Surgery for non-Hodgkin's lymphoma

Elroy Patrick Weledji,[1] George Enow Orock[2]

[1]Department of Surgery, University of Buea, Cameroon; [2]Department of Pathology, Regional Hospital Buea, S.W. Region, Cameroon

Abstract

Non-Hodgkin lymphomas (NHLs) are a diverse group of blood cancers derived from lymphocytes that vary significantly in their severity. Surgery is not often used as a treatment because of the efficacy of chemotherapy, biological therapy, radiotherapy and hematopoietic stem cell transplantation. We reviewed the natural history and possible role of surgery for NHL. Surgery may be useful in confirming or refuting an equivocal radiological diagnosis through biopsy, removing symptomatic limited disease from an affected organ and in splenectomy for primary splenic lymphoma. Emergency abdominal surgery for acute complications of NHL provides palliation and diagnosis. There is as yet no consensus as to the optimum treatment for symptomatic limited disease affecting an organ and timing of chemotherapy perioperatively. Prospective randomized trials are required.

Introduction

Hodgkin lymphoma (HL, Hodgkin disease), described by Thomas Hodgkin in 1832, was the first form of lymphoma described and defined.[1] Other forms were later described but because Hodgkin lymphoma was much more radiation-sensitive than other forms, its diagnosis was important for oncologists and their patients and thus research originally focused on it. The Rappaport classification, proposed in 1956 and 1966, became the first widely accepted classification of lymphomas other than Hodgkin.[2] Surgery is not often used as a treatment because of the efficacy of chemotherapy, biological therapy, radiotherapy and hematopoietic stem cell transplantation.[3-5] However, it may have some definitive roles in planned (elective) surgery but usually a palliative one in the acute abdomen.[6,7] Despite the difficulty and paucity of prospective randomized trials this paper reviewed the possible role of surgery in non-Hodgkin's lymphoma (NHL).

Correspondence: Elroy Patrick Weledji, PO Box 126, Limbe, S. W. Region, Cameroon. Tel.: (237)699922144.
E-mail: elroypat@yahoo.co.uk

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Epidemiology

NHL is the sixth most common cancer in the UK (12,800 in 2011) and, it is the eleventh most common cause of cancer death (4700 in 2012).[8] It resulted in 210,000 deaths globally in 2010 up from 143,000 in 1990.[9] NHL increases with age steadily and up to 45 years is more common among males than females.[10] The five-year survival rates in the United States are 69%.[9,10]

Pathology

The 2008 World Health Organization (WHO) classification largely abandoned the *Hodgkin vs non-Hodgkin* grouping. Instead, it listed over 80 different forms of lymphomas in four broad groups.[11] They are grouped by their grade: low grade (indolent) tend to grow very slowly and compatible with a long survival while high grade (aggressive) tend to grow more quickly and can be rapidly fatal without treatment; the type of cell affected (B cell or T cell) with most patients having B-cell lymphoma; large or small cells; grouped together (follicular type) or spread out (diffuse type); proteins (markers) on the surface of the lymphoma cells (immunohistochemistry) and gene changes in the lymphoma cells (cytogenetics). However, diffuse type can also be used to describe NHL that is widespread in the body that is not the same as the diffuse large B cell lymphoma. In 10-70%, depending on the type, low-grade lymphomas may change into a more aggressive high-grade type lymphoma over time. When a low grade and high-grade lymphoma coexist in the same lymph node, it is assumed that it is in the process of transforming to the higher-grade type and has to be treated as high grade. Unfortunately, a transformed NHL is generally harder to control than when it was low grade and the treatment is therefore more intense.[3]

Sub-types of non-Hodgkin's lymphoma

The subtypes of low-grade and high-grade NHL are listed in Tables 1-3.[12] The Center for Disease Control and Prevention (CDC) included certain types of NHL (AIDS associated NHL) as AIDS-defining cancers in 1987.[13] Additionally, other retroviruses such as human T-lymphotropic virus HTLV may be spread by the same mechanisms that spread HIV leading to an increased rate of co-infection.[13-15] The natu-

ral history of HIV infection has been greatly changed overtime with highly active anti-retroviral therapy (HAART). As a consequence, the incidence of NHL in HIV infected patients has significantly declined in recent years.[15] Lymphoproliferative disorders occur in up to 2% of adult and 4% of pediatric transplant recipients including stem cell or bone marrow transplant due to immunosuppression.[16] Treatment related T cell lymphomas sometimes occur but the B-cell types are more common and are frequently associated with the Epstein-Barr virus (EBV).[17] Thus the treatment for these immune deficiency-associated lymphomas is often different than for conventional lymphomas.

Clinical presentation

Apart from the classical *B symptoms* triad of night sweats, weight loss of >10% or fevers, NHL can present in a variable and atypical manner such as an unusual lump, an intestinal obstruction (ileo-caecal mass, intussusception), gastric outlet obstruction, appendicitis, peritonitis from intestinal perforation, rectal bleeding, hypersplenism or symptomatic splenomegaly, intracranial hypertension, paralysis from spinal cord compression, ischio-rectal abscess, *etc*. Nodular infiltration of the skin may be seen but pruritus is uncommon.[3,12] The clinical features of NHL in transplant recipients may include infectious mononucleosis-like illness, generalized lymphadenopathy, tonsillar enlargement or extranodal masses including skin lesions, which can be biopsied.[16]

Investigations and staging

No one single investigation of NHL is reliable. The diagnosis is reached by a combination of clinical features, serological investigation (*e.g*., EBV antibody titres, clonal antibody activation to EBV), chest radiography, computed tomography (CT) scan of affected areas, and biopsy of lesions. Following clinical examination, staging is usually by imaging: CT, magnetic resonance imaging (MRI), or at best positron emission tomography (PET)/CT scan.[3] The Ann Arbor staging system for lymphomas has roughly the same function as TNM classification staging in solid tumors.[12] The stage depends on both the place where the malignant tissue is located (as located with biopsy, CT scanning and increasingly PET) and on systemic symptoms due to the lymphoma (*B symptoms*: night sweats, weight loss of >10% or fevers) (Table 4). The limitations with the staging system include the fact that it does not take into account the grade (biological behavior) of the tumor tissue. As a result the prognostic significance of bulky disease, and some other modifiers were introduced with the *Cotswolds modification*.[18] Pathological staging as obtained by exploratory laparotomy with splenectomy has fallen out of favor for lymphoma staging as modern imaging renders effective diagnosis and staging except if equivocal.[3]

Treatment

The definitive mode of treatment is systemic chemotherapy as the tumors are chemosensitive although the prognosis will mostly depend on the biology (grade) and the subtype of lymphoma.[3,12] Unlike conventional lymphomas, lesions in immunocompromized individuals may be monoclonal or polyclonal for immunoglobulin light chain expression. The initial treatment consists of a reduction in immunosuppression with monitoring for evidence of allograft rejection and treatment with high-dose acyclovir for B-cell disorders. Conventional lymphoma chemotherapy may be required in clinically aggressive cases that occur late after transplantation.[16]

Table 1. Primary gastrointestinal non-Hodgkin's lymphomas.

B-cell	T-cell
MALT type Low grade High grade with or without low-grade component Immunoproliferative small intestinal disease (low and high grade)	Enteropathy-associated T-cell lymphoma
Mantle cell (lymphomatous polyposis)	Other types not associated with enteropathy
Burkitt's and Burkitt-like	Rare types (including conditions that may stimulate lymphoma)
Other types of low or high grade lymphoma corresponding to lymph node equivalents	-

MALT, mucosa-associated lymphoid tissue-type.

Table 2. Low-grade non-Hodgkin's lymphoma.

Sub-type	Cell type
Follicular lymphoma (25%)	B-type
Mantle cell lymphoma (5-10%)	B-type
Marginal zone lymphoma (12%) Extranodal (mucosa associated lymphoid tissue-MALT) (9%) Nodal marginal zone lymphoma (monocytoid B cell lymphoma) (2%) Splenic marginal zone lymphoma (primary splenic lymphoma) (1%)	Gastric MALT, small bowel, salivary, thyroid, tear glands, lungs, etc. B-type, it occurs within the lymph nodes B-type, it starts in the spleen and can also be found in the bloodstream (villous lymphocytes); over age 50; allelic loss at the 7q chromosomal region; indolent but small subset it follows an aggressive course
Small lymphocytic lymphoma (CLL) (6%)	Leukemia and lymphoma have many similarities: CLL - many of the abnormal cells are in the blood Small lymphocytic lymphoma - involves the lymph nodes in particular
Lymphoplasmacytic lymphomas (Waldenstrom's macroglobulinemia or immunocytoma) (2%)	Blood thicker - high level of immunoglobulin M Abnormal B cells fill up the bone marrow or enlarge the lymph nodes or spleen
Skin lymphomas (mycosis fungoides)	Rare NHL type (CD30 cutaneous T cell) lymphoma

MALT, mucosa-associated lymphoid tissue-type; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma.

Is there a role of surgery for non-Hodgkin's lymphoma?

Elective (planned) surgery

Lymph node; tissue biopsy

The main role of surgery in NHL is to make a histological diagnosis. As the spleen is essentially the largest lymph node in the body and splenic lymphomas are a diverse group of lymphoid malignancies that have clinical behavior ranging from indolent to aggressive and that have both B-cell and T-cell histology, the gold standard for diagnosis of NHL is evaluation of spleen histology. With the much-improved imaging techniques splenectomy is however infrequently worthwhile as a purely diagnostic procedure for it delays definitive treatment (chemotherapy) in addition to the possible hazards of splenectomy.[3,6,19] The highly efficacious fluorodeoxyglucose-PET scan is useful in prediction of splenectomy findings in patients with known or suspected lymphoma.[20] However, because of the wide variety of histopathological appearance in lymphoproliferative disorders in transplant recipients varying from changes consistent with viral lymphadenitis to variants of high grade NHL, accurate diagnosis depends on identifying EBV in biopsy material either by immunohistochemical staining or by *in situ* hybridization.[16,17]

Primary splenic lymphoma

Splenic marginal zone lymphoma (SMZL) is an indolent lymphoma made up of B-cells that replace the normal architecture of the white pulp in the marginal zone ultimately invading the red pulp of the spleen.[21] It is characterized by originating in the spleen prior to invasion of the lymph nodes and blood as villous lymphocytes.[22] Massive splenomegaly is seen commonly without lymphadenopathy or extranodal involvement but generally associated with bone marrow dissemination. There is a 75% 5-year survival rate and 50% 10-year survival rate after diagnosis.[23] Splenectomy is commonly followed by periods of

Table 3. High-grade non-Hodgkin's lymphoma.

Diffuse large B cell lymphoma Mediastinal (thymic) large B cell lymphoma (3%)	Most common (30%), occur any age, mostly mid to late 60's tends to occur in people in their 20s and 30s
Burkitt's lymphomas (3%)	Malignant B cells (30-50% of childhood lymphoma) Endemic variant (chronic malaria reduce resistance to Epstein-Barr virus, jaw commonly involved) Immunodeficiency-associated (post-transplant, AIDS) Sporadic type (ileo-caecal)
PTCL (6%) PTCL not otherwise specified ALCL AITL	It develops from mature T cells It can occur also in the liver, bone marrow, digestive system and skin
ALCL (2%)	It occurs most commonly in children and young adults; more common in males than females; it appears in the skin, in lymph nodes, or in organs throughout the body; several different subtypes with different outcomes and treatment options
AITL (2%)	Quickly growing T cell lymphoma
Lymphoblastic lymphoma (2%)	T cells, but occasionally it develops from B cells Under the age of 35, very rare in adults and most common in children and teenagers Lymphoblastic lymphoma is very similar to ALL. In lymphoma, the abnormal lymphocytes are generally in the chest lymph nodes or thymus gland but in ALL the abnormal cells are mainly in the blood and bone marrow. Similar treatments for lymphoblastic lymphoma and ALL
Blastic natural killer-cell lymphoma	Very rare type of T cell lymphoma; it affects only a few people each year; usually it occurs in adults, grow very quickly and can be difficult to treat; it can start almost anywhere in the body
Enteropathy associated T cell lymphoma or intestinal T cell lymphoma	Usually it occurs in the small bowel (jejunum or the ileum); celiac disease; 30s and 40s; it may spread to the liver, spleen, lymph nodes, gallbladder, stomach, colon or skin and tends to grow very quickly; Crohn's disease with suppressed immune system

PTCL, peripheral T cell lymphomas; ALCL, anaplastic large cell lymphoma; AITL, angio-immunoblastic T cell lymphoma; ALL, acute lymphoblastic leukemia.

Table 4. Ann Arbor staging system (the principal stage is determined by location of the tumor).

Stage	Definition
I	Involvement of a single lymph node region (I) or single extralymphatic organ or site (I_E)
II	Involvement of two, or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement
Costwold's modifiers include letters appended to some stages	A: the absence of constitutional (B-type) symptoms B: the presence S: disease has spread to the spleen E: disease is *extranodal* or has spread from lymph nodes to adjacent tissue X: the largest deposit is >10 cm large (*bulky disease*), or whether the mediastinum is wider than 1/3 of the chest on a chest X-ray

freedom-from-treatment lasting several years, despite persistent bone marrow and peripheral blood involvement. Thieblemont *et al.* reported the findings that splenectomy alone for SMZL (stage IV) rapidly recovered normal hematological parameters in patients with cytopenia at diagnosis and obtained a median survival of 10.5 years. A percentage of 70% of patients had persistent involvement of bone marrow and/or peripheral blood after splenectomy and they suggest that splenectomy should be delayed until the occurrence of symptoms or cytopenia.[24] Disease progression was significantly more frequent and median survival shorter in patients presenting with the immuno/lymphoblastic type - a monoclonal serum component and immunological event (elevated β_2-microglobulin level, leukocyte count >20,000/μL, and lymphocytes >9000/μL). Patients who have a hemoglobin level of less than 12 g/dL, a lactate dehydrogenase level higher than normal, and/or a blood serum albumin level of less than 3.5 g/dL are likely to have more an aggressive disease course and a shorter survival.[25] The counteracting factors would be the side-effects of splenectomy (post-splenectomy sepsis) and hypercoagulable state with increased cardiovascular morbidity, which would be higher in these immunocompromized patients.[6,19] Single-agent rituximab, on the other hand, has minimal impact on quality of life, is associated with a low risk of infection, appears to result in durable remissions in the majority of patients, and may be used successfully at the time of relapse.[26] There is, however, still no consensus regarding the best treatment.[6]

Primary splenic lymphoma may also coexist with hepatocellular carcinoma in chronic hepatitis C but the prognosis is usually poor to benefit from a simultaneous splenectomy and liver resection as the histology is usually of the diffuse large cell type.[27]

Primary non-Hodgkin's lymphoma of the liver

These are usually of the diffuse, large cell (centroblastic-centrocytic) high-grade type but a case with intermediate grade and no spread to lymph nodes, spleen or other viscera have been reported to be treated with partial hepatectomy and chemotherapy.[28]

Early mucosa-associated lymphoid tissue-type tumor: primary gastric lymphoma

Primary gastric non-Hodgkin's lymphoma (PGL) is the most common site for extranodal malignant lymphoma. There are B-cell lymphomas of mucosa-associated lymphoid tissue- (MALT) type. This is rather surprising since the stomach does not normally have any lymphoid tissue like the terminal ileal Peyer's patches from which a lymphoid malignancy could arise. It is a relatively rare but well-defined clinicopathological entity with a distinct histological spectrum and indolent course. The characteristic lesion is lymphoepithelial, which is not pathognomonic of a lymphoma as it can be demonstrated in an *Helicobacter pylori*-associated gastritis, Sjögren's syndrome and Hashimoto's thyroiditis.[3,29] Gastric MALT lymphomas tend not to spread beyond the place where they started. The majority of the lesions are located in the antrum, single lesions more frequent than multiple lesions and lymphoplasmocytic cytoid and centroblastic are the most frequent histological types.[29]

Role of *Helicobacter pylori* eradication therapy

In recent studies up to 90% of the gastric MALT lymphoma were associated with *H. pylori* infection.[30] This has suggested that the bacterial antigens may not only initiate gastritis but also perpetuate the immunological drive from which the lymphomatous process develops. The subsequent development of monoclonal lymphocytosis requires accumulation of genetic abnormalities.[31] Initially the tumor effaces the lymphoid tissue of the adjacent mucosa then spreads to the contiguous lymph nodes. No consensus exists about its treatment but the favorable clinical behavior of most low-grade MALT lymphomas (stage IE or IIE) with slow dissemination may reflect the partial dependence on the *H. pylori* antigenic drive. *H. pylori* eradication is the primary treatment modality for early gastric MALT. Regression of the lymphoma has been shown with an excellent 5- and 10-year survival rates of 91% and 75%.[32] Although there have been reported resistance of gastric MALT to *H. pylori* eradication therapy the prognosis is still better than the low grade nodal lymphomas which are essentially incurable with most patients succumbing to their disease within 7-10 years.[33]

Role of surgery

Surgery is an adequate treatment modality for the early stages of the disease, *H. pylori* negative gastric MALT and *H. pylori* positive gastric MALT lymphoma resistant to *H. pylori* eradication therapy. Gastric resection (subtotal or total) of primary early-stage gastric lymphoma (IE and IIE1), enabled an accurate clinicopathological staging, in addition to obtaining sufficient material for histopathological study and extirpation of the lesion. Surgery for primary gastric lymphoma had low complication rate, and led to good survival rate in stage I disease.[34] The addition of radiotherapy or chemotherapy does not improve the overall survival. For patients with stage IE disease, the gastric resection combined with adjuvant therapy (chemotherapy and/or radiotherapy) was associated with a greater than 5-year survival. The mean overall survival in one series is 42 months. In stage II disease, surgical curability did not affect the survival, implying the necessity of adjuvant chemotherapy. For the advanced stages (IIE2-IV), primary chemotherapy is the best treatment option with surgery being reserved for cytoreduction or chemo-radiotherapy-induced complications.[35]

However, there is still controversy regarding the optimal therapy for primary non-Hodgkin gastric lymphoma with some authors defending surgical extirpation either alone or in association with radiotherapy and or chemotherapy, especially in relation to the earlier stages of the disease. Some of the advantages claimed for surgery in PGL (debulking and abatement of the risk of perforation or hemorrhage during chemotherapy or radiotherapy) may have been overestimated in relation to the intrinsic surgical risk and to the possibility and delay of anticancer therapy. Gastric resection may still be unavoidable as a diagnostic procedure in a minority of cases and may represent the primary therapeutic procedure in clinically assessed early-stage and low-risk patients, but it cannot be considered mandatory whenever possible merely for debulking purposes or to obviate possible perforation or hemorrhage. Chemotherapy and/or radiotherapy can be effective in unresected and even bulky cases, providing minimal risk of severe hemorrhage or perforation.[36] For now management approaches are being individually tailored until prospective randomized studies evaluate the real efficacy of the different types of treatment for primary early-stage gastric lymphoma.

Ileo-caecal non-Hodgkin's lymphoma

There is a lack of quality evidence for the elective and emergency treatment of NHL involving the small and large intestine. It is proposed that in order to develop evidence-based treatment protocols, there should be an intestinal NHL registry.[3,7] NHL involving the ileo-caecal region is a rare occurrence. Optimal management and treatment outcomes of ileo-caecal NHL have not been well defined. Radical resection before chemotherapy should be considered in early-stage ileo-caecal NHL to achieve a better survival. Palliative resection of the primary lesion before chemotherapy may be necessary in T-cell advanced cases to avoid surgical emergencies during chemotherapy. A prospective analysis with larger patient number is highly necessary.[37]

Primary breast lymphoma

Primary breast lymphoma (PBL) is an uncommon disease with

poor clinical outcome. The main subtypes of PBL are diffuse large B-cell lymphoma and peripheral T-cell lymphoma. The effect of radical operation is limited in PBL. The optimal sequence is lumpectomy for histology followed by standard anthracycline-based regimens and radiotherapy. PBL tends to relapse to the central nervous system (CNS) and therefore, CT or MRI of CNS is necessary during follow-up.[38]

Emergency surgery

Intestinal non-Hodgkin's lymphoma

There is a lack of information regarding the impact of an emergency presentation on the timing of postoperative chemotherapy and overall prognosis. In one systematic study emergency surgery was required at disease presentation for between 11 and 64% of intestinal NHL cases. Perforation occurred in 1-25% of cases, and also occurred whilst on chemotherapy for NHL. Intestinal bleeding occurred in 2-22% of cases. Obstruction occurred more commonly in small bowel (5-39%) than large bowel NHL and intussusceptions occurred in up to 46%.[7] Ileo-caecal Burkitt's lymphoma which is usually of the sporadic type may masquerade as appendicitis. Thus, the importance of routine examination of appendectomy specimens, especially in high-risk areas where also the immunodeficiency-associated type has an intestinal preponderance,[39] should be considered. The endemic Burkitt's lymphoma type of the tropics where chronic malaria reduces the resistance to the causative EBV, mostly present as jaw tumors in children.[3,4,11] Prognosis is generally poor, especially for T cell lymphomas and AIDS-associated lymphoma.[40]

Anorectal non-Hodgkin's lymphoma

Malignant neoplasia is remarkably of high incidence for young people with HIV/AIDS.[40,41] This includes NHL in the perianal area, which often presents as a tender, indurated mass. When this presents in the ischio-rectal fossa, it can look exactly like a tense ischio-rectal abscess. The temptation in the middle of the night is for the junior doctor to plunge a knife into and let all the pus out. The diagnosis can be made by a needle biopsy *via* the perineum. A biopsy should not be taken inside the anal canal as the patient will develop a fistula in the lymphomatous tissue.[42]

Impact of HIV/AIDS on surgery for non-Hodgkin's lymphoma

HAART and good nutrition have decreased the prevalence of gastrointestinal pathologies associated with AIDS and improved surgical outcome.[43] Surgery conferred least benefit in patients with *mycobacterium avium-intracellulare* infection or lymphoma because of the underlying low immunity (<500 CD4 cells/uL).[44,45] Appendectomy and colectomy are the commonest abdominal operations in AIDS patients.[39] Being an extranodal lymphoid organ it could be the only initial indication of a lymphoma or an underlying pathology although cytomegalovirus (CMV) has also been isolated from appendix specimens raising the possibility that CMV may be causative or a co-factor.[44,46] It is crucial to have close liaison between AIDS physicians and AIDS surgeons to exclude pre-terminal cases and keep down negative laparotomies to acceptable rate.[46] These factors have led to an increased indication for diagnostic laparoscopy. Care should be taken, however, during laparoscopy by insisting upon using disposable ports with a vestibular flange to prevent splash back, and by deflating the abdomen prior to port withdrawal because any aerosol emanating from the port entry wound will harbor HIV.[46] The long-term benefits of surgery for NHL in HIV/AIDS are determined by the disease process. Survival at 1 month, 3 months and 6 months were 89%, 64% and 48%, respectively.[44]

Conclusions

NHLs are a diverse group of blood cancers derived from lymphocytes that vary significantly in their severity. Surgery is not often used as a treatment because of the efficacy of chemotherapy, biological therapy, radiotherapy and hematopoietic stem cell transplantation. Also, the role *of H. pylori* eradication therapy in gastric MALT should not be undermined. However, surgery may be useful in confirming or refuting equivocal radiological diagnosis through biopsy, removing symptomatic limited disease from an affected organ and in splenectomy for splenic marginal zone lymphoma. There is as yet no consensus as to the optimum treatment for symptomatic limited disease affecting an organ and timing of chemotherapy perioperatively. Emergency surgery for complications of NHLs is mainly for palliation and diagnosis.

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