A RETROSPECTIVE ANALYSIS OF EPIDEMIOLOGY AND CLINICAL OUTCOME OF HODGKIN LYMPHOMA PATIENTS IN CLINICAL ONCOLOGY DEPARTMENT IN AIN SHAMS UNIVERSITY HOSPITALS IN EGYPT.

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ABSTRACT:

Background: Lymphoma is the fourth most prevalent cancer among Egyptian adults, accounting for 76.6 percent non-Hodgkin lymphoma (NHL) and 23.4 percent Hodgkin lymphoma (HL). Most patients with classic Hodgkin lymphoma (cHL) achieve long-term survival free of HL, but late complications of treatment, such as second malignancies, cardiovascular disease, pulmonary disease, and other complications, have emerged as a competing cause of death and morbidity.

Aim of the Work: The aim of this work is to analyse retrospectively epidemiological and clinical outcomes of Hodgkin lymphoma patients treated in Ain Shams University hospitals (clinical oncology department) in Egypt in the period from January 2017 till December 2020.

Patients and Methods: This is a retrospective study that included 70 Hodgkin lymphoma patients who attended the lymphoma clinic at the Clinical Oncology Department, Ain Shams University. In the period between From January 2017 till December 2020. They either treated by chemotherapy only or chemotherapy and radiotherapy.

Result: Overall, of the 70 patients in the present study, 7 patients (10 %) died, and sixty-three patients (90 %) are alive till the end of our follow-up. The median OS is 34.54 months, while the median PFS is 15.67 months which is preliminary results.

Many prognostic factors were selected for analysis to evaluate their impact on EFS.

Some of these factors: age gender, family history and special habits had no statistically significant impact on EFS.

But other factors: ECOG status, staging, B-symptoms, interim PET CT and Radiotherapy had statistically significant impact on EFS.

Conclusion: Despite the increasing availability of guidelines for the treatment of HL, there is always a room for individualization of treatment. In particular, patient preference must be considered with different treatment options, some of which result in a higher recurrence risk at the gain of less toxic initial treatment (without any difference in long-term survival). Treatment should also be individualized when a particular approach might result in a higher risk of a serious late complication eg, the use of lung irradiation and the risk of late breast cancer in young females and of lung cancer in smokers.

INTRODUCTION:

One of the most prevalent lymphomas is Hodgkin lymphoma (HL), a B cell–derived malignancy. The tumour cells, known as Hodgkin and Reed-Sternberg (HRS) cells, are commonly identified in the tissue of people with HL. Despite the fact that HRS cells are produced from mature B cells, they have lost much of their B cell phenotype and exhibit an uncommon co-expression of markers from other hematopoietic cell types[1].

HL is thought to account for about 10% of newly diagnosed lymphoma cases in the United States (8260 out of 80,500 cases), with the rest being non-Hodgkin lymphoma (NHL)[2].

Classic Hodgkin Lymphoma (CHL) and nodular lymphocyte predominant HL are the two types of Hodgkin Lymphoma. Subgroups of classical HL include nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL[3].

Classical Hodgkin Lymphoma is defined by the presence of Reed-Sternberg cells in an inflammatory background, whereas LPHL is defined by the presence of lymphocyte-predominant cells, also known as popcorn cells, but without Reed-Sternberg cells. The pattern of LPHL can be nodular or diffuse[4].

The Ann Arbor staging approach, with a Cotswolds modification, has been in use since 1989, but it includes several older procedures for first staging, including as liver biopsy, laparotomy, and bone marrow trephine. In HL, positron emission tomography (PET)-computed tomography (CT) with fluorodeoxyglucose (FDG) has a high sensitivity and specificity[5].

In most cases, patients with early stage disease are treated with combined modality strategies that include abbreviated courses of combination chemotherapy followed by involved- field radiation therapy (IFRT), whereas patients with advanced stage disease are treated with a longer course of chemotherapy without radiation therapy. Newer lines of treatment are now being included in routine combination therapy, including as brentuximab vedotin and anti-PD-1 antibodies[6].

Although the high first-line cure rates in individuals with Hodgkin's Lymphoma (HL), 10%–20% of patients experience recurrent or refractory illness. For patients with recurrent or refractory HL, high-dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) is standard of care[7].

It is difficult to treat classical Hodgkin Lymphoma (CHL) with conventional cytotoxic treatment after it becomes refractory to chemotherapy or relapses following high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT). Until recently, improvements in the treatment of cHL were mostly based on modifying the cytotoxic chemotherapy and radiotherapy. However, in the last decade, the introduction of brentuximab vedotin (BV), an antibody-drug combination that targets CD30, has markedly altered the treatment landscape for cHL[8].

The immunological checkpoint receptor programmed cell death protein 1 (PD-1) is found on activated T cells. On tumour cells and in the tumour microenvironment, PD-1 connects with its ligand (PD-L1 or PD-L2), promoting tumour evasion tolerance and tumour growth. The PD-1 signalling dependency suggests a vulnerability to checkpoint blockage, which could restore anti-tumor immunity[9].

AIM OF THE WORK:

To analyse retrospectively epidemiological and clinical outcomes of Hodgkin lymphoma patients treated at Ain Shams University hospitals (clinical oncology department) in Egypt in the period from January 2017 till December 2020.

PATIENTS AND METHODS:

This is a retrospective study that included 70 Hodgkin lymphoma patients who attended the lymphoma clinic at the Clinical Oncology Department, Ain Shams University. In the period between From January 2017 till December 2020.

Inclusion Criteria for cases is:

1. Hodgkin lymphoma patients by immunohistochemistry (IHC).

2. Patient aged ≥ 18 years.

The study includes Hodgkin lymphoma patients treated in the Clinical Oncology Department, Ain Shams University Hospitals.

The study was approved by Ain Shams University research ethics committee and all our extracted data which included name, age, sex, pathological diagnosis, time of biopsy & time of the start of radiotherapy were kept confidential and the patients were kept unidentified.

The endpoints of interest were:

Primary End Point: Event-free survival: which is the time elapsed between treatment initiation and tumor relapse or death from any cause, without the patients who lost to follow-up.

Secondary End Point: Overall survival (OS) which is the time from diagnosis to death from any cause, it is a direct measure of clinical benefit to a patient.

Statistical analysis:

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 22.0 for windows; SPSS Inc, Chicago, IL, 2001).

Descriptive statistics: Mean, Standard deviation (± SD), Minimum and maximum values (range) for numerical data, Frequency and percentage of non- numerical data.

Analytical statistics: The Independent-Samples T Test will be used to assess the statistical significance of the difference between the study groups means. Chi-Square test will be used to examine the relationship between two qualitative variables.

Kaplan–Meier survival analysis will be carried out for disease-free survival (DFS), progression free survival (PFS) and overall survival (OS).

Survival analysis will be based on the date of diagnosis.

The log-rank test will be used to examine the statistical significance of the differences observed between the groups. Two-sided $P < 0.05$ will be considered statistically significant.

RESULTS:

I-Patient's characteristics:

In this study, data of 70 patients were collected, who were presented to our department from January 2017 till December 2020. The patient's age ranges from 19 to 80 years old. 33 (47.1%) patients are female, while 37 (52.9%) patients are male

The performance status of patients at presentation were as follows, 22 (31.4%) Patients with Eastern Cooperative Oncology Group (ECOG) 0, 46 (65.7%) patients with (ECOG) 1, 1 (1.4%) patients with ECOG 2, and 1(1.4%) patients with ECOG 3.

The most common comorbidity in the medical history of the patients was Diabetes miletus (DM) which was reported in 8 patients (11.4%), followed by hypertension (HTN)in 6 patients (8.6%), Two patients (2.9 %) were cardiac, one patient had Asthma, one patient has Psoriasis.

66 patients (94.3%) are Negative viral markers ,4 patients 5.7%) are viral infection positive, 3 patients (4.3%) are HCV Positive, one patient (1.4%) was HBV postive

All the patients (100%) complained of lymphadenopathy. But only 31 patients (44.3%) complained of B symptoms.

II- Tumor variables:

Histo-pathological confirmation of diagnosis was done for all patients through core needle biopsy from Lymph nodes .68 patients (97%) were Hodgkin lymphoma classic type,and only 2 patients (3%) were Nodular lymphocytic predominant . 64 patients (91.4%) were CD30 positive and 6 patients (8.6%) were CD30 negative. 46 patients (65.7%) were early stage, but 24 patients (34.3%) were advanced stage.

III- Treatment:

After 2 cycles, the interim PET/CT was negative in 17 pat(24.3%) ,Deauville 2 in 25 patients(35.7%), Deauville 3 in 23 patients (32.9%), Deauville 4 in 4 patients (5.7%),Deauville 5 in 1 patients (1.4%).

End of treatment PET/CT was negative in 2 patients (2.9%), Deauville 2 in 48 patients (68.6%), Deauville 3 in 11 patients (15.7%), Deauville 4 in 4 patients (5.7%), Deauville 5 in 5 patients (7.1%).

Concerning the first-line management in Hodgkin lymphoma patients out of the 70 patients in the present study,67 patients (98.5%) received ABVD, but only 1 patient (1.5%) received EBVD.

Regarding the second-line management in Hodgkin lymphoma patients, out of the 70

patients in our population study, 11 patients (15.7%) received second-line treatment.6 patients (54.5%) received GDP, 3 patients (27.3%) received ICE ,2 patients (18.2%) received GCD.

For the third line management in Hodgkin lymphoma patients, 2 patients received a third-line regimen, from which 1 patient received DHAP, and one patient received ICE.

Regarding radiotherapy in Hodgkin lymphoma patients, 26 patients received radiotherapy, 1 patient from the 25 patients was palliative. The total dose ranges from 4-36 Grey.The most common site of radiotherapy was on mediastinum. 13 patients from the studied sample had replased after from 9-25 months, 9 of them underwent bone marrow transplantation.

Table (1): staging of the disease of the studied population

Staging	
1A	3(4.3%)
1B	5(7.1%)
2A	22(30%)
2 B	16(22.9%)
3A	5(7.1%)
3B	6(8.6%)
4A	0
4B	14(20%)

Table (2): Interim PET/CT after 2 cycles chemotherapy

Deauville	
Negative	17(24.3%)
2	25(35.7%)
3	23(32.9%)
4	4(5.7 %)
5	1(1.4%)

Table (3): End of treatment PET/CT

Deauville	
Negative	2(2.9%)
2	48(68.6%)
3	11(15.7%)
4	4(5.7%)
5	5(7.1%)

IV- Prognostic Factors Affecting PFS and OS:

Overall, of the 70 patients in the present study, 7 patients (10 %) died, and sixty-three patients (90 %) are alive till the end of our follow-up. The median OS is 34.54 months, while the median PFS is 15.67 months.

Table (4 & 5):- EFS of Patients in the Present Study, Final Outcome of Patients in the Present Study.

Total N	N of Events	EFS (months)		95% CI		EFS at		
		Mean	S.E	Lower	Upper	6m	1y	2y
70	13	35.482	1.901	31.756	39.209	98.5%	83.8%	75.4%

Total N	N of Events	OS (months)		95% CI		OS at		
		Mean	**S.E**	**Lower**	**Upper**	**6m**	**1y**	**2y**
70	7	53.172	1.734	49.774	56.569	97.1%	97.1%	90.4%

Many prognostic factors were selected for analysis to evaluate their impact on PFS and OAS. Of these factors: age, gender, family history and special habits had no statistically significant impact on PFS.

On the other hand: ECOG status, staging, B-symptoms, interim PET CT and Radiotherapy had statistically significant impact on EFS.

Patients with advanced initial clinical staging (stage III and stage IV) had worse event free survival (EFS) than patients with early clinical stage (stage I and stage II).

In the present study, the event free survival %(EFS) of early stage patients is 38.3 months, while in advanced stage patients is 20 months (p=0.039).

The EFS in patients with ECOG 0 is 36.9 months, but in ECOG 1 is 33.068 months, in ECOG 2-3 is 7 months.

The patients with interim PET/CT deauville 4,5 have shorter EFS than those with interim PET/CT deauville 0,1,2.
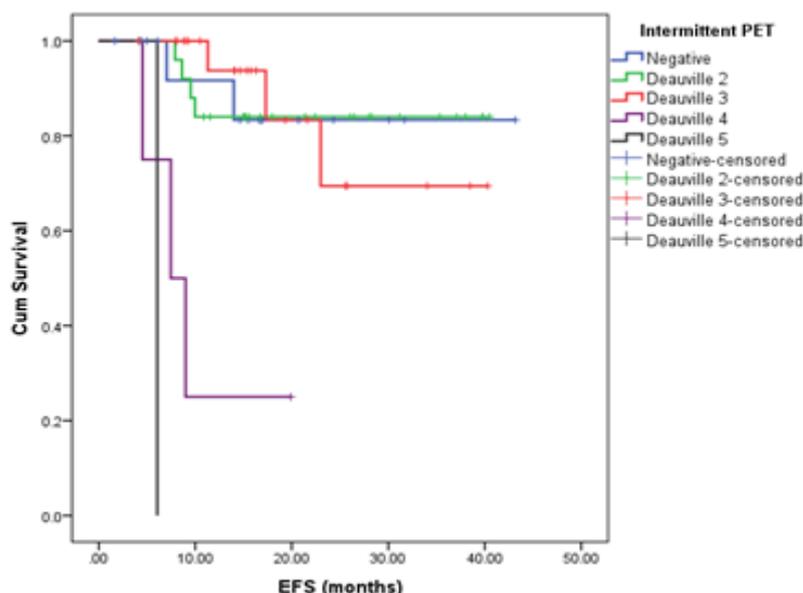

Diagram (1): Effect of interim PET/CT on EFS .

The patients without B symptomas have EFS 39 months. While those who complained of B symptoms have EFS 27.8 month.

The patients who received radiotherapy showed statistically significant better EFS in

comparison to patients who didn't receive radiotherapy, The EFS after 6 months for the patient who received radiotherapy was 100% Vs 92.9% those who didn't receive (P=0.002).
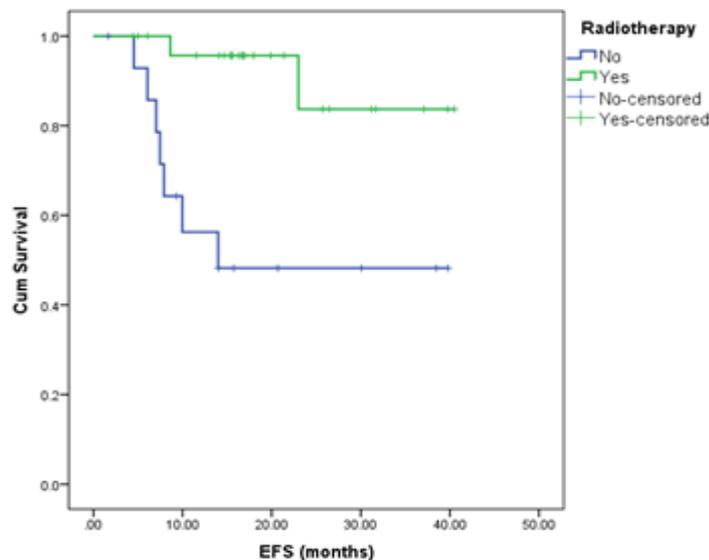

Diagram (2): Effect of Radiotherapy on EFS .

In the present study, these factors: ECOG status, staging,CD30and B symptoms had statistically significant impact on overall survival (OS).

The patients with ECOG 0,1 had longer OAS than those with ECOG 2,3 (P=0.000)

The overall survival (OS) of early stage patients is 56 months, while in advanced stage patients is 42.8 months (p= 0.020).

CD30 positive patients have longer overall survival than CD 30 negative patients (P= 0.045).

The patients without B symptomas have OAS 55.4 months. While those who complained of B symptoms have OAS 48.7 months.

DISCUSSION:

Our study is a retrospective study that included 70 Hodgkin lymphoma patients

attending the lymphoma clinic at the Clinical Oncology Department, Ain Shams University. In the period between From January 2017 till December 2020.

In the present study, we investigated the factors potentially associated with the event-free survival and overall survival of patients, which may in turn provide a novel strategy in increasing survival.

As regards favorable prognosis, early stage HL RFS >90 percent, OS >95 percent. But Unfavorable prognosis, early stage HL RFS >85 percent, OS >90 percent. Advanced stage HL – RFS 60 to 85 percent, OS 85 to 90 percent[10].

In our present study, the median age of diagnosis of Hodgkin lymphoma is 36 (22 – 49). Similarly, in a study done in USA, the median age of diagnosis is 39 years(20 – 34 year)[11].

As regard the age , in our study , 33 (47.1%) patients are female, while 37 (52.9%) patients are male. Simila rly a study was conducted in Bahrin. The overall male to female ratio was 1.48:1[12].

In this study, the staging of the disease has significant effect on the EFS 38.3 months versus 20 months (early versus advanced stage) (P=0.03).

A study conducted in Italy showed that early stage (I and II) has a borderline statistical effect on EFS (80 compared to 66% in patients with advanced disease, p=0.05), but not on OS (p=0.26)[13].

In our study patients who received radiotherapy had event free survival 37 months in comparison to those who didn't receive 23.4 months (p=0.002).

A study by Sasse S and his colleagues in 2017[14], showed that 15-year PFS estimates of 52% and 73% and an HR of 0.5 (95% CI, 0.3 to 0.6), superiority of CMT compared with EF-RT was confirmed (P < .001). OS did not differ significantly between trial arms (P = .3).

A study by Ganesan P and his group in 2015[15], showed that PET-2-positive patients had an inferior EFS when compared with PET-2-negative patients despite escalation of therapy (2-year EFS 82% versus 50%; P = 0.013.

In the present study; The interim PET/CT positive patients had inferior EFS when compared with the interim PET negative patients (2 years EFS 37.7 months versus 10 months); P=0.001.

In our study, the overall survival is 56 months in early stage patients versus 42.5 months in advanced stage patients.

A study conducted in USA Showed that the overall survival decreased with advanced stage with stage 4 disease patients twice as likely to die compared to stage 1 (P<0.0001)[16].

The cases in the current study who complained of B symptoms has less overall survival when compared to those without B symptoms (48.7 months vs 55.4 months) (P=0.022).

A study conducted in Hong kong, showed that of the potentially prognostic factors analyzed, presence of B symptoms was found to adversely a ect overall survival (p = 0.01, hazard ratio 3.65 (CI 1.32–10.11)) (Law M, et al. 2014)[17].

Conclusion:

Despite the increasing availability of guidelines for the treatment of HL, there must remain room for individualization of treatment. In particular, patient preference must be considered with different treatment options, some of which result in a higher recurrence risk at the gain of less toxic initial treatment (without any difference in long-term survival). Treatment should also be individualized when a particular approach might result in a higher risk of a serious late complication (i.e, the use of lung irradiation and the risk of late breast cancer in young females and of lung cancer in smokers).

Conflicts of Interest: The authors state that the publishing of this paper is free of any conflicts of interest.

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تحليل بأثر رجعي للوبائيات والنتائج السريرية لمرضى هودجكين ليمفوما في قسم الأورام السريرية في مستشفيات جامعة عين شمس في مصر

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المقدمه :سرطان الغدد الليمفاوية هو رابع أكثر أنواع السرطانات انتشارًا بين البالغين المصريين ، حيث يمثل ٧٦,٦ بالمائة من سرطان الغدد الليمفاوية اللاهودجكين (NHL) و ٢٣,٤ بالمائة من سرطان الغدد الليمفاوية هودجكين (HL). يحقق معظم المرضى الذين يعانون من سرطان الغدد الليمفاوية هودجكين (cHL) البقاء على قيد الحياة على المدى الطويل خالية من HL ، ولكن المضاعفات المتأخرة للعلاج ، مثل الأورام الخبيثة الثانية ، وأمراض القلب والأوعية الدموية ، وأمراض الرئة ، ومضاعفات أخرى ، ظهرت كسبب منافس للوفاة والمراضة.

الهدف من العمل: الهدف من هذا العمل هو تحليل النتائج الوبائية والسريرية بأثر رجعي لمرضى سرطان الغدد الليمفاوية هودجكين الذين تم علاجهم في مستشفيات جامعة عين شمس (قسم الأورام السريرية) في مصر في الفترة من يناير ٢٠١٧ حتى ديسمبر ٢٠٢٠.

نتيجة: بشكل عام ، من بين ٧٠ مريضًا في الدراسة الحالية ، توفي ٧ مرضى (١٠٪) ، ولا يزال ٦٣ مريضًا (٩٠٪) على قيد الحياة حتى نهاية المتابعة. متوسط نظام التشغيل هو ٣٤,٥٤ شهرًا ، بينما يبلغ متوسط 15.67 PFS شهرًا.

تم اختيار العديد من العوامل الإنذارية للتحليل لتقييم تأثيرها على PFS. من بين هذه العوامل: لم يكن للعمر والجنس والتاريخ العائلي والعادات الخاصة أي تأثير ذي دلالة إحصائية على PFS.

من بين هذه العوامل: كان لحالة ECOG، والتدريج ، وأعراض B، والتصوير المقطعي بالإصدار البوزيتروني المؤقت والعلاج الإشعاعي تأثير مهم إحصائيًا على EFS.

استنتاج:- يرتبط العلاج النموذجي المشترك ببقاء أعلى خالية من الأمراض ، ولكن البقاء على قيد الحياة بشكل عام متشابه مع كلا النهجين. من المرجح أن يرتبط العلاج الإشعاعي الحديث بجرعة أقل وحجم مجال أصغر بسمية أقل على المدى الطويل من العلاج بجرعات أعلى وحجم مجال أكبر ، دون فعالية ، ولكن لا يمكن تأكيد ذلك إلا من خلال متابعة أطول.