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Classification of Hodgkin's Disease: Yesterday, Today and Tomorrow

John E. Ultmann

THIS BRIEF review of staging classifications for Hodgkin's disease will trace the development of various classifications over the nearly 100 years since a clinical classification was devised by Dorothy Reed in 1902 [1]. Classifications are an attempt to predict outcome of disease as affected by its extent, the current philosophies of pathophysiology of spread, and of course, the treatment modalities available.

When Reed developed a staging classification in 1902, no treatment was available and the classification simply addressed the fact that there were two stages, localised disease and advanced disease; the former usually preceded the latter. The strategy for identification of risk factors was largely unknown; the aim of treatment was palliation; treatment in fact consisted of support. There were no complications of treatment, but the disease eventuated in death in all instances (Table 1).

When Gilbert [2] proposed to treat Hodgkin's disease with radiotherapy, he made a major conceptual and therapeutic contribution which was first tested in a rigorous manner by Peters and Middlemiss in Toronto [3], and by Easson and Russell in Great Britain [4].

Because of their approach to the treatment of Hodgkin's disease with radiotherapy and because of their understanding of the limitations due to the technical aspects of such treatment, a new classification was devised and a staging technology proposed. This allowed Peters as well as Easson to identify stages I and II, which could be cured. Thus, Peters proposed three stages of Hodgkin's disease: involvement of a single site, stage I; involvement of 2 or 3 proximal lymphatic regions, with or without symptoms, stage II; and involvement of 2 or more distant lymphatic regions, stage III. The technological approaches to classifying patients consisted of a physical examination and radiological examinations comprising a chest film, intravenous pyelogram, and inferior vena cavagram. The aim of treatment was cure for stage I and II patients; the treatment modality consisted of orthovoltage radiotherapy given in wide fields. There were treatment complications, and of course, there were also treatment failures (Table 1).

The results, however, were astonishing compared to historical data. 5-year disease-free survival rates were 30%–40%, and 10-year disease-free survival rates were 20%–26% in Manchester and Toronto, respectively [3–5]. Peters' contribution was a landmark, since her selected cases had a 6-fold improvement in 5-year disease-free survival compared to the untreated cases reported by Croft in 1940 [6].

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Table 1. Overview

Reed 1902 / Gilbert	Peters 1950–1960 / Kaplan Smithers	Rye 1965	Mussoff, DeVita	Ann Arbor 1970	Bonadonna & many others	Cotswolds 1989	Modified 'Reed' Classification 1991 A return to the past with risk factor analysis			Future 2000±
Classification										
Localised	I	I		I		I	*RT only	?CT		
				I_E		I_E				
	II	II		II		II	*RT only	?CT		
				II_E		II_E				
						$II_{X(bulk)}$		°CT only ± RT	CT vs. RT	
Advanced	III	III		III		III	*RT only			
				III_E		III_E		°CT only ± ?RT		
				III_S		$III_{1 or 2}$		°CT only		
						$III_{S \pm 3}$ nodules		°CT only ± ?RT		
		IV		IV		IV		°CT only		
		L		etc.		etc.				
		H								
		M								
		etc.								
Strategy (for identification of risk factors)							All patients receive CT except selected ones			Molecular markers
	Physical exam	A vs. B								Oncogenes
	X-rays	CS vs. PS								Cytogenetics
	Chest					LAG vs.				Immunological markers
	IVP	Lymphangiography		(^{67}Ga)		computed				Virological markers
	IVC	Laparotomy				tomography				
		Splenectomy				(MRI)				
Aim										
Palliation	Cure I & II	Cure I, II, & III	Cure III & IV	Cure I–IV	Cure I–IV					
Treatment										
Supportive	RT	RT	MOPP	Selectivity	ABVD	CT				
	wide-field	wide-field	'E'		Sequ.	CT & RT				
	orthovoltage	linear		RT	Hybrid	RT				
		accelerator		RT & CT						
		high dose		CT						
Complications										
	Local	Local	N & V			Local				
			Sterility			Systemic				
	Recurrence	Recurrence				Late				
		2° cancer	2° ANLL			2° ANLL				
		Staging				2° cancer				
						Recurrence				

Histology
Stage
- Sites of involvement
- No. of sites
- Mass
- IV
- A vs.B
- E
- Splenic nodules
- CS vs. PS
- Staging complications

Age
Sex
Haematocrit
ESR
Serum albumin
Alkaline phophatase
Lactic dehydrogenase
Total leucocyte count
Lymphocyte count
sCD8 antigen level
Interleukin-2 receptors (sCD25)
Quality of radiotherapy
Quality of chemotherapy

CT, chemotherapy; RT, radiotherapy.

Using the Rye classification criteria in a retrospective analysis, Peters reclassified her cases and compared her own classification with that of the staging classification to be proposed in Rye. She showed that the patients she was able to cure were basically stages I and IIA, whereas she was having no real effect on the outcome of treatment of IIB, IIIA and IIIB, and IV patients [5].

Two of the pioneers in conceptual and tactical approaches to the staging and management of Hodgkin's disease were Henry Kaplan [7] in the United States and David Smithers [8] in Great Britain. Both had made major contributions to the theories of the spread of Hodgkin's disease, the approach to staging, and the approach to more aggressive treatment for the disease. With their contributions, it became apparent that a conference should be held that would bring together all these newer concepts. The driving force of these concepts was the theory that Hodgkin's disease spread in a contiguous, orderly manner, as well as the technological advance that permitted megavoltage radiotherapy to be given to large fields with tumoricidal doses. Thus, Kaplan was among the first to show that less than 5% recurrences would be seen in fields given 4 000–4 400 rads; and a number of radiotherapy fields, including the mantle, inverted Y, para-aortic, hepatic, pelvic, and other fields, were proposed to deliver these curative doses of megavoltage therapy with the fewest local complications. Shortly before the Rye conference, Kaplan proposed a revised classification of Hodgkin's disease that consisted of four stages and the A and B subclassification. Kaplan could bring to the Rye conference the information that by using the 6 MeV linear accelerator to treat eligible patients it was possible to attain a 73% rate of 5-year disease-free survival [7, 9].

With this information available, the 1965 Rye conference became a landmark occasion to review the classification of Hodgkin's disease, propose a staging technology, and to state treatment goals [10, 11] (Table 1). The staging, now well known, was in four stages: stage I, local disease in one site or one extralymphatic site; stage II, lymphatic disease on one side of the diaphragm or the other; stage III, disease in lymphatic sites, including the spleen, above and below the diaphragm; and stage IV, systemic widespread disease in such organs as the lung, liver, bone marrow, etc. The subclassification of A for asymptomatic, and B for symptomatic, as already proposed by Peters and emphasised by Kaplan, was retained. The proposed staging technology emphasised 'clinical stage' (CS) short of a second biopsy and 'pathological stage' (PS) in which biopsy-proven extent of disease could be demonstrated. The technology included lymphangiography as a keystone for the demonstration of retroperitoneal disease followed in appropriate cases by laparotomy and splenectomy for assessing extent of disease below the diaphragm [10]. With this information in mind, the aim of the treatment was cure for stages I, II and III, using wide-field, high-dose linear accelerator radiotherapy.

Complications occurred and recurrences were seen despite this careful staging, and there were, in fact, complications from the staging. What was not known at the time is that secondary cancers, including secondary acute non-lymphocytic leukaemia and solid tumours, would be seen many years later.

Over the next few years, a number of new developments occurred. In the first of these, Musshoff pointed out that extralymphatic disease that was contiguous with a lymphatic area did not have the same bad prognostic implication as extralymphatic disease that was more widespread [12, 13]. This contribution led to the concept of extralymphatic disease, 'E', which as I_E, II_E or III_E could be shown to have no negative prognostic implication but to have the same survival results as stages I, II and III, respectively.

The other major conceptual development, which occurred around 1965–1966, was the introduction and demonstration of the usefulness of a combined four drug regimen developed by DeVita and associates at the National Cancer Institute. The regimen, which was known by the acronym MOPP, consisted of nitrogen mustard, vincristine, procarbazine and prednisone given in a carefully developed cycle over 14 days with 14 days of rest and usually administered in 6 cycles [14]. The aims of Musshoff's and DeVita's approaches were to cure by radiotherapy the I_E, II_E and sometimes III_E patients and to cure with MOPP the patients classified by the Rye staging as stage IIB, III or IV. The treatment then was quite aggressive; complications included nausea, vomiting and sterility; and as it later turned out, a secondary acute non-lymphocytic leukaemia was a further serious complication of this type of approach.

With these developments just a short 5 years after the Rye meeting, it was considered important to call another meeting of Hodgkin's experts, this time in Ann Arbor, Michigan (Table 1). In this conference, the Rye classification was modified in several important ways to include some of the conceptual and practical developments which had occurred in the previous 5 years. These included a redefinition of clinical and pathological staging into stages I or I_E, II or II_E, III or III_E; but this time, staging also specified whether the spleen was involved, since although the spleen in Rye was considered 'a large lymph node', its involvement was clearly having additional prognostic implications. Finally, stage IV with disseminated, diffuse involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement. The A or B substaging classification was retained, and a biopsy documentation was encouraged for other organs involved in stage IV [15].

The diagnostic work-up proposed at that time consisted of a careful history with attention to B symptoms, physical examination with emphasis on peripheral lymph node change, liver, spleen and bone tenderness, a roentgenological work-up consisting of chest roentgenograms and a whole lung tomography if mediastinal or hilar adenopathy was present. A keystone of the identification of abdominal involvement was bilateral lower extremity lymphangiography. Certain blood tests were advocated but not considered critical in the classification scheme. Recommended approaches were a staging laparotomy, including splenectomy and biopsy of suspicious para-aortic, coeliac, porta hepatis, splenic, hilar and/or iliac nodes, and of liver and iliac crest bone marrow in cases where this group of procedures would affect the treatment strategy and management of the patient. Other tests including radioisotopic scans and a measurement of the late hypersensitivity were advocated but not required [16, 17].

Almost 20 years later, looking back at the effects of staging laparotomy on staging Hodgkin's disease as published by Moormeier *et al.* [18], it was apparent that for stage I, 25% of patients were upstaged; for stage IB, 57% were upstaged; for stage IIA, 26% were upstaged; but for stage IIB, 42% were upstaged. Likewise for clinical stage IIIA, 9% were upstaged, but for IIIB, 19% were upstaged. Interestingly enough, particularly for clinical stage IIIA, 34% were downstaged. Thus, staging changes occurred in 25%–57% of cases, supporting the idea that laparotomy had a significant effect on changing the stage of Hodgkin's disease as assessed clinically. The question remains whether this procedure was important in changing treatment strategy. As

subsequently became apparent other factors, including further risk analysis, place laparotomy in a different light, 25 years after it was proposed.

Farah *et al.* [19], demonstrated for our own group of pathologically staged patients with stage I and II Hodgkin's disease the effectiveness of performing laparotomy/splenectomy staging for these patients. Furthermore they could show, in 135 patients, a disease-free survival of 80% or more at 5 and 10 years and an actuarial probability of survival of almost 96% at 5 years and 83% at 10 years. The latter was due in part to the salvage possible for the few patients who relapsed.

At the same time, DeVita and associates at the National Cancer Institute, analysing their 159 patients treated with MOPP, could show a 5-year cure rate of 80% of the complete responders as well as a disease-free survival of over 70% of the complete responders. It also became apparent in the study that induction failures had a dismal response, with 50% of the patients dying within 17 months [20]. The Ann Arbor conference was then able to demonstrate clearly the curability of Hodgkin's disease of all stages: I, II, III and even IV. There was evidence of treatment selectivity in that radiotherapy alone, chemotherapy alone, or radiotherapy and chemotherapy could lead to significant 5-year disease-free responses and many cures.

Following this landmark conference, other developments occurred which made possible new approaches and new ideas. Among these were the development by Bonadonna and his associates in Milan, of a regimen which was non-cross-resistant, that is, non-cross-resistant to MOPP for the treatment of advanced Hodgkin's disease. It was referred to as ABVD and consisted of doxorubicin, bleomycin, vinblastine and dacarbazine imidazole carboxamide (DTIC) [21]. With the availability of this regimen, it could be shown that ABVD had approximately the same complete remission induction rate as MOPP, nearly 70%. Moreover it was possible to demonstrate that ABVD failures treated with MOPP and MOPP failures treated with ABVD, that is to say, crossover, showed an absence of cross-resistance.

Following this development, a large number of combination chemotherapy regimens were developed, all based on the idea that three or more drugs would be useful and all addressing on the one hand the curability potential and on the other hand the diminution of toxicity of each of these regimens. As a consequence of the development of multidrug regimens, it became possible to address two other issues, namely sequential and hybrid therapy. Sequential therapy was based on administering 1 month of MOPP followed by a month of ABVD, in sequence, for 6–12 months, whereas the hybrid concept permitted the administration of MOPP the first week and ABVD the second week of a 4-week treatment cycle (Table 1). An enormous quantity of data was developed indicating possible improvement in complete remission induction, possible diminution of toxicity, and possible new complications from the administration of eight or more drugs.

As a result of these many endeavors and the publication of many and occasionally contradictory findings, it was felt useful to call another conference which was convened in 1989 in the Cotswolds. At this conference, the proposal was made to modify the Ann Arbor staging classification and to emphasise bulk and sites of risk [22, 23] (Tables 1, 2). Thus, stages I and I_E, II_E, were retained, but II_X (bulk) was added to emphasise a widened mediastinum more than one-third the thoracic diameter or bulky lymph nodes greater than 8 or 10 cm in diameter. Stages III and III_E were also retained, and the proposal by Desser *et al.*

*Table 2. The Cotswolds staging classification**

Stage I:	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
Stage II:	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site, hilar lymph nodes are lateralised). The number of anatomical sites should be indicated by a suffix (e.g., II_3)
Stage III:	Involvement of lymph node regions or structures on both sides of the diaphragm
	III_1: with or without splenic hilar, coeliac, or portal nodes
	III_2: with para-aortic, iliac, mesenteric nodes
Stage IV:	Involvement of extranodal site(s) beyond that designated 'E'
	A: no symptoms
	B: fever, drenching sweats, weight loss
	X: bulky disease:
	> 1/3 widening of mediastinum
	> 10 cm maximum dimension of nodal mass
	E: involvement of a single extranodal site, contiguous or proximal to known nodal site
	CS: clinical stage
	PS: pathological stage

*Ref. [23].

for a stage III_1 or III_2 was entered into the classification [24]. Moreover, the observation by Rosenberg and collaborators at Stanford of the prognostic implication of more than five splenic nodules was also taken into consideration in this classification [25]; stage IV was retained as before. With this classification in mind, the strategy for identification of risk factors was reviewed. For mediastinal involvement, computed tomography was clearly useful and superseded the traditional radiological examination of the chest, which was also required because it permitted comparison with old data [26–28].

But more importantly, questions arose regarding the usefulness of CT scan *vis-à-vis* the lymphangiogram which were the topics of great debate. Clearly, the lymphangiogram was more specific and accurate, but its results confine themselves to the retroperitoneal lymph nodes. In contrast, CT was not as specific, but did address issues of splenic, hepatic and mesenteric lymph node involvement. The role of magnetic resonance imaging could not yet be ascertained.

As before, with all treatment approaches, radiation or chemotherapy or both, the aim was cure. But a new view regarding the potential complications of treatment approaches was carefully analysed. Local complications from radiotherapy, as well as systemic complications from radiotherapy and chemotherapy, were addressed and put in perspective with the stage, risk factors, and treatment aims. Furthermore, consideration of late complications, in particular acute non-lymphocytic leukaemia and secondary cancer, received considerable analysis. Recurrences were still seen and were the subject of careful review to glean retrospectively risk factors which could have been identified and which could have led to more intensive treatment in selected patients with these risk factors.

In the period 1980–1984, as was pointed out by Lister and Crowther [23], the spectrum of treatment approaches had shifted considerably. Thus, in a study conducted during the preceeding decade, 31 of 31 patients received radiotherapy alone; in the 1980–1984 period, 22 of 51 patients received radiotherapy alone, 13 received radiotherapy and chemotherapy, and 16 received chemotherapy alone.

*Table 3. Recommended guidelines for investigation of patient with Hodgkin's disease**

Recommended
History and examination
'B' symptoms: weight loss > 10% during previous 6 months, documented fever, night sweats
Radiology
Plain chest radiograph
Computed tomography of thorax
Computed tomography of abdomen and pelvis
Bipedal lymphogram
Haematology
Full blood count†
Lymphocyte count†
Erythrocyte sedimentation rate‡
Bone marrow biopsy‡
Biochemistry
Tests of liver function†
Albumin, LDH, calcium†
Under special circumstances
Ultrasound scanning
Magnetic resonance imaging
Other imaging techniques
Isotope scanning
Gallium
Technetium

*Ref. [23].
†Do not determine stage: may not influence management.
‡Not for stage IA or IIA with 'favourable features'.
Note. Both computed tomography of abdomen and pelvis and bipedal lymphogram not usually required.

The Cotswolds staging classification is summarised in Table 2. The recommended guidelines for investigation of patients with Hodgkin's disease as proposed at the Cotswolds meeting are summarised in Table 3.

It is now important to consider the direction in which we may hope to see staging classifications advance during the last decade of the 20th century. From all that has been said, it appears that there are really only two stages of Hodgkin's disease, namely, the stage that should be treated with chemotherapy and the stage that should be treated with radiotherapy alone. A few patients identified as being at high risk by old and new technological approaches in the clinic and in the laboratory might be subjected to a combined modality treatment of chemotherapy followed by radiotherapy or radiotherapy followed by chemotherapy.

Table 1 lists the risk-factor analysis which must now be undertaken to select the best treatment, that is, the one that offers the highest degree of curability with the least cost in terms of complications to the patients. Among these are histology and stage, including sites of involvement, number of sites, the mass of each site, stage IV, the implication of 'B' symptomatology, the implication of extranodal involvement that is contiguous to lymph nodes, the implication of splenic nodules, and, in fact, the implication of the necessity of performing staging laparotomy with its complications. Furthermore, recent data indicate that age, sex, symptoms, mass of lymph nodes, III_1/III_2, number of splenic nodules, haematocrit level, erythrocyte sedimentation rate, and certain laboratory tests including alkaline phosphatase, albumin, etc., might also have prognostic implications. As regards histology, further analyses are under way to study the subsets of nodular sclerosis. In the near future, additional prognostic factors will become important including soluble interleukin-2 receptor levels.

The future classifications for Hodgkin's disease which will be developed at the turn of the century will include not only these new laboratory parameters, but molecular markers such as oncogenes, results of cytogenetic analysis, immunological markers, and virological markers. How these will be incorporated in our risk analysis is not yet certain.

In summary then, the development of staging classifications during the last century has kept pace with new concepts in the pathogenesis and spread of Hodgkin's disease, new staging technology, and new therapeutic interventions aimed at curing patients. Each of these epochs is marked by conceptual and technological progress and an analysis of risk factors to enhance curability and to diminish toxicity and risk of complications and recurrence. The future looks bright.

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