PROFILE OF B-CELL NON-HODGKIN LYMPHOMA AND RESPONSE TO CHEMOTHERAPEUTIC REGIMENS IN A TERTIARY CARE CENTRE IN SOUTH INDIA

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ABSTRACT Introduction: Non-Hodgkin lymphoma's (NHL) are a group of malignant lymphoproliferative disorders arising predominantly in lymph nodes with different patterns of behaviour and responses to treatment. NHL clinical presentation varies with histologic subtype and with sites of involvement. Accurate staging is important, which helps in risk stratification and management decisions. **Aim:** The aim was to study the clinical profile of patients with B-cell NHL and to assess response to various chemotherapeutic agents. **Materials and methods:** We evaluated data of patients diagnosed with B-cell NHL between 2015 and 2019 at a tertiary care cancer hospital in Andhra Pradesh, India. Data regarding demographic variables, clinical features and examination findings were collected using a pre-designed study proforma. In addition, lab investigations, including complete blood picture, liver and renal function tests, bone marrow examination, immunohistochemistry and treatment details, were noted. **Results:** A total of 91 patients with B-cell NHL were managed. The mean age was 53yrs, with males accounting for 60%. The mean duration of the presentation was 4.32 months. The most common presentation was lymphadenopathy, followed by loss of appetite, weight loss, fever and night sweats. The majority of study subjects were diagnosed with DLBCL 70 (76.9%), followed by Follicular lymphoma 10 (11.0%), and Small lymphocytic lymphoma 7(7.7%). Bone marrow involved in 22 (24.2%); Stage IV accounted by 34 (37.4%) followed by Stage III. CHOP regimen of 6 cycles was received by 30 (33.0%) patients, out of which23 patients had complete response; 61 (67.0%) patients received R-CHOP, out of which 58 had complete response. **Conclusion:** B-cell NHL has an early onset in India compared to western literature. Accurate staging is important, which helps in risk stratification and management decisions. Treatment with R-CHOP is superior to CHOP regimen with better prognosis and survival. Monitoring at periodic intervals for possible relapse is important as many patients whose disease recurred can be salvageable.

KEYWORDS B-cell Non Hodgkin Lymphoma, DLBCL, RCHOP.

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Introduction and Background

Lymphomas are malignant disorders of cells arising from lymphoid tissues. They are classified into two types, Hodgkin's and Non-Hodgkins lymphomas, depending upon histopathological evidence from an enlarged lymph node or extranodal tissue of suspicion. Non-Hodgkin lymphoma (NHL) is a group of malignant lymphoproliferative disorders arising predominantly in the lymph nodes with different patterns of behaviour and responses to treatment [1]. Non- Hodgkin's lymphoma is the fifth leading cause of cancer death, representing approximately 4.% of all cancer diagnoses and ranking seventh in frequency. NHL is five times more common than Hodgkin's disease [2].

Non- Hodgkin's lymphoma (NHL) is divided into two main types, whether it starts in B lymphocytes or T lymphocytes into B cell lymphomas or T cell lymphomas respectively.The majority of NHLs (85.%) are of B-cell origin [2] with CD22, a B-cell antigen, expressed in more than 90.% of B-lymphoid malignancies [3]. NHL accounts for 4.% of all new cancer cases and 3.% of all cancer-related deaths in men and women [4]. Diffuse large B cell lymphoma (DLBCL) and follicular lymphoma are the most common NHL subtypes, accounting for about 31.% and 22.%, respectively, of new NHL cases [5].

According to Globocan-2018, the estimated incidence of Non-Hodgkin lymphoma (NHL) is 2.8/100,000 (509,590 new cases), with a mortality rate of 2.6/100,000 (248,724 deaths) worldwide [6]. The burden of NHL in 2012 for India was estimated to have an incidence rate of 2.2/100,000 (23,801 new cases) and a mortality rate of 1.5/100,000 (16,597 deaths0 [6]. In India, the age- adjusted incidence rates for NHL in men and women are 2.9/100,000 and 1.5/100,000, respectively [7]. Compared to rates from Western Europe or North America, these are about one-fourth of the incidence rates.

Within India, the incidence is several-fold higher in urban cancer registries than in rural areas; the incidence is higher in metropolitan cities and Indian immigrants, suggesting that urban lifestyles and economic progress may increase the cancer incidence. Compared to developed nations, the key differences in the presentation in India include median age of 54 years (almost a decade less), higher male to female ratio, a higher proportion of patients with B- symptoms (40–60 vs. 20–30.%), low ECOG performance status ($\geq$2) at diagnosis (50 vs. 20–30.%), higher frequency of diffuse large B-cell lymphomas (60–70 vs. <40.%) [8], lower frequency of follicular NHL (<20 vs. 30–40.%) and T-cell type in 10–20 vs. <10.%. The estimated mortality rate due to NHL is higher in India than in North America and Western Europe.

Diagnostic and treatment delays, incorrect diagnosis, and inappropriate or suboptimal treatment may be possible reasons for the poor outcome. The current study was conceived to review the clinical profile and the response of B-cell Non-Hodgkin lymphomas to various specific chemotherapeutic regimens and contribute the data regarding Non-Hodgkin's B cell lymphoma from this part of the country.

Materials and Methods

A study of prospectively maintained sevenyear database of patients with B-cell Non Hodgkin lymphomas was undertaken in a teaching medical college hospital. The records of patients ofB-cell Non Hodgkin lymphomas generated between Jan 2015 to Dec 2019 were analyzed from the Central record section. Institutional Ethics Committee (IEC) approval was taken.

Aim of the study was to study the clinical profile of B-cell Non Hodgkin lymphomas and to assess the response of B-cell Non-Hodgkin lymphomas to various chemotherapeutic agents.

The analysis was done for cases that were present during the current study period. Information regarding the demographics and disease characteristics were obtained from the patient's medical records. If the data regarding patient's whereabouts was not available in the medical records, the patients were contacted on the phone, and if they could not be traced out, the patients were censored on the day of their last visit. A review was done after four months of the treatment to evaluate tumour response. Data regarding demographic variables, clinical features, and clinical examination findings of Non-Hodgkin's lymphoma were collected using a pre-designed study proforma.

Lab investigations including complete blood picture, liver function tests, renal function tests, bone marrow examination, immunohistochemistry were done, and results noted. A lymph node biopsy was done to establish the diagnosis of Non-Hodgkin's lymphoma. Radiological investigations were done whenever necessary in the form of chest X-ray, USG abdomen, CT, or MRI chest and abdomen and PETCT scan. Data regarding the treatment regimens administered and response to therapy were noted.

Results

A total of 91 patients were diagnosed with B-cell Non Hodgkin lymphoma between 2015 and 2019. Mean age was 53.12 years (range 18 years to 85 years).Most patients 70.% (64) were in the age group of 40 to 69 years. Males accounted for 60.4.% (55) of B-cell Non Hodgkin lymphoma patients.

Duration of Symptoms

The patient's presentation to the hospital from the initial onset of symptoms ranged from a time period of 2to 8 months. The mean time of presentation is 4.32 ± 1.776 months.

Clinical Presentation

Out of 91 study subjects, majority (71) presented with lymphadenopathy followed by loss of weight (64), loss of appetite (63), fever (48), night sweats (31), hepatomegaly (19), splenomegaly (18). (Table 1)

Hemoglobin

In the current study with 91 subjects, 19 (20.9 .%) had haemoglobin levels below 8 gm/dl, 34 (37.4 .%) between 9 to 10 gm/dl, 25 (27.5 .%) between 10 to 12 gm/dl and 13 (14.3) had their haemoglobin level above 12 gm/dl. The mean haemoglobin value is 10.560 ± 2.0422, suggestive of anaemia.

WBC Count

In the present study with 91 subjects, 5 (5.5.%) had TLC levels<4000,67 (73.6%) between 4000-11,000, 19 (20.9 .%) >11,000 and The mean TLC value was 10435.82 ± 10269.218

Platelet Count

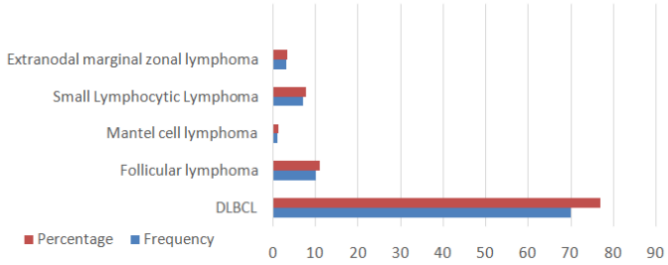
In the present study with 91 subjects9 (9.9.%) had platelet count <1.4 lakhs,64 (70.3.%) between 1.4-4lakhs, 18 (19.8 .%) had >4 lakhs. The mean platelet value was 2.89758 ± 1.375471.

Table 1 Clinical Presentation.

Symptoms	No of patients (n)	Percentage (%)
Fever	48	52.7
Night sweats	31	34.1
Loss of appetite	63	69.2
Loss of weight	64	70.3
Hepatomegaly	19	20.9
Splenomegaly	18	19.8
Lymphadenopathy	71	78

Subtypes of NHL

The below table shows the distribution of study subjects according to the types of NHL. Majority of the study subjects were diagnosed as DLBCL 70 (76.9.%), followed by Follicular lymphoma 10 (11.0.%),Small lymphocytic lymphoma 7(7.7.%),Extra-nodal Marginal Zonal (MALTOMA) 3(3.3.%), Mantel cell lymphoma 1(1.1.%). (Graph 1)



Graph 1 Subtypes of NHL.

Bone Marrow

In the present study with 91 subjects, Bone marrow involvement is seen in 22 (24.2.%) and no involvement in 69 (75.8.%).

Correlation Between Types of NHL with Maximum Bone Marrow Involvement

With 91 study subjects, DLBCL subtype had 18 patients with bone marrow involvement, Follicular and Mantel cell subtypes had 1 patient with bone marrow involvement, and Small lymphocytic lymphoma had 2 patients with bone marrow involvement. (Table 2)

Ann Arbor Staging

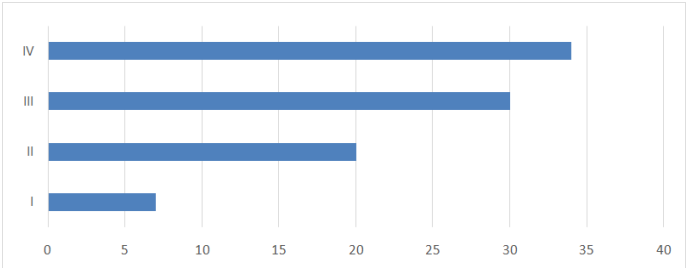
Ann Arbor staging system was used to stage the study subjects and, out of 91 study subjects, majority of subjects belonged to Stage IV 34 (37.4.%), Stage III 30 (33.0.%), Stage II 20 (22.0.%), Stage I 7(7.7.%). (Graph 2)

Treatment

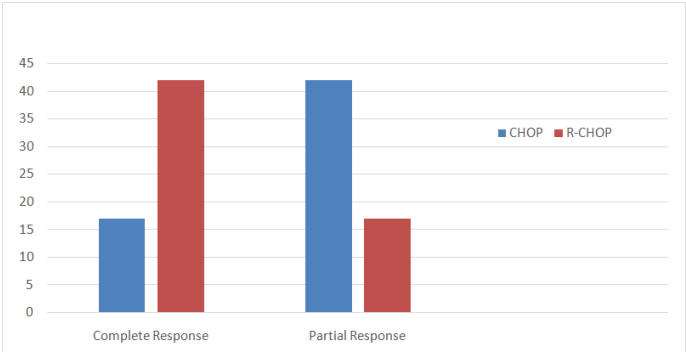
In the present study with 91 subjects, 6 cycles of CHOP regimen was received by 30 (33.0.%) patients, 61 (67.0.%) patients received R-CHOP. (Table 3)

Response

Out of 91 patients, 30 patients were given CHOP regimen, out of which 17 patients had Complete Response, and 9 had partial response, 61 cases were given R-CHOP, out of which 42 had Complete Response and 17 had Partial Response. (Graph 3)



Graph 2 ANN Arbor Stagging.



Graph 3 Treatment Response.

Relapse

Out of 91 patients, 30 patients were given CHOP regimen, out of which 4 patients had relapse, and 26 had no relapse. 61 cases were given R-CHOP, out of which 2 had relapses, and 59 had no relapse.

Overall Survival of Study Population

From survival analysis, it is proclaimed that the median follow up of study subjects is 450 days (14 months 25 days) and the overall survival is 754days (24 months 24 days with a 3yr survival of 84.61.% (95.% CI between 360 to 730 days). (Graph 4)

Comparision of Survival Analysis Among Subjects with Chop and R-chop Treatment Regimens

From Kaplan Meier chart, the survival of study subjects with CHOP regimen is 567 days (18 months 22 days), and the 3yr overall survival for patients treated with CHOP is 80.6.%. The survival of study subjects treated with R-CHOP regimen is 831 days (27 months), and the 3yr survival is 86.6.% for R-CHOP regimen. (Graph 5)

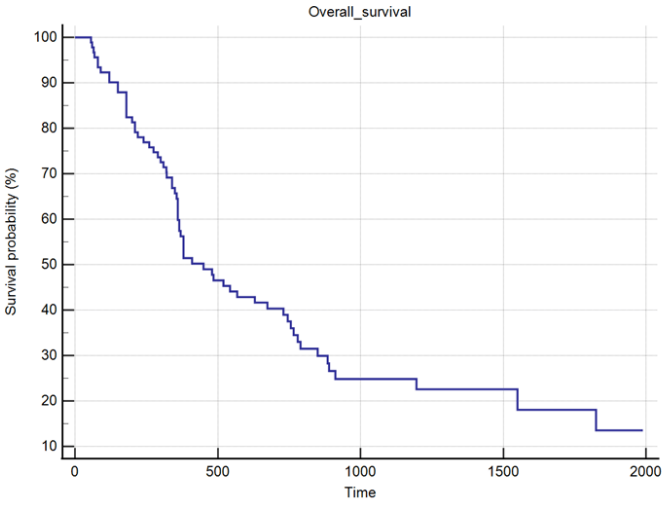
Hazards ratio between the groups receiving different treatment regimens showed 2.2280for R-CHOP over CHOP, showing

Table 2 Bone Marrow Involvement in Different NHL Subtypes.

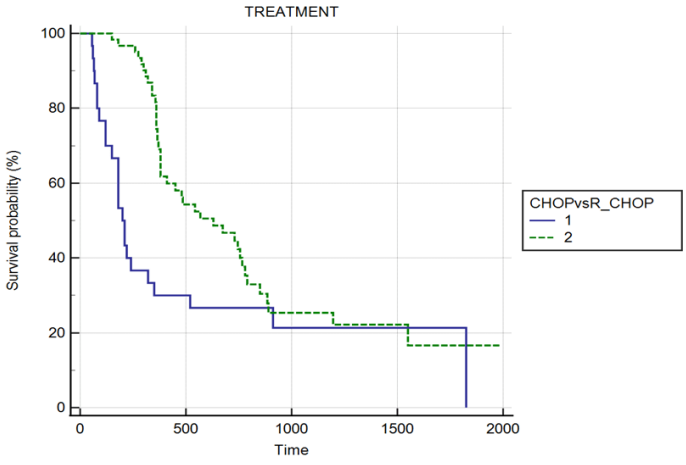
	Bone marrow involvement (Percentages)	No involvement
DLBCL	18 (34.6%)	52
Follicular	1(11.1%)	9
Mantle Cell	1	0
Small Lymphocytic Lymphoma	2 (40%)	5
Extra Nodal Marginal Zonal (MALTOMA)	0	3
Total	22	69

Table 3 Treatment Regimens.

Treatment	Frequency	Percentage (%)
CHOPx6cycles	30	33.0
R-CHOPx6cycles	61	67.0
Total	91	100



Graph 4 Overall Survival Analysis.

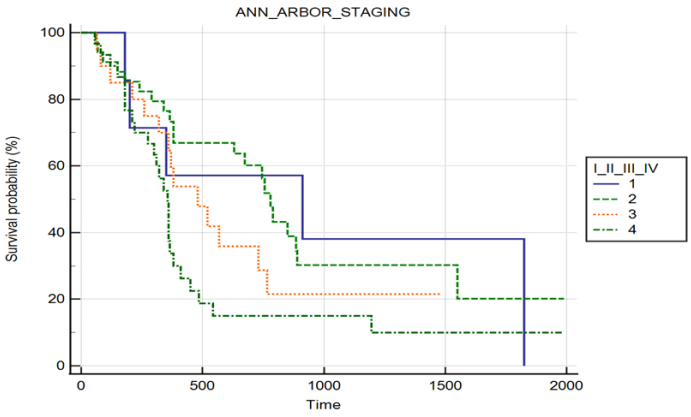


Graph 5 Survival Analysis to CHOP & RCHOP.

there is approximately 18.% risk reduction or superiority of R-CHOP over CHOP. With a P-value of 0.0073, which is statistically significant.

Comparision of Survival Analysis Among Subjects with Ann Arbor Staging

The Kaplan Meier survival analysis shows that the mean survival of subjects belonging to Ann Arbor stage I is 973 days, and that of stage II is 922 days, stage III is 632 days, and that of stage IV is 510 days. P-value-0.0338, which is statistically significant. (Graph 6)



Graph 6 Ann-Arbor Stage & Survival analysis.

Discussion

In the current study, the age of the study population ranges from as low as 18 years to 85 years, and the mean age was 53.12 ± 14.552 years, with maximum incidence seen in the 4th and 5th decade of life. The age distribution was compared with a few studies around the world, and observations are as follows, In an Indian-based study involving 100 patients by A.P. Dubey et al. [9]. The average age of onset was around 45.36 + 14.577 years, with the highest number of patients in the 5th and 6th decades. In a study conducted in Manipur, India, by Adhikarimayum et al. [10], the mean age was54.01 ± 18.1 years. The median age of patients with NHL in India is lower by almost one decade compared to the Western population. This is similar to the median age of 54 years in other Asian countries [8,11,12]. The younger age at presentation in India is possibly due to the large

proportion of young Indians: 65.% of the population in India is under 35 years of age.

In our present study, the mean duration of symptoms is 4.32 ± 1.776 months. In comparison to other studies across the world: In a study conducted in south India with 114 patients by Ananth Pai et al. [13], the mean duration of presentation of symptoms is 3.6 to 4 months.

In the present study carried out among 91 subjects, the various clinical manifestations are as follows: Lymphadenopathy is the most common clinical feature, manifested in about 78 .% of the study population. 70.3 .% of the study population complained of weight loss, while 69.2 .% had loss of appetite. Fever was noticed in 52.7 .% of patients, and Night sweats in 34.1.%. Hepatomegaly is seen in 20.9.%, and splenomegaly in 19.8.%. The incidence of clinical manifestations in various studies is as follows: In an Indian-based study involving 100 patients by A.P. Dubey et al. [9], lymphadenopathy is seen in 70.%, loss of weight 30.%, loss of appetite 30.%, Fever 45.%, Night sweats 45.%, Hepatomegaly17.%Splenomegaly 9.%.

In our study majority of the study, subjects were diagnosed with DLBCL 70 (76.9.%), followed by Follicular lymphoma(11.0.%), Small lymphocytic lymphoma 7(7.7.%), Extranodal Marginal Zonal (MALTOMA) 3(3.3.%), Mantel cell lymphoma 1(1.1.%). The types of Non-Hodgkins lymphoma were compared with a few studies around the world. Observations are as follows, In an Indian-based study involving 100 patients by A.P. Dubey et al., DLBCL 56.%, Follicular lymphoma 17.%, Small lymphocytic lymphoma 1.%, Extra-nodal Marginal Zonal (MALTOMA) 8.%, Mantel cell lymphoma 4.%[9].In a study conducted in Manipur, India by Adhikarimayum et al, DLBCL 45 .%, Follicular lymphoma 5.%,Small lymphocytic lymphoma 1.%,Extra-nodal Marginal Zonal (MALTOMA) 1.%, Mantel cell lymphoma 5.% [11].In a study conducted by Nawaf Alyahya et al. in Saudi Arabia, DLBCL 59 .%, Follicular lymphoma 7.%, Small lymphocytic lymphoma 5.%, Extra-nodal Marginal Zonal (MALTOMA) 1.%, Mantel cell lymphoma 1.% [14]. In a study conducted by Ananth Pai et al., DLBCL 43 .%, Follicular lymphoma 9.%, Small lymphocytic lymphoma 3.%,Extranodal Marginal Zonal (MALTOMA) 2.%, Mantel cell lymphoma 2.% [13]. In comparison to other studies, it is evident that the most common type of Non-Hodgkins B cell lymphomas is Diffuse large B cell lymphoma, followed by Follicular lymphoma, Small lymphocytic lymphoma Extra-nodal Marginal Zonal (MALTOMA), Mantel cell lymphoma.

Ann Arbor staging system was used to stage the study subjects. Out of 91 study subjects, the majority of subjects belonged to Stage IV 34 (37.4.%), followed by Stage III 30 (33.0.%), Stage II 20 (22.0.%), and Stage I 7(7.7.%).

The age distribution was compared with a few studies around the world, and observations are as follows. In an Indian-based study involving 100 patients by A.P. Dubey et al.,32 (32.%) patients presented with an Ann Arbor stage 1 or 2 diseases, whereas 68 (68.%) patients were with stage 3 or 4 diseases [9].

In a study conducted in Manipur, India, by Adhikarimayum et al., Stage I was 12.0.%, Stage II 36.%, Stage III 25.%, and Stage IV 27.% [10]. In a study conducted by Nawaf Alyahya et al. in Saudi Arabia, stage I was 3.%, Stage II was 7.%, Stage III 31, and Stage IV 59.% [14]. Finally, in a study conducted by Ananth Pai et al., Stage I 31.%, Stage II 41.%, Stage III 58.%, StageIV73.%[13].

In the present study, among 91 subjects with NHL, the overall survival was 754 days (24 months 24 days). In a study by Tarella C et al involving 3,315 NHL patients, the overall median survival for the entire Cohort was 7.3 yrs [15]. In a study by O. Bairey et al. in Isreal involving 109 patients, the median survival time was 26 months [16]. In a survey conducted by L. Lee and M. Crump et al. in Canada, the overall survival was 5 years [17]. In a study by B. Glass et al. in Germany, the median overall survival was 2yrs [18].

In the present study with 91 patients,30 patients were given the CHOP regimen, out of which 17 (65.3.%) patients had a Complete Response, and 9 (34.6.%) had a partial response. On the other hand, 61 cases were given R-CHOP, of which 42 (71.18.%) had Complete Response, and 17 (28.8.%) had Partial Response. In a study conducted in France by Bertrand Coiffier, 399 patients out of the 197 were treated with CHOP and 202 with R-CHOP [19]. CR was achieved in 76.% in R- CHOP and partial response in 34.% CR, 63.% PR in CHOP and 37.% PR. In a study by O. Bairey et al. in Isreal involving 109 patients, 82.% of patients received CHOP, 56.5.% CR, and 25.5.% PR [16]. R-CHOP was received by 93.%, among which CR in 57.% and PR 36.%.In a study by B.Glass et al. in Germany, patients who received CHOP had CR 83.%, PR17.% [18]. Among people who received R-CHOP, CR was 84.%, and PR was 16.%.

Limitations of This Study

PET CT is an imaging modality of choice for staging and assessing response to therapy in patients of B-cell NHL. Every patient of B-cell NHL has been explained the benefit of PETCT. However, limiting factors for getting PETCT in our centre are lack of provision of PETCT in Aarogyasri Scheme governmental insurance(majority of our patients were beneficiaries of Aarogyasri Scheme, the flagship healthcare program of all health initiatives, introduced in combined Andhra Pradesh (AP) in April 2007, high cost of around INR 20,000 and logistic issues (PETCT provision is there at around 250km from our hospital).

The same with the prescription of rituximab. Patients have benefited from Rituximab since 2016 after it's been included in Aarogyasri Scheme.

Conclusions

- Non-Hodgkins B cell lymphoma has an early onset in India compared to western literature.
- Early detection of asymptomatic disease and early treatment helps improve the mortality rates, provide a better quality of life and decrease the disease burden.
- Accurate staging is important, which helps in risk stratification and management decisions. Prognosis is strongly dependent on this information.
- Treatment with the R-CHOP regimen is superior to the CHOP regimen, with a better prognosis and survival.
- There is a broad consensus that the initial treatment of patients with B cell NHL should include rituximab(anti-CD20 monoclonal antibody).
- Patients benefited from the addition of Rituximab to the CHOP regimen. Most patients in the present study were beneficiaries of the Aarogyasri Scheme. The impact on overall survival from the addition of rituximab suggests the need to develop support services like Aaryogyasri to improve a person's cancer care.
- Monitoring at periodic intervals for possible relapse is important as many patients whose disease recurred can be salvageable.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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