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Original Research

High Dropout & Early Deaths on Chemotherapy in Real World Sounds Alarm Bells: Audit from Department of Medical Oncology of a Tertiary Care Cancer Centre in South India

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Background: Comprehensive data on early outcome of cancer management including treatment drop out, mortality, follow-up and survival, for all registered cases is scarce.
Methods: From a prospectively maintained record system in the department of Medical Oncology, an audit was done for all patients registered in the calendar year 2015 for diagnosis, treatment course, follow-up and vital status. We follow a system of outpatient clinic booked appointment and for patients who default, serial phone calls are made to counsel about compliance and give a next review date.
Results: Of total 1173 cases registered, 73.5% had solid (n = 863), and 25.5% had hematological malignancies (n = 300). Median age was 48 (1 month – 85 years); 11% pediatric, 72% adults and 17% were elderly. Male to female ratio was 0.74:1. Five most common cancers were breast (27.7%), lymphoma (11.6%) acute leukemia (9.4%), esophago-gastric (9.2%), followed by ovarian and lung carcinoma, 7% each. Almost a quarter (28%) were lost to follow up (LTFU) on different treatment phases and another one third (33%) had died during the study period. Almost half of all deaths were for patients on chemotherapy with either curative or palliative intent. Significantly higher rate of LTFU was noted for patients' age > 18 years, with solid malignancies and with longer distance (>100 kilometres) from hospital.
Conclusion: Periodic audit is essential for effective functioning of any cancer treatment program. High rates of treatment defaults and early deaths on chemotherapy demands strengthening of counselling and supportive care services to improve overall outcomes.

Introduction

Cancer is rising in incidence globally and particularly in developing countries making it a significant public health problem. From 14 million new cases reported for the year 2012 worldwide, incidence is expected to increase to over 20 million new cancer cases annually by the year 2025 [1]. For India, the annual incidence is expected to increase from estimated 1.19 million cases in 2011 to 1.86 million cases in 2026 [2]. Population based cancer registries (PBCR) and Hospital based cancer registries (HBCR) in India provide data on the incident and prevalent cases from different regions of the country and though they cover a small population (less than 10% of total) it gives a fair estimate of the extent of cancer burden in the country [3, 4]. Furthermore, there are few

studies describing profile of all the patients attending an oncology outpatient clinic [5, 6] . Realising the problem of treatment drop outs and essentiality of long term follow up, ICMR (Indian Council of Medical Research) have initiated pattern of care and survival studies (POCSS) on three of the most common cancers of the Cervix, Breast and Head & Neck which are underway in all the HBCRs of India [4]. However, comprehensive data on outcome of cancer including information on intent of treatment, treatment drop-out, follow-up, mortality and survival for all registered or diagnosed cases is generally lacking either from population based cancer registries or hospital based cancer cohorts. In this study we have attempted to analyze the clinical profile of all cases registered in the department of Medical Oncology, in a calendar year and determined their treatment course and outcome over a one year period.

Materials and Methods

The department of Medical Oncology started functioning in 2009 as part of the Regional Cancer Centre (RCC) in JIPMER, a central Government teaching Institute and tertiary care centre. The Department has inpatient bed strength of 32, dedicated 2 bedded BMT unit and a 12 bedded day care chemotherapy facility. The number of patients attending Medical Oncology clinics are increasing on an average 15% each year. This is attributable to the tertiary level of care provided, as well as the highly subsidised (or free) treatment provided by various government schemes. Presently, the department is registering about 1200 new cases annually with an average annual OPC (out-patient clinic) attendance of 34,000 patients who are either on treatment or follow up. HBCR in RCC, JIPMER started functioning from 2014 and has initiated POCSS on cancers of breast, cervix and head and neck.

Medical Oncology registration and OPC appointment system

Department of Medical Oncology started a separate in-house registration and follow up system from January 2015 for improved record keeping. Besides the common hospital number a separate department registration number is assigned to all patients who are registered for treatment in Medical Oncology. The basic demographic and contact details of the patients are collected along with this. The treatment decisions are generally taken in a joint intradepartmental forum or after discussion in multi-disciplinary tumor clinic. The registration process is a well organised and systematic process that is being implemented with help of social workers and multitask workers who are supported by the hospital and various non-governmental organisations.

We follow a system of OPC booked appointments where all registered patients are given next follow-up date depending on their phase of treatment and based on the entries in the system a daily appointment list is prepared for OPC review.

For all patients who defaults their scheduled OPC or chemo day care or procedure appointment, a telephonic enquiry is made to identify the reason for default, and they are counselled about compliance. They are given a next review date which is updated in the appointment system. If the patient again defaults on the given date, a second call is done and another OPC review date is given. During the period of missed OPC appointment patient is labelled as default and if he or she fails to come on the second given date, they are labelled as LTFU and no further regular phone calls are done. If a death at home or at another hospital is identified from the phone call, it is updated to the system as home death. All in-hospital (JIPMER) deaths and discharge against medical advice for in-patients are also updated in the system. Patients who come back for OPC review after the first or second phone call are counselled by the social worker, to prevent further defaults. A periodic screening, every 6 or 12 months, from the system is done to identify all LTFU patients who are then contacted by phone call or post card for vital status.

From this prospectively maintained record system, an audit was done for all the patients registered

in the calendar year of 2015 for their demographic characteristics, clinical profile of their cancer, treatment course, follow-up and vital status. The study was conducted in accordance with the Declaration of Helsinki and ICMR guidelines.

Statistical analysis

Descriptive statistics were used for baseline diagnosis, demographic profile, follow-up pattern and vital status. Chi square test and logistic regression were used to identify factors significantly affecting default, LTFU and deaths. All statistical analyses were 2-sided and performed at 5% significance level. Data on follow up were censored on December 31, 2016. SPSS v 16.0 was used for analysis.

Results

From a total of 1420 microscopically confirmed and clinically/radiologically suspected cases of cancer referred from various other intramural departments or hospitals, a total of 1173 cases were registered and indexed in the department of Medical Oncology for further management. Our department is not registering cases for concurrent or palliative chemotherapy for head & neck carcinoma, cervical carcinoma and brain tumors, and these tumors are currently primarily dealt by the department of Radiotherapy and the respective surgical departments.

Baseline Clinico-demographic Characteristics

Median age of our study cohort was 48 years (range 1month – 85 years) and male to female ratio was 0.74:1. As shown in Tabl 1, 11% (n=126) of all diagnosis was recorded in pediatric age group patients (≤ 18 years), 72% (n=847) in adults (19 - 60 years) and 17% (n=200) in elderly patients (≥ 61 years). Of the total (n=1173) registrations, 25.5 % (n=300) was for hematological malignancies, 73.5% (n=863) for various solid tumors and 10 patients (0.8%) had no malignancy after review and complete work-up. For patients with solid tumors, majority (76.5%, n=661) presented with locally advanced and metastatic disease while only 21% patients (n=183) had early localized disease at diagnosis. Tabl 2 and supplementary Tabl 1 illustrates the diagnosis sub groups for all patients with evidence of malignancy (n=1163). Acute leukemia comprised 36.6% (n=110) of all hematological malignancies, Non-Hodgkin’s lymphoma 32.6% (n=98), Hodgkin’s lymphoma 12.3% (n=37) and myeloma 8.6% (n=26). Of the solid tumors (n=863) indexed, most common was breast carcinoma (37.4%, n=323), followed by upper gastro-intestinal (esophagus & stomach; 12.4%, n=107), ovarian (9.5%, n=82), lung (9.2%, n= 80) and colorectal (7.9%, n=69) carcinoma.

Features	**n = 1173**	**%**
Age –groups	0-18 years	126
	19 – 60 years	847
	> 61 years	200
Gender	Male	499
	Female	674

Home state	Pondicherry	246
	Tamil Nadu	892
	Others	35
Diagnosis	Hematological malignancies	300
	Solid tumors	863
	Others (non-malignant)	10
For solid tumor – extent of disease (n = 863)	Early	183
	Locally advanced	336
	Metastatic	325
	Not known	19

Table 1: Baseline Clinico-demographic characteristics

Diagnosis	**n = 1163**	**% of hematological / solid malignancies**	**% of total cases**
Hematological (n = 300)	Acute lymphoblastic leukemia	71	23.6%
	Acute Myeloid Leukemia	39	13%
	Non-Hodgkin’s lymphoma	98	32.6%
	Hodgkin’s lymphoma	37	12.3%

	Chronic myeloid leukemia	17	5.6%
	Chronic lymphoid leukemia	10	3.3%
	Multiple Myeloma	26	8.6%
	Others	2	0.6%
Solid tumors **(n=863)**	Lung carcinoma	80	9.2%
	Breast Carcinoma	323	37.4%
	Colorectal carcinoma (& Small Intestine)	69	7.9%
	Esophageal & Stomach Carcinoma	107	12.4%
	Head & Neck Carcinoma	35	4.05%
	Ovarian tumors (epithelial /germ cell/ stromal)	82	9.5%
	Hepatic -Pancreatico-biliary tumors	39	4.5%
	Genitourinary (male)	22	2.5%
	Germ Cell tumor (testis /mediastinum)	10	1.1%
	Bone sarcoma (Osteosarcoma & Ewing’s)	23	2.6%
	Soft tissue Sarcoma	21	2.4%

	Gastrointestinal stromal tumor	8	0.9%
	Pediatric solid tumor	17	1.9%
	CUPS (Carcinoma of Unknown primary site)	10	1.1%
	Others	17	1.9%

Table 2: Diagnosis for all cases with malignancy

Site groups	**ICD 10**	**Gender**	**Total**
		Male	Female
		N	%
	C00-C14	24	4.8
	C15- C26	142	28.6
	C30 – C39	64	12.9
	C40 – C41	15	3
Melanoma of skin	C43 – C44	0	0
	C45 – C49	13	2.6
Breast	C50	7	1.4
Female Genital Organs	C51 – C58	0	0
Male Genital Organs	C60 – C63	18	3.6
Urinary tract	C64 – C68	10	2

	C69 – C72	4	0.8
	C73 – C75	3	0.6
	C76 – C80	7	1.4
	C81 – C96	186	37.5
All Sites	C00 – C96	496	100

Supplementary Table 1: Gender wise distribution of the type of malignant neoplasm according to the ICD. *10 classification*

Vital stats and follow up details for all the registered cases (n=1173) of calendar year 2015 were recorded till the date of last follow up, as on 31st December 2016. Patients who were alive and continuing treatment or completed treatment and were on regular follow-up were 38.2% (n=448) of the total. Almost one third (33.5%, n=393) of the indexed patients had died either in our hospital (5.4%, n=64) or at home/outside hospital (28%, n=329). A quarter of the registered patients (28%, n=332) either defaulted (2.7%, n=32) or were lost to follow up (25.5%, n=300) during this period. Of the total patients who were labelled LTFU (n=300), vast majority (82.6%, n=248) were on treatment while 17.3% (n=52) patients had completed their planned treatment but did not come for scheduled follow up even after multiple phone calls.

Analysis of death cases for their diagnosis, cause of death for hospital deaths and last treatment status for home deaths is shown in Tabl 3. Proportionate to the major sub-groups at diagnosis, of the total death cases (n=393), 25% (n=97) died from a hematological malignancy and 75% (n=296) had a solid tumor. Besides progressive or refractory disease, death during induction chemotherapy for acute leukemia (n=18, 28%) and chemotoxicity (n=17, 26.5 %) were the most common cause for in- hospital death. Of the patients who died at home or at an outside hospital, 53% (n=176) were on chemotherapy with palliative/curative intent, 15.5% (n=51) had completed treatment and possibly died of relapse or causes other than their primary malignancy, and 19% (n=63) were on best supportive care because of poor performance status, poor chemotherapy tolerance, exhaustion of available treatment options or by personal/family’s decision. In addition, 39 patients (12% of home deaths) died even before start of their planned treatment.

Death Cases: Diagnosis / Cause of death / treatment Status	**N**	**%***
Diagnosis of Patients who Died (n = 393)		Acute leukemia
		Lymphoma
		Others

		Breast carcinoma
		Lung carcinoma
		Gastro-intestinal
		Ovarian
		Sarcomas
		Pediatric solid tumors
		Others
	Solid tumors† (extent of disease) (n = 296)	Early
		Locally advanced
		Metastatic
		Unknown
Cause of Death for Hospital Deaths (n = 64)	induction death (for acute leukemia)	18
	progressive disease / refractory disease	26
	Chemotoxicity (on adjuvant / consolidation therapy)	10
	Chemotoxicity (on palliative therapy)	7

	Other causes	3
Treatment Status for Home Deaths§ (n = 329)	On chemotherapy	Palliative chemotherapy
		Curative intent chemotherapy
	Off treatment	51
	Before start of planned treatment	39
	On best supportive care	63

Table 3: Analysis of Death Cases

a) (*) Percentage of total death cases, b) † Percentage of total solid tumors , c) § Percentage of total home deaths

Disease - wise Outcome Summary

Tabl 4 summarizes the outcomes in terms of deaths, LTFU and patients alive & on follow up for the total registered cases in the respective major diagnostic subgroups. Of note highest death rate was seen in lung carcinoma (60%, n=48/80), upper gastrointestinal (esophageal and stomach) carcinoma (56%, n=60/107) and acute leukemia (42%, n=46/110). Highest survival rate was noted for lymphomas (58%, n=78/135), myeloma (54%, n=14/26) and breast carcinoma (52%, n=167/323). Almost a third of all solid tumor patients were lost to follow-up (25% to 38%) while LTFU rate was 15% to 18% for hematological malignancies.

Disease (ICD 10)	Total Cases registered	On follow-up	Died	LTFU
Acute Leukemia	110	44 (40%)	46 (42%)	20 (18%)
Lymphoma	135	78 (57.7%)	35 (26%)	22 (16.3%)
Multiple Myeloma	26	14 (54%)	8 (30.7%)	4 (15.3%)
Breast Carcinoma	323	167 (51.7%)	57 (17.6%)	99 (30.6%)
Lung Carcinoma	80	12 (15%)	48 (60%)	20 (25%)
Colorectal Carcinoma	69	23 (33.3%)	20 (29%)	26 (37.7%)
Stomach & Esophageal Carcinoma	107	14 (13%)	60 (56%)	33 (31%)
Ovarian tumors	82	31 (38%)	24 (29%)	27 (33%)

Table 4: Disease wise Outcome Summary

Factors affecting lost to follow-up and death

Tabl 5 describes analysis of baseline factors affecting the follow up and vital status of patients.

Significantly higher rate of regular follow up was noted for patients' ≤18 years, with hematological malignancies and with shorter distance (≤100 kilometres) of place of residence from our hospital. Significantly higher death rates were seen in age >61 years, male gender, and for patients with diagnosis of a solid tumor. In the same calendar year, we had evaluated the reasons for default over a period of 3 months (May to July 2015) for 229 patients for their first episode of default. Most common reasons were miscommunication and patients not understanding the hospital appointment system (22%), patients waiting to complete the investigations advised or who were visiting other departments (22%), family and social issues as no attendant to accompany (16%), patient was too sick to come for outpatient visit (10%), not happy with our centre and taking treatment at other hospital (7%), financial issues (3.5%), and other causes (8.5%). Furthermore, 26 (11%) patients had died before their next scheduled visit.

Factors affecting default and LTFU*		LTFU (n = 332)	**p**	**OR**	**p**
Age	≤ 18 (n=85)	64 (14.3%)	21 (6.3%)	0.002	1
	19-60 (n=579)	321 (71%)	258 (77.7%)		2.44
	> 61 (n=116)	63 (14%)	53 (16%)		2.56
Gender	Male (n= 290)	165 (36.8%)	125 (37.7%)	0.815	1
	Female (n= 490)	283 (63.2%)	207 (62.3%)		0.741
Diagnosis	Hematological (n=211)	156 (34.8%)	55 (16.6%)	0.000	1
	Solid tumor (n =569)	292 (65.2%)	277 (83.4%)		2.69
Distance from hospital (kms)	≤ 100 (n= 436)	274 (61.2%)	162 (48.8%)	0.006	1
	101 – 300 (n = 289)	149 (33.3%)	140 (42.2%)		1.58
	301 – 500 (n = 36)	16 (3.6%)	20 (6.0%)		2.11
	> 500 (n = 19)	9 (2.0%)	10 (3.0%)		1.87
Factors affecting death#	**On Follow up (n = 448)**	**Death (n = 393)**			
Age	≤ 18 (n=105)	64 (14.3%)	41 (10.4%)	0.010	1
	19-60 (n= 589)	321 (71.7%)	268 (68.2%)		1.30
	> 61 (n=147)	63 (14.1%)	84 (21.4%)		2.08

Gender	Male (n=374)	165 (36.8%)	209 (53.2%)	0.000	1.94
	Female (n=467)	283 (63.2%)	184 (46.8%)		1
Diagnosis	Hematological (n=253)	156 (34.8%)	97 (24.7%)	0.001	1
	Solid tumor (n =588)	292 (65.2%)	296 (75.3%)		1.630
Distance from hospital (kms)	≤ 100 (n=482)	274 (61.2%)	208 (53%)	0.119	1
	101 – 300 (n =309)	149 (33.3%)	160 (40.7%)		0.877
	301 – 500 (n =32)	16 (3.6%)	16 (4.1%)		-
	> 500 (n =18)	9 (2.0%)	9 (2.3%)		-

Table 5: Factors affecting default/lost to follow up and death

a) (*)death cases censored from this analysis , b) # LTFU cases censored from this analysis

Discussion

In this audit for a calendar year we attempt to describe the real world data of a short term comprehensive follow up of all cases registered for treatment in Medical Oncology unit of a government tertiary care cancer centre. It gives an indication of the general epidemiology of different malignancies in the region and helps in understanding the treatment seeking behaviour and patterns of compliance to treatment. This data is not to be read as a complete hospital based data since this is biased by registrations of Medical Oncology department alone. In our study cohort, median age was 48 years (range 1month–85 years) with 11% pediatric (0–18 years), 17% elderly (> 60 years) and 72% adult (19-60 years) patients. A similar pattern of age distribution has been reported from the eight major HBCRs in India with 1.6% to 8.5% patients in 0-14 years age group, 68% to 85% in 15-64 years age group and 16% to 25% in the elderly (> 65 years) age group in the different registries [4].

Solid tumors constituted three fourth of the total registered cases whereas one fourth had hematological malignancy in our cohort. This distribution has to be considered bearing in mind exclusion bias for head and neck and cervical carcinoma, and referral bias for hematological malignancies. Nevertheless, the five most common cancers in our audit in both sexes combined were breast carcinoma (27.7%), lymphoma (11.6%) acute leukemia (9.4%), esophago-gastric tumors (9.2%), followed by ovarian and lung carcinoma, 7% each. Similar profile of common cancers has been reported from the PBCRs and HBCRs in India and other hospital based series from developing regions, though with some regional variations [3,7]. In our study majority of patients with solid tumors presented with locally advanced and metastatic disease (76%). Though it’s common perceptive and rationale that most cancers in developing low and middle income countries present at advanced stages than in developed high income countries, actual evidence to support this is scant. Some hospital based studies for breast cancer from developing regions report the percentage of advanced cancer from 30 to 98 percent (Countries et al., 2007) and another report from eastern India had 74% patients with advanced stage at diagnosis [8].

Treatment for cancer is rigorous, protracted, resource and labour intensive with narrow

therapeutic window and thin margin for error, associated with several acute and long term toxicities as well as inherent risk of recurrence and hence the necessity for thorough compliance and careful follow up need not be underscored. However data on this vital element of treatment compliance and default is very sparse either from population based cancer registries or hospital based reports. Almost a third of patients (28%) in our study had delayed or defaulted treatment while on active therapy (83%) or did not come for regular follow up after treatment completion (17%), even with the availability of standard treatment at highly subsidized cost and despite a good system of default tracking and counselling in the department. The default and LTFU rate was more for solid tumors (25% to 38%) than hematological malignancies (15% to 18%); Odds ratio (OR) for solid tumors = 2.69, p<0.000, which we presume to be related to multimodality treatment and visit to multiple departments for solid tumors while treatment in a single department for hematological malignancies possibly led to relatively better compliance. Other factors leading to higher LTFU rate were adult and elderly age group compared to pediatric patients and longer distance (>100 kilometres) from hospital. In a similar audit from a university hospital in Uttar Pradesh, India, significant proportion of patients defaulted after undergoing preliminary investigations (16%). Only 54% of females and 58% of males took treatment out of which 68% and 63% completed the prescribed treatment [8]. About 73% of all patients were lost to follow up within one year of completion of treatment in an audit of cancer cases done by Das (2005) in Haryana over a period of 21 years. Sadly, the default and LTFU rate remains the same even after a decade. Some other hospital based series from major cancer centres in India and other developing and developed countries have reported variable treatment and follow up compliance and dropout rates for certain common solid tumors [9,15]. Few studies have attempted to describe the various reasons for non-compliance some of which includes transport constraints, socioeconomic factors, perceived disrespect by the healthcare system and not understanding the scheduling system [9, 11, 14, 16]. The most common reasons for default at our centre were miscommunication and patient not understanding the hospital system and waiting to complete their advised investigations. Though treatment default and loss to follow up is a universal problem, it is more enormous in developing regions and compounded by more drop-outs during active treatment, lack of patient's understanding of their disease, treatment and hospital functioning system, and most important inadequate resources for comprehensive care.

Besides treatment default and LTFU, another area of greatest concern observed in our study was a 33% death rate within the first year of diagnosis either in hospital (n=64) or at home (n=329) and mainly for patients on active treatment with chemotherapy with either curative or palliative intent (54% of hospital deaths and 53% of home deaths). Induction mortality for acute leukemia (28% of total hospital deaths, n=18) mostly from complicated infections and deaths from chemotoxicity after hospital admission (26% of hospital deaths, n=17) demands strategies to improve monitoring, hospital infection control practices and supportive care for reducing these as causes of hospital deaths. Precise cause of home deaths for patients who were on chemotherapy (53% of home deaths, n=176) was not definitely known, most likely it would have been chemotoxicity or progressive/refractory disease. Many of the chemotherapy related toxicity deaths are potentially preventable if timely medical attention is sought and management started urgently. High number of deaths while on palliative chemotherapy (31% of total deaths, n=122) calls for a more appropriate patient selection and accurate assessment of fitness before start of palliative therapy. Keeping aside some reports on treatment related mortality for specific cancers or in hematopoietic stem cell transplant setting, comprehensive real world data on chemotherapy related deaths and early deaths (within 6 months or a year after diagnosis) is sadly lacking from either developed or developing regions. A few studies from centres in developed countries that have described mortality within 30 days of the last chemotherapy cycle have reported a mortality rate of 4% to 8% with approximately 7% of these deaths related to chemotherapy with curative intent [17,19]. A population-based, observational study of 30-day mortality after systemic anticancer treatment for breast and lung cancer in England have reported a 30 day mortality rate of 8.4% for lung cancer and 2.4% for breast cancers mostly after palliative intent chemotherapy [20]. The authors identified age, performance status, and low body mass index among other factors that affected 30 day mortality. In our analysis the factors causing significantly higher death rates were age > 61 years, male gender,

and diagnosis of a solid tumor. In our analysis of disease wise outcomes in terms of patients who are alive (and on treatment or follow up), or died &/or LTFU, hematological malignancies seem to be doing better than solid tumors with 40% to 55% of patients with leukemia, lymphoma and myeloma being alive compared to 13% to 52% for various solid tumors. However, this requires an in depth analysis of possible elements of bias and of risk factors affecting early deaths and defaults for specific tumors and patient groups. An area of particular concern was the high death rate for lymphoma (26%) mostly Non-Hodgkin's lymphoma within the first year of diagnosis and treatment. A recent Surveillance, Epidemiology and End Results (SEER)-Medicare database for older patients with diffuse large B cell lymphoma receiving contemporary immunochemotherapy have reported a cumulative incidence of death at day 30 as 2.2% [21]. Another SEER-Medicare database report by Urban et al (2016), for ovarian cancers have reported a 43.6% death rate within first year after diagnosis and in a similar study on ovarian cancers in England 36% patients died in the first year of diagnosis [22]. In our study period, 29% of ovarian cancer patients died and additionally 33% were lost to follow up in the first year.

There were some limitations in our audit including absence of detailed information on the causes of LTFU and home deaths, missing data in some areas, short follow up, besides inherent bias of hospital based data. Prospective study is warranted to know outcome of all diagnosed cases and to identify other logistics factors for adverse early and long term outcomes. A more sturdy system of default tracking, counselling and follow up supported with adequate resources and availability of treatment facilities close to home can help minimize dropouts which would be otherwise much more in similar patient strata. In conclusion, our audit has given some insight into real world problems of treatment delivery and assessment of its effectiveness which would be akin across most centres in resource limited settings and have sensitized us to work towards reducing our specific problem of default and early deaths. Identification of similar or related problem areas at a national level can help in policy decisions, in equitable distribution of limited resources, as also suggested by Gulia et al (2016), in enhancement of treatment facilities and thereby in improving end results.

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