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ORIGINAL ARTICLE

Non-Hodgkin's Lymphoma: In a Class All Its Own

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Non-Hodgkin's lymphoma (NHL) incidence rates have increased more than 50% over the past 15 years, making it the sixth leading cause of death from cancer in the United States and the fourth most significant malignancy in terms of economic impact. Comparable trends are noted worldwide. Improved diagnostic techniques have resulted in reclassifying some tumors that in the past would have been classified as Hodgkin's disease. In this article, the latest diagnostic, prognostic, and treatment options for NHL are reviewed and a cross-reference chart for these evolving class systems provided.

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Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of tumors of the lymphoid system. These neoplasms are grouped into different distinct clinical entities, each representing a clonal expansion of an abnormal cell line. These various cell types can be separated by various criteria, including genetic, immunologic, histologic, and clinical factors. Recent scientific advances have allowed more precise classification of these tumors.[1]

INCIDENCE AND DISTRIBUTION OF DISEASE

NHL has a similar geographic pattern to that seen with Hodgkin's disease but is about five times more common. Comparable trends are noted in developed countries worldwide. However, there are some variations in the global patterns of disease for various subtypes of NHL. For example, some forms of Burkitt's lymphoma are more common in the malaria belt of Africa.[1–3]

One of the multiple reasons for the increased occurrence of NHL is AIDS-related lymphoma. As the number of HIV cases climbs, so do the rates of NHL. Environmental factors, such as the rising use of pesticides, also play a part in the increasing incidence.[2,3]

In general, NHL is more common in men than women and more common with whites than blacks or Asians. Incidence rates have been highest in farming communities and in large cities with a large population of HIV-positive individuals. The average age at diagnosis is 56. There is also a steady increase in rates from childhood through old age. However, certain subtypes occur more frequently in certain age groups. For example, Burkitt's and lymphoblastic lymphomas are more common in children, while indolent follicular lymphomas are more common in older age groups.

CAUSE OF DISEASE

The cause of NHL, as a whole, is multifactorial. However, there are certain risk factors that lead to a higher incidence of disease.

These factors include immune deficiency, certain infectious agents, and chemical or physical carcinogens.

Immune Deficiency

Immune deficiency factors include both congenital and acquired conditions. Congenital conditions associated with NHL include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, and others. It is estimated that 25% of individuals with inherited immune dysfunction will develop cancer and about half of those will be a lymphoma.

HIV is the most common of the acquired immune conditions leading to NHL. Individuals infected with HIV have an approximately 100-fold increased risk of NHL since lymphoma is one of the major late complications of HIV. As HIV-positive individuals live longer, the overall rates of secondary lymphoma are expected to increase significantly, representing up to one fourth of cases over the next decade.

NHL is seen with other immune deficiency conditions as well. Hodgkin's disease itself may increase the risk of NHL 20-fold. In addition, the posttransplant state and certain other autoimmune disorders, such as Hashimoto's thyroiditis, Sjögren's syndrome, and other chronic inflammatory conditions (rheumatoid arthritis, lupus, and nontropical sprue), may have a higher risk of lymphoma.[2,3]

Infectious Agents

Certain infectious agents are also associated with a higher risk of NHL. Epstein-Barr virus (EBV) belongs to the herpes virus group and may infect B-lymphocytes. EBV is associated with the development of endemic Burkitt's lymphoma, a disease found primarily in children in Africa's malaria belt.

Human T-Cell lymphotropic virus type I (HTLV-I) is a type C RNA retrovirus that has been isolated from T-cell lymphomas. In these lymphomas, the viral genetic material is integrated into the genome of malignant cells. HTLV-I is endemic to certain areas of the world, including the southern islands of Japan and the Caribbean, and has also been found in the southeastern United States. The virus is transmitted by sexual contact, through blood transfusion, and through breast milk.

Helicobacter pylori infections have been found to increase the incidence of low-grade, mucosa-associated lymphoid tissue (MALT) lymphomas in the stomach.[2,3]

Chemical or Physical Carcinogens

Environmental factors may also lead to an increased incidence of NHL. Pesticide exposure and the long-term use of permanent dark hair dyes have been associated with an increased risk of lymphoma. Evidence on the risk of other solvents or chemicals is mixed. Some chemotherapy or radiation treatment programs have also been associated with NHL. The chronic use of seizure medication phenytoin (Dilantin) may be associated with the development of lymphoid hyperplasia or pseudolymphoma. Malignant transformation of this condition may occur but is uncommon.[2,3]

CLASSIFYING THE DISEASE

A number of different classification systems have been developed to describe lymphomas over the years. These have included the Rappaport, Lukes-Collins, and Kiel systems. In 1982, the international Working Formulation (WF) classification system was introduced, sponsored by the National Cancer Institute. This system divided lymphomas into 10 categories, labeled A–J, and grouped them by their biologic behavior (ie, low grade or indolent, intermediate grade, and high grade).[1,4,5] However, with improved immunologic and genetic techniques, existing types of lymphomas no longer fit into the WF system. In addition, the system did not adequately predict the clinical outcomes for many subtypes. Because of this, the International Lymphomas Study Group proposed a

new classification system in 1994, called the Revised European-American Lymphoma (REAL) system.[1,5]

Like the WF, the REAL system grouped lymphomas into prognostic categories, which are useful from a clinical and underwriting perspective. One major departure from the WF system was that the REAL methodology separated lymphomas into B-cell and T-cell groups.

Medical records may still classify lymphomas using any of the systems. With that in mind, Table 1 contains a comparison chart of the various classification systems for use in assigning an individual tumor to the appropriate grade for underwriting. Based on a review of the mortality data, presented later in this article, this chart combines the low- and intermediate-grade lesions into one category.[3,5,6]

STAGING THE DISEASE

In addition to describing lymphomas by their morphologic classification, they also are categorized by the extent of disease or stage. The staging system for NHLs (see Table 2) is similar to that used for Hodgkin's disease. However, this system is less helpful in staging NHLs. The reason is that Hodgkin's disease spreads in an organized manner from one lymph node group to another. On the other hand, non-Hodgkin's disease tends to spread unpredictably and often involves extranodal sites and noncontiguous node groups.[1] In general, the low-grade lymphomas tend to be more advanced at the time of diagnosis. Only 15–25% of indolent tumors will present in stages I or II. On the other hand, about 50% of high-grade lymphomas will present in stages I or II.[1] Primary extranodal involvement occurs in about 25% of cases and is often found in certain locations with certain cell types. These extranodal sites include the stomach, intestine, bone, central nervous system, testes, thyroid, eye, and skin. The most frequently encountered cell type in these sites is diffuse large B-cell lymphoma. However, others such as Burkitt's, Burkitt's-like, follicular, mantle cell, and MALT lymphomas may be associated with disease in these organs as well.[1,3] MALT lymphomas are particularly common in the gastrointestinal tract.

CLINICAL FINDINGS

Because lymphomas may involve multiple organs, the presenting manifestations can take multiple forms and may differ among the various subtypes. The most common presentation is with painless enlargement of a lymph node or nodes. A firm node greater than 1 cm in size that persists more than 3–6 weeks is highly suggestive of lymphoma. Unlike Hodgkin's disease, non-Hodgkin's lymphoma may involve unusual lymphoid sites, such as epitrochlear (near the elbow) and mesenteric (intestinal) nodes and the area of the Waldeyer's ring (tonsillar tissue in the oropharynx).

In addition, some individuals will present with ''B'' symptoms, including fever (>100.4°), night sweats, or weight loss (>10% of body weight). These symptoms occur less frequently than in Hodgkin's, and their presence is indicated by placing a ''B'' after the appropriate stage designation.[1,3,7,8]

Other findings may relate to extranodal involvement. These may include abdominal pain, mass, or bleeding; bowel obstruction; splenomegaly; cough; bone pain; neurologic findings; salivary, testicular, or thyroid enlargement; or superior vena cava syndrome.[3,7,8]

Laboratory findings are usually nonspecific and may include abnormalities of the red blood cells and/or white blood cells, elevated liver function tests, and an elevated erythrocyte sedimentation rate. An isolated elevation of the lactate dehydrogenase (LDH) enzyme is common. It may be the only sign of an unsuspected lymphoma in an individual with nonspecific symptoms. The degree of elevation of LDH has prognostic importance.[3,7,8]

A detailed review of all of the various subtypes of lymphoma is beyond the scope of this article. However, common features of fre-

Table 1. Lymphoma classification for underwriting (Listed most recent to oldest)

REAL Terminology	WF Category/terminology	Kiel Terminology	Luke-Collins Terminology	Rappaport Terminology
Low/intermdiate-grade lymphomas				
Follicular	A, Small lymphocytic	Lymphocytic/CLL and promyelocytic-B and T-cell	Small lymphocyte B or T, B-CLL	Nodular, poorly differentiated lymphocytic
Lymphoplasmacytic	B, Follicular small cleaved cell	Lymphoplasmacytic/lymphoplasmacytoid	Plasmacytic-lymphocytic	Well differentiated lymphocytic
Monocytoid B (nodal)	C, Follicular mixed small/large cell	Plasmacytic	Small lymphocyte B, monocytoid	Nodular, mixed lymphocytic/histiocytic
Splenic marginal zone	D, Follicular, large cell	Centroblastic/centrocytic	Small cleaved follicular center cell (FCC)	Nodular, histiocytic
Small lymphocytic	E, Diffuse small cleaved cell	Centrocytic	Large cleaved FCC	Diffuse lymphocytic, poorly differentiated
Mantle cell		Monocytoid B-cell	Large noncleaved FCC	Plasmacytoid
Disseminated MALT		Pleomorphic, small cell	Small lymphocytic T-cell	Lymphocytic/Plasmacytoid
Chronic lymphoctic B- and T-cell				
Large granular lymphocytic				
High-grade lymphomas				
Precursor B-cell	F, Diffuse mixed small and large cell	Centroblastic	B-Immunoblastic	Diffuse, mixed lymphocytic/histiocytic
Diffuse large B-cell	G, Diffuse large cell	Immunoblastic	T-Immunoblastic sarcoma	Diffuse, histocytic
Burkitt's	H, Large cell immunoblastic	Lymphoblastic, Burkitt's	T-Immunoblastic lymphoma (IBL)	Undifferentiated lymphoma, non-Burkitt's
Burkitt's-like	I, Lymphoblastic	Lymphoblastic, convoluted	IBL-like T-cell lymphoma	Diffuse lymphoblastic convoluted and nonconvoluted
Araplastic large cell	J, Small noncleaved cell, Burkitt's, non-Burkitt's	Pleomorphic, medium and large cell	Small noncleaved FCC, Burkitt's, Non-Burkitt's	Burkitt's tumor
Lymphoblastic		T-cell angioimmunoblastic	T-cell convoluted lymphocytic	Lymphoblastic
Peripheral T-cell		Lymphoblastic, B-cell	Undefined cell	
Intestinal T-cell		Large cell anaplastic B- and T-cell		
Intestinal T-cell		T lymphoblastic		
Precurser T-cell		Lymphoepitheloid		
Angioimmunoblastic T-cell				
Angiocerteric				
Adult T-cell				

Table 2. Ann Arbor Non-Hodgkin's Lymphoma Staging*

Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) alone or with localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) alone or with localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement

* Addition of letter B indicates presence of fever (>100.4°), night sweats, or weight loss (>10% of body weight).

quently encountered lesions are summarized in Tables 3 and 4.[1,3,4,6,9–11]

PROGNOSTIC FACTORS

The following factors may have greater prognostic significance than stage alone in non-Hodgkin's lymphoma:

- Factors that reflect the tumor's growth rate and invasive potential, such as LDH level, size of the tumor, and the number of nodal and extranodal sites,
- The patient's response to the tumor, including the presence of B symptoms and degree of disability,
- Indicators of the individual's likelihood for tolerating therapy are tumor-specific factors such as age and degree of marrow involvement.[1,3]

The International Prognostic Index (IPI) is used to predict the prognosis for short-term survival in high-grade lymphomas. The index uses 5 risk factors to gauge the likelihood of response to therapy in the more rapidly progressive lymphomas. Factors indicating a

Table 3. REAL Subtypes—Clinical Characteristics

Type	Grade	Frequency (%)	Mean Age	B Symp (%)	Increase in LDH (%)	Stage III, IV (%)	8-Year Survival (%)	Distinctive Characteristics
Follicular	Low	35	60	30	30	65	65	50% transform-diffuse large cell
Diffuse large B	High	30	65	30	50	50	50	May occur in children
Small lymphocytic	Intermed	5	65	35	40	90	50	10%–20% progress to CLL
Mantle cell	Intermed	5	65	30	40	80	20	Males, t(11;14), poor prognosis
Peripheral T-cell	High	5	60	50	65	80	25	Frequently extra-nodal, poor prognosis
Marginal zone (MALT)	Low	5	60	20	30	35	80	Frequently extra-nodal, good prognosis
Mediastinal large B-cell	High	2	40	38	80	33	45	Females, younger, mediastinal mass
Anaplastic large T/Null	High	2	35	50	45	50	80	Frequently extra-nodal, good prognosis with Rx
Lymphoblastic T/B)	High	2	30	20	70	90	20	Common in children, poor prognosis
Burkitt's-like	High	2	55	40	60	50	40	Similar to diffuse B
Marginal zone-nodal	Low	1	60	40	40	75	60	Prognosis worse than local MALT type
Lymphoplasmacytic	Low	1	65	15	15	80	50	Waldenstrom's-like, t(9;14)
Burkitt's	High	<1	30	20	75	40	50	Common in children, associated with EBV

Table 4. Features of Various Subtypes of Non-Hodgkin's Lymphoma

Follicular lymphomas
Most individuals are asymptomatic but present with disseminated disease
Disseminated disease progresses slowly but responds poorly to therapy
May progress to aggressive large-cell lymphoma
Diffuse B-cell lymphoma
May arise de nova or as transformation from low-grade lymphoma
Clinically aggressive but responds to therapy
Represents 30% of lymphomas in adults and 25% in children
Mantle cell
Presents with widespread and bulky disease
Extranodal involvement is frequent, especially bone marrow, peripheral blood, and GI tract
More common in males
Chromosomal abnormally with translocation t(11;14) is common
Progresses rapidly and responds poorly to therapy
MALT lymphomas
Involves mucosa-associated lymphoid tissue that develops in response to infection or inflammation
Sites of involvement include stomach, thyroid, lung and lacrimal and salivary glands
MALT of stomach is usually related to infection with *Helicobacter pylori* and responds to treatment with antibiotics
Localized MALT generally follows indolent course and responds to local therapy
Disseminated MALT progresses slowly and responds poorly to treatment
Anaplastic large-cell lymphoma
May mimic carcinoma
Presents in two forms; disseminated and cutaneous
Disseminated form is aggressive and frequently involves extranodal sites but responds well to therapy
Cutaneous form is generally indolent and spontaneous remissions are common
HTLV-I-associated T-cell lymphoma
Caused by retrovirus HTLV-1
Stage IV presentation with extranodal involvement is common
Elevated cell counts, hepatosphenomegaly, hypercalcemia, and lytic bone lesions are common
Is a very aggressive tumor

lesser likelihood of response to therapy and a worse short-term survival include[12]

1. Age > 60
2. LDH level > normal
3. Reduced performance status
4. Stage III or IV
5. More than 1 extranodal site of involvement

However, only stage is predictive of long-term survival.[13]

TREATING THE DISEASE

The treatment of lymphomas varies with the grade of the tumor. For low-grade lymphomas presenting in stage I or II (about 15–25% of these patients), the usual treatment is regional radiation therapy. With this treatment, about 40% of individuals will be disease free beyond 10 years and will have a low likelihood of relapse.[14,15] Individuals who have a staging laparotomy to confirm early-stage disease and those that are younger than age 60 will do the best.[14] Most relapses occur in the first few years but may still be documented at a reduced rate out to 10 years. Only occasional recurrences happen after 10 years. Average yearly recurrence rates in a population treated at Stanford University were 11% at 0–5 years, 4% at 6–10 years, 1.9% at 11–15 years, and 1.5% at 16–20 years.[15]

Nevertheless, the vast majority of individuals with low-grade lymphomas will present with stage III or IV disease. Many of these

patients will respond to chemotherapy and may achieve complete remission. However, most individuals will have a recurrence. While these tumors follow an indolent course and prolonged survivals are common, for the most part, they are not considered curable. In asymptomatic individuals, the usual approach is watchful waiting, with treatment only when symptoms develop. Early therapy has not proven to be of benefit.[1–3,11] Prognostic indicators for poor outcome in follicular lymphomas include male sex, older age, B symptoms, increased number of extranodal sites, and increased levels of LDH and sedimentation rates.[16]

Treatment of high-risk individuals with high-dose chemotherapy and bone marrow transplant has shown some improved survival short term but is still considered investigational.[17] Other forms of therapy with some promising early results but with yet unproven long-term benefits include nucleoside analogues (2-deoxycoformycin, 2-chlorodeoxyadenosine, fludarabine), alpha interferon, and monoclonal antibodies (rituximab).[1,3,8]

Approximately 50% of high-grade lymphomas will present with localized stage I or II disease. Several studies have demonstrated that these lesions (nonbulky disease) are best treated with a combination of three courses of chemotherapy followed by radiation therapy. The usual chemotherapy regimen is designated CHOP, an acronym derived from the trade names of the agents involved, namely, cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone. With this therapy, up to 85% of treated patients achieve long-term, disease-free survival.[1,3,11]

For bulky stage II disease and stage III or IV tumors, the standard therapy in high-grade lymphomas is combination chemotherapy using the CHOP regimen. With this approach, approximately 30–40% of treated patients can achieve long-term, disease-free survival. A variety of other regimens have been tried, but none have proved to be superior to the CHOP regimen. Individuals with a poor IPI have less of a response to treatment. Once a relapse occurs, the outcome is poor. Individuals with a relapse are treated with additional chemotherapy. Then, if at least a 50% reduction of tumor mass is achieved, bone marrow transplantation is performed. The rate of long-term survival after transplantation is still uncertain.[1–3,8,11]

One group that falls outside the usual treatment regimens is the MALT tumors. These low-grade tumors arise in organized extranodal lymphoid tissue that develops in response to the stimulus of a chronic infection (stomach) or autoimmune process (salivary glands, thyroid). Infection with *Helicobacter pylori,* the bacteria that causes stomach ulcers, is the inciting source in the stomach. This infection provides an antigenic stimulus that sustains the growth of the MALT tumor.[18,19] Several studies found that long-term, disease-free survival can be achieved in two thirds of patients with gastric MALT stage IE (localized, extranodal involvement) with antibiotic treatment of the *Helicobacter* infection alone. In those individuals who do not respond to antibiotics, radiation therapy, single-agent chemotherapy, or both may be used with good results. Overall, long-term survival of 80–85% can be achieved with low-grade MALT lesions of the gastrointestinal tract as well as of other extranodal areas.[18–20] Advanced-stage MALT lesions behave like the usual low-grade lymphomas, and long-term cure is unlikely.

Primary central nervous system (CNS) lymphoma responds poorly to therapy. Radiation therapy is the usual treatment, but response rates are poor and long-term survival is rare. Recent attempts at using both chemotherapy and radiation therapy have not been encouraging, and CNS lymphoma remains, for the most part, incurable. Ocular lymphoma, considered a variant of CNS lymphoma, is treated similarly and is also considered incurable in most instances.[21,22]

In children, NHL is the third leading cause of cancer. More than 90% of children with NHL will present with high-grade, extranodal disease. However, most of them respond well to modern therapy. Long-term survival

numbers are comparable with, and in some studies better than, that in adults.[23–25]

One important consideration with NHL is the possibility of developing a second tumor. Treatment of lymphoma increases the risk of both solid and hematologic malignancies. The relative risk is about 1.3 and continues for at least 20 years after therapy.[26]

MORTALITY PATTERNS

The mortality patterns in NHLs are somewhat counterintuitive in that the low-grade, indolent subtypes generally have a worse long-term prognosis compared with the more aggressive, high-grade lesions. The reason for this pattern is that, while the indolent lesions tend to follow a slowly progressive course, they generally present in a more advanced stage and respond poorly to conventional therapy. For the most part, they are incurable.

On the other hand, the high-grade lymphomas are quite aggressive and capable of causing death in a relatively short time. However, about 50% of patients will present with localized disease. In addition, even those individuals who present with stage III or IV disease have a good chance of response to combination chemotherapy. About a third of these patients may achieve long-term survival with available treatments.

A review of the survival data from the Surveillance, Epidemiology, and End Results (SEER) public-use database from 1973 to 1995[27] provides quantification of this effect. This database conveniently provides survival data by the Working Formulation subtypes. Hence, survival can be combined by low- (B, C, D), intermediate- (A, E), and high-grade (F, G, H, I, J) groups. Select mortality ratios for each 5-year span after diagnosis, subdivided by age and risk group, are presented in Table 5.

Table 5. Non-Hodgkin's Lymphomas—Select Mortality Ratios by Grade (all Stages Combined)

Age	Years	Low Grade (%)	Moderate Grade (%)	High Grade (%)
20–49	0–5	4525	5988	17,589
	6–10	2628	1716	1232
	11–15	1035	557	445
50–59	0–5	1705	2633	4628
	6–10	743	726	546
	11–15	368	476	306
60–69	0–5	991	1579	2538
	6–10	429	523	362
	11–15	245	249	225
70–79	0–5	637	1007	1537
	6–10	264	312	215
	11–15	152	175	116
≥80	0–5	344	454	775
	6–10	150	167	155
	11–15	156	120	133

From the SEER data in Table 5, the following observations can be made:

- While absolute survival is lower in the oldest groups, relative mortality is substantially higher in the younger age bands.
- Mortality ratios are highest in the first 5 years after diagnosis and then diminish in subsequent time periods.
- In the first 5-year time period after diagnosis, mortality ratios are greatest in the high-grade tumors. However, in subsequent time periods, 6–10 years and 11–15 years, the high-grade lesions have the lowest relative mortality ratio.
- The mortality ratios are higher in the intermediate rather than the lower grade group. However, the difference between the low- and intermediate-grade groups is small.
- Mortality ratios remain quite high until 10 years after diagnosis in those under age 70.

Unfortunately, the SEER data combines mortality ratios for all stages. The database started collecting stage information on lymphomas in 1988. For that reason, mortality ratios can only be calculated for a relatively short period for local-regional and distant disease. In general, mortality ratios are almost double in higher stage groups compared with lower stage groups in years 6–8 after diagnosis. However, it should be kept in mind that only about 15–25% of individuals with low- and intermediate-grade disease will present in stage I or II. The correspond-

ing percentage in high-grade lesions is around 50%.

Although data contained in clinical articles is much less detailed than that in the SEER database, they seem to support this general breakdown of stage-specific mortality ratios.[15,26]

Information on mortality with low-grade MALT lesions is not available in the SEER database and is limited in the clinical literature. However, from the available data, the 10-year geometric annual average select mortality ratio for gastrointestinal tract MALT lesions is estimated at 160–180%.[20,27] In addition, the mortality risk associated with lymphomas increases markedly with the following factors:

- Current or previous evidence of recurrence, even if presently in remission
- Current treatment with interferon, nucleoside analogues, or monoclonal antibodies
- Treatment with bone marrow transplant
- Coexisting hereditary or acquired immunodeficiency syndrome currently present
- HTLV-1-related disease
- Evidence of an active EBV infection
- CNS or ocular lymphoma
- Currently abnormal CBC, LDH level, B-2 microglobulin level
- Current B symptoms (fever, night sweats, or weight loss).

Factors that are variably related to higher risk that may require careful review for appropriate risk selection include

- Currently elevated sedimentation rate or liver function tests
- History of mantle cell lymphoma.

Recent attempts at using both chemo and radiation therapy have not been encouraging, and CNS lymphoma remains, for the most part, incurable.

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