho-oncology) was found to be statistically significant (p < 0.01). While some of the patients evaluated (16.3%) did not need any psychotropic medications, almost half of the patients (48.52%) were managed with only one medication for their symptoms. An almost equal percentage of patients (45.6%) also needed psychological interventions in the form of psychoeducation, psychological support, coping strategies, suggestion for lifestyle modifications including sleep hygiene techniques, or a combination of these.

# Discussion

Studies in various parts of the world suggest that patients require individualized treatment plans according to their needs. 16-18 In the current article, around half of the patients who accessed psycho-oncology services presented in advanced stages (stage 3 or 4), while others presented in earlier stages. The majority of the patients received curative surgery, radiation therapy, and/or chemotherapy based on the weekly multidisciplinary group discussions. The common reasons for referral to psycho-oncology from the perspective of the oncologist were low mood, fragmented sleep, restlessness, and being agitated or expressing suicidal thoughts. It was rare that a syndromic psychiatric diagnosis was mentioned in the referral. Of the patients who were referred, most were diagnosed with depressive disorder (n = 100, 29.6%), followed by adjustment disorders (n = 68,20.1%) and anxiety disorders (n = 66, 19.5%). European and American guidelines stress the need for the incorporation of psychological interventions in breast cancer services. 19,20 Even with significant improvement in the outcome of breast cancer over the last few decades, a survey conducted in 32 countries in Europe showed that only one-third of the countries had documented requirements and specific indicators for psychosocial interventions, resources they require, and educational requirements.<sup>19</sup> The role of psychosocial support remains crucial in treatment. "The SARS-CoV-2 pandemic had affected cancer care and service delivery around the world and we published the impact of the pandemic on psycho-oncology services separately."<sup>21</sup>

A recent review<sup>22</sup> covering several studies around the globe, including India, concluded the prevalence of depression in breast cancer to be around 32%. The higher rates of psychiatric morbidity reported in this audit were perhaps because we only evaluated patients who were referred. All patients are assessed by the breast surgery or medical oncology teams and referred to psycho-oncology as per accepted disease management guidelines when suspected to have psychological or psychiatric morbidity. Some patients diagnosed with syndromic psychiatric morbidity needed pharmacological management. Depression in breast cancer is associated with increased morbidity, suicidality, and longer hospital stays for treatment.<sup>23</sup> Depression can result in poorer adherence to cancer-specific treatments<sup>24</sup> and that may indirectly increase the risk for mortality. Antidepressants including selective-serotonin reuptake inhibitors are recommended for managing syndromic depression and these are effective in this group of patients.<sup>25</sup>

**Table 2** Cancer disease characteristics of our sample group

Variable		n = 338	%
Type of cancer	Invasive ductal carcinoma	319	94.4
	Invasive lobular Carcinoma	9	2.7
	Other	10	3.0
Stage of breast cancer	0	3	0.9
	1	9	2.7
	2	171	50.6
	3	110	32.5
	4	45	13.3
Estrogen receptor status	Positive	218	64.5
	Negative	120	35.5
Progesterone receptor status	Positive	191	56.5
	Negative	147	43.5
HER2 receptor status	Positive	79	23.4
	Negative	233	68.9
	Equivocal	26	7.7
Type of surgery	Breast-conserving surgery	118	34.9
	Mastectomy	174	51.5
	None	46	13.6
Chemotherapy	Yes	300	88.8
	No	38 11	
Radiotherapy	Yes	281	83.1
	No	57	16.9
Trastuzumab therapy	Yes	44	13.0
	No	294	87.0
Hormone therapy	Yes	226	66.9
	No	112	33.1
Metastasis	Yes	90	26.6
	No	248	73.4
Brain metastasis	Yes	20	5.9
	No	318	94.1
Number of comorbidities	No comorbidities	148	43.8
	Comorbidities	190	56.20
	1	105	31.06
	2	59	17.45
	>2	26	7.69
Comorbidity types	Diabetes	68	35.78
	Hypertension	123	64.73
	Diabetes and hypertension	35	10.35
	Hypo/hyperthyroidism	55	28.94
	Electrolyte imbalance	2	1.05
	Sepsis	1	0.52
	COPD	5	2.63
	Others	47	24.73

Abbreviations: COPD, chronic obstructive pulmonary disease; HER2, human epidermal growth factor receptor 2.

**Table 3** Psycho-oncology factors and services

Variable		n=338	%
Psychiatric diagnosis given	No psychiatric diagnosis	48	14.2
	Delirium	8	2.4
	Adjustment disorder	68	20.1
	Depressive disorder	100	29.6
	Anxiety disorder	66	19.5
	Substance abuse	1	0.3
	Schizophrenia	11	3.3
	BPAD	14	4.1
	Other psychotic disorder 5		1.5
	Organic mood and psychotic disorder	9	2.7
	Dementia	3	0.9
Number of medications	No psychotropic medication	55	16.3
	Prescribed medications	283	83.7
	1	164	48.52
	2	99	29.28
	>2	20	5.90
Type of medication	Sedative	93	32.86
	Antidepressant	210	74.20
	Mood stabilizer	26	9.18
	Antipsychotics	66	23.32
	Others	27	9.54
Psychological intervention	Yes	154	45.6
	No	184	54.4
Number of visits	All patients (n = 338)	Median = 2 (IQR: 1-4) Maximum = 24 Minimum = 1	
	SMD (n = 30)	Median = 3.50 (IQR: 1.75–9.25) Maximum = 15 Minimum = 1	
Previous psychiatric diagnosis (past history)	Yes	113	33.4
	No	225	66.6
Family history of	Yes	44	13.0
psychiatric diagnosis	No	294	87.0

Abbreviations: BPAD, bipolar affective disorder; IQR, interquartile range; SMD, severe mental disorder. Note: Severe mental disorders (schizophrenia, BPAD, other psychotic disorders).

The majority of patients treated by us were managed with a single psychotropic combined with psychological interventions. Only around one-third of the assessed patients needed more than one psychotropic medication. This was mostly due to the use of nonsedative antidepressants like Venlafaxine, with less propensity to interfere with the metabolism of Tamoxifen,<sup>26</sup> but occasionally requiring additional shortterm low-dose benzodiazepines for fragmented sleep. Overall, avoiding polypharmacy is recommended.

Psychological interventions were initiated for almost half of the patients seeking help, which is often the preferred mode of intervention for the management of issues related to coping with a cancer diagnosis and related predicaments like procedural anxiety, body-image issues, fear of recurrence, and psychological distress at the end of life. Psycho-education about possible symptoms, treatment needed, and behavioral and lifestyle interventions such as sleep hygiene were used frequently. Lifestyle interventions empower the patient and their relatives to initiate simple changes that may help them navigate through complex treatment processes when the psychological distress is transient.<sup>27,28</sup> Psycho-educational approaches, on the other hand, attempt to address realistic concerns by instilling a sense of control within transiently distressed patients; people with more serious psychological issues may need more specific psychological interventions.<sup>29</sup> As evident from our data, psychological interventions are brief as many patients accessed the service for a few sessions only. The people who came for repeated consultations usually had a pre-existing mental illness. The study emphasizes the need for an integrated psycho-oncology service model. This can improve access to mental health care in resource-poor low and middle-income countries like India. 30,31

The typical referrals of patients with breast cancer patients managed by psycho-oncology services are represented in **Table 4**.

Service delivery model for psycho-oncology services for women with breast cancer in low- and middle-income countries:

Therefore, an integrated hospital-based psycho-oncology service for patients with cancer is proposed. It is necessary that clinicians treating women with breast cancer are initially sensitized about the magnitude of the problems and made aware of early warning signs of mental health difficulties that warrant a referral. The institutional breast cancer

**Table 4** Typical presentation and psycho-oncology management of patients with breast cancer

Demographic and clinical profile	Psychological issues	Usual reason for referral and treatment goals	Interventions offered by psycho-on- cology services
40–65-year-old lady, recently diagnosed with breast cancer, presenting with episodes of palpitation, breathlessness, feelings of impending doom whenever entering the hospital or day-care to receive chemotherapy.	Adjustment disorder with panic attacks	Reason: difficulty to accept the diagnosis, distress Goal: assist in adaptation	Psychological intervention addressing anticipatory anxiety, catastrophization and coping. If required, antidepressants with or without (for a short duration) benzodiazepines
40-60-year-old lady with breast cancer undergoing adjuvant chemotherapy and awaiting surgery with worries about the side effects of chemotherapy, surgery, outcome, and implication on her family especially children	Anxiety	Reason: anxiety about cancer and predicaments Goal: address anxiety and improve coping	Psychological intervention to address anxiety, relaxation techniques, psycho- logical support If required, add antidepressants like Citalopram, Venlafaxine
45–65-year-old lady postsurgery for breast cancer with low mood, crying spells, terminal insomnia, diurnal variation of mood, anhedonia, de- creased appetite	Depression	Reason: depressed mood, de- creased motivation for treatment, suicidal risk Goal: assessment of depressive cognition and risk of suicide	Pharmacological (SSRI/TCA) and non- pharmacological intervention (cogni- tive behavioral techniques) for depression. Suicidal risk assessment and management
30–50-year-old lady postsurgery, postchemotherapy being upset with mastectomy and hair loss, presenting with interpersonal issues with her husband along with a feeling of estrangement in marital relationship	Body-image issues, marital discord	Reason: feelings of loss of physical identity, social stigma, and marital disharmony Goal: address body image concerns, empowering her, and improving communication within the marital dyad	Psychological interventions addressing body image and sexuality-related con- cerns, helping the partners to express their feelings and distress about cancer and the relationship, encourage dyadic coping
25–40-year-old married lady with living daughter presenting with known HBOC (hereditary breast and ovarian cancer) and anxiety related to need for ovary removal early in life, implication on perceived femininity, the implication of hereditary cancer on her daughter and unmarried cousins	Anxiety in the context of hereditary cancer	Reason: worries about risk reduction surgery; worries about passing the gene to offspring and social implication Goal: psycho-education, psychological support	Psychological support with validation of her concerns, allowing her to evaluate the pros and cons of the diagnosis, the chance of prevention of early cancerrelated fatality in her and multiple family members by screening or risk-reducing surgery
50–70-year-old lady with metastatic breast cancer, currently undergoing end-of-life care under the department of palliative medicine, presents with being tearful, expressing remorse about multiple decisions she took in her life, with fragmented sleep.	Anticipatory grief	Reason: low mood, being upset since their transition from cura- tive to palliative Goal: providing support	Pharmacological intervention for adequate control of physical symptoms like pain, and fragmented sleep. Psychological intervention to address the feeling of devastation, anticipatory grief, and abandonment. Arrange a meeting with close ones, helping to sort out things that she finds important, helping to find meaning and peace.
20–60-year-old family member of index breast cancer patient presenting with worries, low mood, and fragmented sleep since index patient received the diagnosis of cancer	Anxiety and depressive reaction in relatives	Reason: anxiety about treatment outcome, implication on family, relationship Goal: address anxiety and help to cope	Psychological intervention for anxiety, encouraging lifestyle modification, sleep hygiene, providing support. If required, add antidepressants like Mirtazapine, SSRIs

Abbreviations: SSRI, selective-serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

treatment protocol practiced included specific pointers for such a referral. The psycho-oncology services are offered for both out-patients and hospitalized patients and are almost always started on the day of referral. The psycho-oncology team used pharmacological and nonpharmacological methods of treatments delivered by consultant psychiatrists and clinical psychologists. The typical patient profiles and interventions offered are discussed in ►Table 4.

# **Strengths and Limitations**

All patients were reviewed by consultant psychiatrists as per the International Classification of Diseases 10 Revision. The psycho-oncology services were provided in the same hospital, available every day of the week, and most patients are seen on the same day of the referral whenever possible. The nature of the services was comprehensive for both outpatients and inpatients. Despite being a single-center study, this center caters to a wide geographical region in India and surrounding countries, and thus provides a large catchment area. Additionally, the robust electronic hospital management system resulted in thorough and consistent patient records. This emphasizes the role of an integrated service model in low- and middle-income countries.

The article presented data on those women with breast cancer who accessed psycho-oncology services. This article cannot comment on the patients with breast cancer who did not attend psychiatry consultations or the overall prevalence of psychiatric morbidity in women with breast cancer. The data are presented using simple descriptive statistics and further associations were not presented as the study was originally not powered for multiple testing and there were no a priori hypotheses. Also, for some patients, the stage of cancer progressed over time. Hence testing for associations was avoided.

## Conclusion

This study showed that a significant number of women with breast cancer access psycho-oncology services, of whom around half of the patients had anxiety or depressive illnesses, one-fifth had stress-related adjustment disorders and only a minority (10%) had major psychiatric disorders like schizophrenia or bipolar affective disorder. The availability of integrated psycho-oncology services in the cancer center improved the access to mental health care for patients who wanted to seek help. This article attempts to highlight the importance and need for a psycho-oncology service model managing common psychiatric comorbidities in the present health care milieu.

Statement: all authors have participated in the write up of the article and approved the submitted version of the manuscript. All the authors fulfil the authorship criteria and declare that the manuscript represents honest work. The contents of this manuscript have not been copyrighted or published previously and are not under consideration for publication elsewhere. In addition, this manuscript will not be copyrighted, submitted, or published elsewhere while

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Conflict of Interest None declared.

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