Risk Assessment in the Management of Newly Diagnosed Classical Hodgkin Lymphoma

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running title: Risk assessment for Hodgkin lymphoma

keywords: Hodgkin lymphoma; risk factors; prognostic score; biomarkers; prognosis; failure free survival
Abstract

The modern treatment of Hodgkin lymphoma is associated with two major types of risk: the risk that the treatment will fail to cure the disease and the risk that the treatment will prove unacceptably toxic. Careful assessment of the amount of the lymphoma (tumor burden), its behavior (the extent to which it has invaded or compromised specific organ function) and special host-related factors (age, coincident systemic infection and organ dysfunction, especially of the hematopoietic system, heart and lungs) is essential to optimize treatment outcome. Elaborately assembled prognostic factor scoring systems, such as the International Prognostic Factors Project score, have lost much of their accuracy and value as increasingly effective chemotherapy and supportive care have been developed. A new era in which specific biomarkers derived from sophisticated exploration of Hodgkin lymphoma biology are being identified and validated brings promise of further improvement in targeted therapy in which effectiveness is increased at the same time that off-target toxicity is diminished. Parallel developments in the application of functional imaging are bringing additional potential to evaluate the efficacy of treatment even as it is being delivered allowing dynamic assessment of risk in the midst of chemotherapy and adaptation of the treatment regimen in real time. Risk assessment in Hodgkin lymphoma is continuously evolving and promises even greater precision and specific clinical relevance in the future. In this article we will explore the past usefulness and emerging potential of risk assessment for this imminently curable malignancy.
Introduction

Over the past 60 years continuous improvement in the management of Hodgkin lymphoma has brought clinicians and patients to an era in which the large majority of patients are cured, regardless of disease presentation. (1-7) This improvement in outcome has brought a new obligation to those who wish to manage this previously lethal malignancy optimally, an obligation to maintain very high cure rates while simultaneously minimizing toxicity, especially persistent late toxicity, which may permanently reduce the quality of life of survivors or even cause their death. A fine balance must be maintained in which maximal effectiveness of treatment, which presently is built around multi-agent chemotherapy and judicious use of radiation, is maintained while minimizing exposure to interventions associated with major late toxicity. In brief, clinicians must recommend just enough treatment to achieve the greatest efficacy and yet induce the least harm. Careful assessment of risk is an essential part of achieving this balance. Such risk assessment must, in turn, address multiple factors, some of which are intrinsic to the host, others related to tumor burden and tumor biology and, finally, several that are evaluable at diagnosis and determinable as the treatment course unfolds (Figure 1). Full appreciation of important factors that increase the risk of treatment failure or the likelihood of undesirable, potentially avoidable, acute or late toxicity and how to minimize these risks is essential to optimal management of Hodgkin lymphoma today. In this review we will examine these risk factors and identify strategies that minimize their impact on our patients. Even as we do this, however, it is necessary to acknowledge that important risk-altering biological characteristics may
remain undescribed at present but be identified and become important with further research.

**Risk factors intrinsic to the patient**

Many studies have identified patient-related risk factors that impact outcome of treatment for individuals with Hodgkin lymphoma. Table 1 lists those most relevant to current day management including age, sex, human immunodeficiency virus (HIV) infection and prior organ compromise such as pulmonary disease related to smoking and cardiac dysfunction reflecting underlying coronary artery disease. Each of these factors has a profound, highly significant effect on outcome; however, not all can be altered or addressed effectively using currently available interventions. Previously acquired pulmonary compromise, usually related to cigarette smoking, may necessitate omission of bleomycin from primary treatment. Deciding when to drop bleomycin is made more challenging due to the lack of useful objective screening assessment tools. Formal pulmonary function testing, even with inclusion of carbon monoxide diffusion capacity, is quite unreliable at identifying patients at risk for significant bleomycin toxicity. The decision to omit bleomycin must be made on clinical grounds. I have found a useful rule of thumb is to consider the potential impact of a relatively rapid loss of 30% to 40% of current respiratory reserve. If a patient appears, based on a review of current activity levels and exercise tolerance, capable of absorbing that much loss of lung function from current pulmonary reserve, bleomycin can be safely, but still carefully, included in planned chemotherapy. The patient has adequate reserve to tolerate pulmonary injury if it occurs. If I do not think such a loss could be endured safely, I omit bleomycin, at least
until pulmonary reserve improves, as may happen if the compromise was due to the
Hodgkin lymphoma, perhaps reflecting a large mediastinal mass or lung involvement, or
permanently, if prior damage from smoking or occupational exposure appears
irreversible. Concern has been expressed that coincident use of bleomycin and neutrophil
growth factors may exacerbate bleomycin-related pulmonary toxicity.(11) However, two
well conducted studies, one a retrospective review (12) and the other a prospective
clinical trial,(13) have failed to substantiate this suspicion. Neutrophil growth factors
should be used sparingly in the management of Hodgkin lymphoma;(14) however, when
they are necessary there is no need to avoid them due to concern over coincident use of
bleomycin.

Underlying cardiac disease may similarly affect the safety of chemotherapy, in
this case the use of anthracyclines. A prior history of congestive heart failure or ongoing
evidence of impaired cardiac reserve such as a left ventricular ejection fraction less than
50 % should prompt careful consideration of the risk that exposure to doxorubicin or
doxorubicin plus mediastinal radiation will worsen underlying cardiomyopathy. In such
cases careful serial monitoring of ventricular function must be included in the patient’s
assessments during treatment and omission of the anthracyclines and substitution with an
alternative chemotherapeutic agent such as etoposide should be considered.

Another aspect of organ function affecting risk is that of bone marrow tolerance
for exposure to cytotoxic agents. This emerges clearly in studies focused on the
relationship between sex and bone marrow function. Because myelosuppression is
reflected in number and depth of episodes of neutropenia and female sex correlates with
increased sensitivity to marrow suppression these studies typically demonstrate that
women have more episodes of neutropenia and deeper and more prolonged nadirs in neutrophil counts compared to men given the same doses of chemotherapy. Since depth and length of myelosuppression reflect biological potency of chemotherapy agents, patients experiencing greater myelosuppression, in this case women, have better outcomes, reflecting the more effective dosing of the chemotherapy.

Coincident infection with HIV alters the behavior of Hodgkin lymphoma leading to more frequent systemic symptoms, earlier spread to extranodal tissue and a markedly decreased failure free and overall survival. There is now ample evidence that the use of highly active anti-retroviral treatment (HAART) not only reduces the incidence of HIV-associated Hodgkin lymphoma but that both HAART and vigorous supportive care employing prophylactic anti-*Pneumocystis*, anti-fungal and anti-*Herpesvirus* antibiotics, neutrophil growth factors and comprehensive social intervention substantially improve outcome in patients with coincident Hodgkin lymphoma and HIV infection. Most studies indicate that such interventions reduce the risk of death by at least 50%.

A final factor relevant to treatment of Hodgkin lymphoma is older age, which has quite consistently been noted to have an adverse impact, although the threshold for its impact has varied across studies from age 45 years to greater than 70 years. The challenge when considering age is that it is in many ways simply a proxy for physiologic function. Ignoring age places the patient at exaggerated risk but unduly emphasizing it risks under-treatment. In addition to assessment of specific organ function, such as cardiac or pulmonary function as discussed above, a reasonable and practical approach to adjusting treatment based on age is to start treatment with a modest dose reduction by 20% to 30% of the myelosuppressive chemotherapy agents but to subsequently escalate...
to full doses with subsequent cycles seeking to reach the maximum that can be achieved without undue toxicity as early in overall treatment as feasible.

Knowledge of relevant patient specific risk factors is important in the crafting of optimal treatment. Thus, treatment outcome for Hodgkin lymphoma patients with certain patient-specific risk factors indicating a diminished prognosis or signaling specific organ dysfunction can be substantially improved employing individualized interventions.

**Risk factors related to tumor burden and tumor biology**

Risk factors related to tumor burden and tumor biology can be roughly divided into two categories, older assessments describing global clinical factors and laboratory tests, which often reflect not only disease specific factors but also, indirectly, patient specific characteristics, and newer assessments based on specific biologic characteristics of the lymphoma itself.

**Risk factors describing global clinical factors and laboratory tests**

The most obvious clinical risk factor impacting outcome for patients with Hodgkin lymphoma is stage of disease, which is equally obviously reflective of net tumor burden. The most recent version of the staging system entitled the Cotswold revision of the Ann Arbor system includes a basic measure of tumor bulk, the diameter of the largest single tumor mass.(28, 29) There is universal agreement that stage affects risk of treatment failure and must be considered in treatment planning. Patients are most often divided into two groups, those with limited stage disease, typically including those with stage I or II, and those with advanced stage disease, those with stage III or IV disease. Often,
especially in Europe, additional substaging focuses on specific risk factors such as bulk of tumor, presence of B symptoms, number of involved nodal groups and certain laboratory measurements such as erythrocyte sedimentation rate, assigning patients to favorable and unfavorable substages of limited disease.(30, 31) Because stage and substage directly determine planned duration of treatment with limited stage disease typically treated using two to four cycles of chemotherapy and advanced stage, six or more cycles, this aspect of tumor burden as a distinct risk factor for treatment failure is intrinsically acknowledged in the modern treatment of Hodgkin lymphoma.

Over several decades extending from the 1970s to the 1990s clinical factors impacting prognosis and outcome of patients with Hodgkin lymphoma were described in many studies, some of which focused on all patients while others attempted to identify factors specific to stage of disease or defined subsets of patients such as those with specific histologic subtypes.(27, 30, 32-43) The extent to which these clinical factors impact patient outcomes has diminished substantially as the effectiveness of interventions has improved. Obvious and clinically important changes in the accuracy and diminished relevance of clinical risk factors can be readily seen when one examines the impact of the factors needed to assign a score using the pivotal International Prognostic Factors Project (IPFP) score.(42) The IPFP was an international effort coordinated by the German Hodgkin Study Group (GHSG) in which investigators assembled data on a large number of potentially relevant prognostic factors and treatment outcomes from 25 Hodgkin lymphoma treatment centers or cooperative groups on 5141 patients with advanced stage Hodgkin lymphoma treated primarily (> 75 %) with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)(44-46) as delivered in the late 1980s and early 1990s. In their
final multivariable analysis they identified seven independently prognostic factors, shown in Table 2, each of which contributed approximately equally to the impact on freedom from progression and overall survival: age, sex, stage, hemoglobin level, serum albumin level, peripheral blood white blood cell count and degree of peripheral blood lymphopenia. Given one point for each factor present, patients were assigned a score from 0 to 7 resulting in a wide range of outcomes measured as 5-y freedom from progression (FFP) and 5-y overall survival (OS). For example, the authors found that a patient with no adverse factors (IPFP score 0) had 5-y FFP and 5-y OS of 84 % and 89 %, respectively, while one with four factors (IPFP score 4) had 5-y FFP and 5-y OS of 51 % and 61 %, respectively. The strengths of the IPFP were the large number of patients examined, the international participation, ready availability in standard clinical practice of the factors identified and the use of ABVD as the primary treatment in the large majority of patients, although the inclusion of some patients treated with regimens other than ABVD somewhat weakens the strength of this latter observation. As useful as this index has proven, there are several limitations in the original publication. Four hundred and forty-six patients were excluded due to age outside the range from 15 to 65 years or receipt of non-curative chemotherapy; 40 % of the included patients also received treatment with radiation; 25 % of the patients had stage I or II disease; all seven variables included in the final score were available for only 1618 (34 %) of the patients, forcing the statisticians to interpolate the missing variables based on assumptions about their probable distribution; and, finally and most importantly, the patients were primarily treated in the 1980s and early 1990s, before secondary treatment with high dose
chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) came into wide use for patients with relapse or primary progression despite ABVD.(47-55)

Much has changed in the management of patients with advanced stage Hodgkin lymphoma since the analysis underlying the IPFP scoring system was conducted. Diagnostic imaging has improved, first with the introduction of faster computed tomographic scanning (CT) with its ability to provide finer and more exact detail and later with the introduction of functional imaging based on flurodeoxyglucose positron emission tomography (PET). Improved imaging increases the accuracy of disease identification but also introduces the artifact of stage migration, which, in turn improves apparent treatment outcomes.(56) Chemotherapy dose delivery has improved coincident with the widespread use of neutrophil growth factors although the necessity to employ such growth factors frequently has been questioned. Evens, 2007 #5137} Diagnostic accuracy has improved reducing the modest but still important number of patients with poorer prognosis non-Hodgkin lymphomas such as anaplastic large cell lymphoma (57, 58) and T-cell/histiocyte rich large B-cell lymphoma (58-60) erroneously included in series of patients thought to have classical Hodgkin lymphoma Finally, and most importantly, as described above, ASCT for patients with relapse after or primary progression during ABVD as standard secondary, potentially curative, treatment has been universally adopted. The combined impact of these mitigating factors, stage migration due to improved imaging, improved dose delivery, more accurate diagnoses and wide use of ASCT, can be seen when one examines the outcome achieved by primary treatment with ABVD in major clinical trials and large single institution series over the years from the late 1980s through the early 2000s (Table 3). Five-year overall survival has increased
from just over 70% to approximately 90% despite the nominal use of exactly the same chemotherapy regimen, ABVD.

The impact of this apparent improvement in outcome after primary treatment with ABVD for advanced stage Hodgkin lymphoma on the usefulness of the IPFP scoring system can be clearly seen in the results we have seen at the British Columbia Cancer Agency (Table 4 and Figure 2) (7) Table 4 shows a comparison of outcomes for subgroups of patients with varying IPFP scores as seen in the original IPFP report (42) and our single institution experience for 579 consecutive patients treated with ABVD or equivalent chemotherapy. (7) Figure 2 shows updated freedom from progression curves for 675 consecutive patients treated with ABVD or equivalent chemotherapy at BCCA through 2009 broken down by IPFP score. These results show the 42% spread in 5-y freedom from progression, which ranged from 84% to 42% in the original publication for patients with a score of 0 compared to those with a score ≥ 5, has markedly narrowed to a 17% spread, ranging from 83% to 66%, using ABVD today. Even more importantly, presently, for the 94% of patients with advanced stage Hodgkin lymphoma who present with IPFP scores of 0 to 4 the 5-y overall survival has improved to approximately 90%. Clearly, the usefulness of the IPFP score has diminished markedly with time. The same is true for the individual factors that make up the IPFP score and those that have been described in multiple other publications addressing clinical prognostic factors. This change reflects the general principle that as overall treatment strategies improve the impact of individual, and even aggregated prognostic factors, diminishes. With even the worst subsets of patients, such as the small group (6%) of patients with an IPFP score of five or more, having a likelihood of cure with ABVD
exceeding 65% and 5-y overall survival greater than 85% prognostic models based on clinical factors such as those used in the IPFP scoring system no longer have useful clinical relevance. We must search for a different approach to estimating risk.

**Risk factors reflecting specific biologic characteristics**

Risk factor assessment systems for cancer based on global clinical factors and/or laboratory tests are fundamentally crude in that they reflect a mix of intrinsic host factors, such as age, co-morbid conditions, sex and others, plus factors that primarily but not exclusively reflect tumor burden, such as largest mass size, stage, number of extranodal sites and constitutional symptoms. Even specific clinical laboratory tests such as hemoglobin level, lactate dehydrogenase level, serum albumin level, erythrocyte sedimentation rate or degree of peripheral blood lymphopenia blend tumor and patient characteristics obscuring the contribution of intrinsic tumor biology to disease behavior and treatment outcome. It is appealing to hope that examination of specific biologic characteristics of the malignant cells themselves may be more informative and less confusing to interpret. Additionally, identification of factors unique to malignant cells may provide attractive specific targets for therapeutic intervention that promise to improve the therapeutic index of treatment by concentrating the treatment effect on the malignant cells and sparing normal cells.

A large and steadily growing number of variously specific biologic characteristics of Hodgkin lymphoma (biomarkers) have been identified with apparent impact on risk (Table 5).(61-88) These biomarkers are of several types: antigens expressed on the Hodgkin Reed-Sternberg cells; antigens expressed on circulating lymphocytes; antigens
expressed on microenvironmental cells within the tumor and associated biologically with the Hodgkin Reed-Sternberg cells; presence of Epstein-Barr virus in the Hodgkin Reed-Sternberg cells; circulating biomarkers detectable in the serum; specific gene expression and microRNA profiles obtained by analysis of biopsied tumors; and specific germline polymorphisms. All are of interest; however, different subsets are relevant to risk assessment for clinical management in different ways. Increased expression of antigens expressed by Hodgkin Reed-Sternberg cells, including aberrant T-cell antigens, FOXP3, CD20, BCL-XL and p53 and loss of HLA class II markers can be assessed at the time of diagnosis and may predict a worse outcome. In most, but not all, studies that have focused on their presence, increased numbers of macrophages within the tumor microenvironment measured by various immunohistochemical markers, especially CD68 and CD163, reproducibly identified patients with higher risk of relapse and higher risk of eventual death from Hodgkin lymphoma. Elevated levels of specific serum biomarkers, including TARC (thymus and activation-regulated chemokine), galectin-1, CD163, IL-10, IL-10 receptor, IL-6, CD30, TNF (tumor necrosis factor), TNF receptor, CD4, CD8, CD25 and CD54 have been reported to be associated with a worse prognosis. A polygene gene expression profile including approximately 15 genes performed on tumor biopsies and, therefore, primarily reflecting microenvironmental cells, appears to identify a subset of Hodgkin lymphoma patients with a markedly higher risk of treatment resistance.(62, 69) Finally, certain germline polymorphisms of IL-10, IL-6 and NPAT may be associated with poorer prognosis (IL-10 and IL-6) or risk of development of nodular lymphocyte predominant Hodgkin lymphoma (NPAT).(71) Several challenges arise, however, as we try to turn these interesting biological observations into clinically relevant biomarkers.
Most problematic is the lack of wide validation of the significance of these biomarkers, which have typically only been demonstrated in small series of selected patients and have not been reproducibly shown to be significant in multiple independent series of patients. Additionally, many of these biomarkers, especially those detected in serum or those expressed as surface markers on Hodgkin Reed-Sternberg cells, are not independent in their impact on prognosis. Rather, they travel together such that elevated levels or elevated expression of one is often associated with elevation of several others.

Although there remain challenges due to lack of validation and/or cross-association among the many potentially important biomarkers for increased risk of treatment resistance in Hodgkin lymphoma, some of these biomarkers have emerged as more attractive candidates to signal higher risk. In particular, the increased presence of tissue infiltrating macrophages, whether measured by immunohistochemistry (66, 68, 70, 72) or implied by specific gene expression profiles (62, 69) appears to be a reproducible and powerful negative prognostic factor. Appropriately, the presence of increased numbers of tissue infiltrating macrophages is now being examined in prospective clinical trials to see if this finding can be sufficiently reproducibly demonstrated to justify its use to identify patients either for reduction of treatment because macrophage numbers are very low or escalation of treatment because they are very high. Certain serum markers also seem promising, especially serum TARC, galectin-1 and IL-10, because their prognostic impact has been validated independently (63-65, 73, 76, 78, 79) and because they can be readily measured not only at diagnosis, when their prognostic importance can be assessed, but also serially during treatment to determine if they can reliably identify patients whose treatment response is proving to be suboptimal. Finally, examining the
overall gene expression profile detectable in biopsied tissue involved with Hodgkin lymphoma, which necessarily profiles the gene expression of the host reactive cells and not the malignant Hodgkin Reed-Sternberg cells, appears capable of separating a minority (29%) of patients with six-fold worse prognosis from a majority (71%) with a much more favorable prognosis using modern chemotherapy.(62)

**Risk factors that become recognizable during treatment**

Treatment of Hodgkin lymphoma is typically delivered over several months and treatment of advanced stage disease often takes at least six to eight months to complete. It is, therefore, attractive to try to identify risk factors during treatment that signal a higher likelihood that treatment will fail so that a change in or addition to treatment can be considered. Attempts to find such an assessable factor in the past have proven unreliable. Speed of response has been assessed with the hope that rapid responders would do well and that a change in treatment plan would improve outcome for slow responders but this has not proven reliable. Quality of response early in the delivery of multiple cycles of chemotherapy is conceptually similar and is discussed below. Finally, the absence of a complete response at the end of planned chemotherapy may identify patients with higher risk of relapse. Unfortunately, in the past response assessment relying on such techniques as gallium, magnetic resonance and even computed tomographic (CT) imaging has run afoul of the tendency of Hodgkin lymphoma to be associated with residual, sometimes large, fibronecrotic masses even when viable tumor cells have been eradicated. Thus, slow or incomplete response, as previously measured with historically available imaging techniques, has not reliably identified poor prognosis patients nor has intensification of
chemotherapy dosing or addition of radiation based on speed or quality of response proven effective at reducing treatment failures.(89-96) This situation may now be changing, however, with the wide availability of functional imaging using fluorodeoxyglucose positron emission tomography (PET). Further complicating interpretation of the available literature is the possibility that PET during treatment, so-called interim PET, may have different usefulness in the management of limited stage Hodgkin lymphoma compared to advanced stage disease.

**Interim PET as a risk factor for limited stage Hodgkin lymphoma**

Current management of adults with limited stage Hodgkin lymphoma (stage IA or II A, non-bulky (< 10 cm greatest diameter), typically consisting of either brief chemotherapy followed by involved field or involved nodal radiation or only brief chemotherapy cures almost all patients and secondary treatment rescues many of those who relapse, virtually eliminating death from Hodgkin lymphoma in this population.(97, 98) For that reason the current focus of clinical research is on identifying subsets of patients with limited stage disease for whom treatment can be de-escalated without forfeiting effectiveness, perhaps by reducing the number of chemotherapy cycles or eliminating the radiation. Substantial consistency of results is apparent in the reported experiences employing interim PET after two to three cycles of ABVD for patients with limited stage Hodgkin lymphoma (Table 6).(99-102) Approximately 80 % to 85 % of patients reach a PET negative state after two to three cycles of ABVD and such patients have an approximately 90 % likelihood of remaining free of relapse even if radiation is omitted from their management. Thus, patients with a negative PET scan after two cycles
of ABVD are at low risk of treatment failure. The prognostic value of a positive PET scan is less clear because most investigators have chosen to change treatment modality based on it, switching to radiation (Table 8), leaving the PET scan's usefulness in indicating a need to use radiation and the scan's impact on risk unclear.

**Interim PET as a risk factor for advanced stage Hodgkin lymphoma**

The accuracy and usefulness of interim PET as a risk factor in patients with advanced stage Hodgkin lymphoma are considerably less clear than for limited stage patients. ABVD is the only multi-agent chemotherapy program for which interim PET has been evaluated extensively. Table 7 shows the outcome for patients treated with ABVD for advanced stage Hodgkin lymphoma comparing results for those with an interim positive PET during chemotherapy with those whose PET had become negative. A negative interim PET is found in approximately 80% of patients and appears to be strongly predictive for a favorable outcome. In addition, a negative interim PET appears to override or at least rival the prognostic impact of the IPFP score. However, for the approximately 20% of patients with a positive interim PET, the positive PET’s impact is much less clear even if the chemotherapy regimen is not altered. Reported failure free survivals range from zero to almost 40%. (Table 7) Furthermore, it remains quite unclear if the negative prognostic impact of a positive interim PET can be overcome by changing the treatment approach. Preliminary observations that a switch to escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) after a positive interim PET may as much as double 2- to 3-year failure free survival require confirmation. (106) Once again, similarly to its value in
limited stage Hodgkin lymphoma, the primary usefulness of an interim PET scan in the
assessment of patients with advanced stage Hodgkin lymphoma appears to be in
consistently identifying patients with a low risk of eventual treatment failure with strong
negative predictive impact after a negative interim PET; however, the usefulness of a
positive interim PET scan remains problematic with its value in assessing risk obscured
by the potential impact of altering treatment mid-way though management. Thus, in both
situations in which we can extract instructive observations, interim PET scan seems most
valuable for its ability to identify low risk of treatment failure and the value of a positive
interim PET scan remains undetermined.

Risk adapted treatment of Hodgkin lymphoma

The assessment of risk has three basic purposes in the management of serious disease
such as Hodgkin lymphoma. First, risk assessment establishes reasonable assumptions in
terms of prognosis, aligning the expectations of the patient, the patient’s family and the
treating physicians and often, especially in the case of Hodgkin lymphoma, providing
solid justification for optimism that the disease will be permanently eradicated. Second,
identification of some risks may suggest specific additions to or alterations of the
treatment plan that can meaningfully alter the risk of treatment failure. An example of
such a modifiable risk factor is coincident HIV infection, with the need to add markedly
enhanced supportive care and coincident highly active anti-retroviral therapy. Third,
isolation of risk factors based on specific biologic characteristics of the disease may
suggest avenues for the development of targeted therapy that can focus its impact
exclusively on the malignancy or the malignancy and the elements in the
microenvironment providing a growth advantage and avoid the negative impact of off-target toxicity, a characteristic all too often retained by conventional chemotherapeutic agents and radiation treatments. The clinical, biological and imaging-related risk factors described in this paper reach across this spectrum of purposes for assessing risk in Hodgkin lymphoma.
Acknowledgments

The author thanks his clinical colleagues at the British Columbia Cancer Agency and the physicians of British Columbia for their continued support and referral of patients; Ms Suman Singh for help with maintenance of the BC Cancer Agency Lymphoid Cancer Database.

Authorship

J. C. composed this entire article and has no relevant conflict of interest to declare.
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Table 1. Risk factors affecting outcome of treatment of patients with Hodgkin lymphoma that are intrinsic to the patient.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Frequency*</th>
<th>5-y OS**</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 45 y</td>
<td>34 %</td>
<td>96 % vs 77 %</td>
<td>&lt;0.0001</td>
<td>(27, 33, 38-42, 111-117)</td>
</tr>
<tr>
<td>Age &gt; 60 y</td>
<td>18 %</td>
<td>95 % vs 64 %</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 79 y</td>
<td>2 %</td>
<td>91 % vs 34 %</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>55 %</td>
<td>91 % vs 88 %</td>
<td>0.018</td>
<td>(27, 33, 39-42)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.2 %</td>
<td>89 % vs 41 %</td>
<td>&lt;0.0001</td>
<td>(16, 17, 20-27)</td>
</tr>
<tr>
<td>Prior reduced lung function, major</td>
<td>5 % to 10 %</td>
<td>##</td>
<td>not applicable</td>
<td></td>
</tr>
<tr>
<td>Prior reduced cardiac function</td>
<td>5 % to 10 %</td>
<td>##</td>
<td>not applicable</td>
<td></td>
</tr>
</tbody>
</table>

* Frequency with which the risk factor was encountered and **single variable impact (5-y overall survival (OS) %, absent vs present) in a large sample (n = 1443) of consecutively diagnosed, unselected patients with Hodgkin lymphoma in British Columbia between 1998 and 2013; note, a steady improvement in overall survival has occurred across this time interval

## Presence reduces overall survival by approximately 20 % (hazard rate for overall survival approximately 0.75)

HIV, human immunodeficiency virus
Table 2. Prognostic factors with independent impact on outcome for patients with advanced stage Hodgkin lymphoma identified in the International Prognostic Factors Project.(42)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 44 y</td>
<td>21 %</td>
</tr>
<tr>
<td>Sex</td>
<td>male</td>
<td>61 %</td>
</tr>
<tr>
<td>Stage</td>
<td>IV</td>
<td>42 %</td>
</tr>
<tr>
<td>Albumin, serum (g/L)</td>
<td>&lt; 40</td>
<td>35 %</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>&lt; 105</td>
<td>~ 20 %*</td>
</tr>
<tr>
<td>White blood cell count (WBC)</td>
<td>&gt; 15</td>
<td>19 %</td>
</tr>
<tr>
<td>Lymphocyte count x 10^9/L</td>
<td>&lt; 0.6 or &lt; 8 % of total WBC</td>
<td>21 %</td>
</tr>
</tbody>
</table>

* estimated from primary publication
Table 3. Improvement in 5-y overall survival after primary treatment with ABVD or equivalent chemotherapy for advanced stage Hodgkin lymphoma seen in serial major international clinical trials and large single institution series over treatment eras from the late 1980s to the 2000s.

<table>
<thead>
<tr>
<th>5-y OS %</th>
<th>Year of publication</th>
<th>First author</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>73</td>
<td>1992</td>
<td>Canellos</td>
<td>(45)</td>
</tr>
<tr>
<td>78</td>
<td>1998</td>
<td>Hasenclever</td>
<td>(42)</td>
</tr>
<tr>
<td>82</td>
<td>2003</td>
<td>Duggan</td>
<td>(46)</td>
</tr>
<tr>
<td>83</td>
<td>2003</td>
<td>Diehl</td>
<td>(118)</td>
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<td>86</td>
<td>2008</td>
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<td>(119)</td>
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<td>84</td>
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<td>Federico</td>
<td>(6)</td>
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<td>Hoskin</td>
<td>(5)</td>
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<tr>
<td>91</td>
<td>2012</td>
<td>Moccia</td>
<td>(7)</td>
</tr>
<tr>
<td>88</td>
<td>2013</td>
<td>Gordon</td>
<td>(1)</td>
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</table>
Table 4. 5-y freedom-from-progression (5-y FFP) and 5-y overall survival (5-y OS) according to International Prognostic Factor Project scores comparing the results seen in 579 consecutive patients treated with ABVD for advanced stage Hodgkin lymphoma at the British Columbia Cancer Agency with the projected outcome seen in patients included in the International Prognostic Factor Project.

<table>
<thead>
<tr>
<th>IPFP score</th>
<th>Number of patients (%)</th>
<th>5-y FFP (%) BCCA</th>
<th>5-y FFP (%) IPFP report</th>
<th>5-y OS (%) BCCA</th>
<th>5-y OS (%) IPFP report</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48 (8.3)</td>
<td>83±6</td>
<td>84±4</td>
<td>98±2</td>
<td>89±2</td>
</tr>
<tr>
<td>1</td>
<td>166 (28.7)</td>
<td>86±3</td>
<td>77±3</td>
<td>97±2</td>
<td>90±2</td>
</tr>
<tr>
<td>2</td>
<td>157 (27.1)</td>
<td>80±3</td>
<td>67±2</td>
<td>92±2</td>
<td>81±2</td>
</tr>
<tr>
<td>3</td>
<td>109 (18.8)</td>
<td>74±4</td>
<td>60±3</td>
<td>87±4</td>
<td>78±3</td>
</tr>
<tr>
<td>4</td>
<td>62 (10.7)</td>
<td>67±6</td>
<td>51±4</td>
<td>85±5</td>
<td>61±4</td>
</tr>
<tr>
<td>≥5</td>
<td>37 (6.4)</td>
<td>66±8</td>
<td>42±5</td>
<td>74±8</td>
<td>56±5</td>
</tr>
<tr>
<td>Ref</td>
<td>(7)</td>
<td>(42)</td>
<td>(7)</td>
<td>(42)</td>
<td></td>
</tr>
</tbody>
</table>

Ref, reference
Table 5. Biomarkers with potential impact on outcome in patients treated for Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment of Hodgkin-Reed Sternberg cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aberrant T-cell antigen expression, IHC/HRS</td>
<td>negative</td>
<td>(61)</td>
</tr>
<tr>
<td>FOXP3 expression, IHC/HRS</td>
<td>negative</td>
<td>(66)</td>
</tr>
<tr>
<td>CD20 expression, IHC/HRS</td>
<td>negative</td>
<td>(66)</td>
</tr>
<tr>
<td>BCL-XL, IHC/HRS</td>
<td>negative</td>
<td>(77)</td>
</tr>
<tr>
<td>p53, IHC/HRS</td>
<td>negative</td>
<td>(77)</td>
</tr>
<tr>
<td>HLA class II, IHC/HRS, loss</td>
<td>negative</td>
<td>(75)</td>
</tr>
<tr>
<td>presence of Epstein-Barr virus (EBV)</td>
<td>negative</td>
<td>(82-86)</td>
</tr>
</tbody>
</table>

| Assessment of microenvironmental or circulating non-neoplastic cells, cytokines and membrane associated antigens |                     |           |
| fibroblast growth factor 2, IHC/circ                                   | negative            | (67)      |
| syndecan-1, IHC/circ                                                   | negative            | (67)      |
| tumor-associated macrophages, IHC/TM                                   | negative            | (68, 70, 72, 87, 88) |
| CD68 expression, IHC/TM                                                | negative            | (66)      |
| serum TARC, elevated                                                   | negative            | (63, 65)  |
| serum galectin-1, elevated                                             | negative            | (64, 79)  |
| serum CD163, elevated                                                  | negative            | (65)      |
| serum IL-10, elevated                                                  | negative            | (73, 76, 78) |
| serum IL-10 receptor, elevated                                         | negative            | (76)      |
| serum IL-6, elevated                                                   | negative            | (76)      |
| serum CD30, elevated                                                   | negative            | (76, 78)  |
| serum tumor necrosis factor (TNF), elevated                            | negative            | (76)      |
| serum TNF receptor, elevated                                           | negative            | (76)      |
| serum CD4, elevated                                                    | negative            | (78)      |
| serum CD8, elevated                                                    | negative            | (78)      |
| serum CD25, elevated                                                   | negative            | (78)      |
| serum CD54, elevated                                                   | negative            | (78)      |

| Gene expression and miRNA profiling reflecting the tumor microenvironment |                     |           |
| gene expression profiling                                              | positive or negative | (62, 69) |
| Global microRNA levels including MIR21, MIR30E, MIR30D and MIR92B       | positive or negative | (80, 81) |

| Host germline polymorphisms and mutations                               |                     |           |
| *IL-10* specific polymorphism 592AA                                     | negative            | (74)      |
| *IL-6* specific polymorphism 174GG                                      | negative            | (74)      |
| germline NPAT mutation                                                  | marker for risk of nodular lymphocyte predominant Hodgkin lymphoma | (71)      |
IHC/HRS, present by immunohistochemistry on tumor Hodgkin Reed-Sternberg cells; IHC/circ, present by immunohistochemistry on circulating peripheral blood CD30 positive cells; IHC/TM, present by immunohistochemistry on tumor microenvironment cells; TARC, thymus and activation-regulated chemokine
Table 6. Selected large studies reporting interim fluorodeoxyglucose positron emission tomography (PET) results in patients with limited stage Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>n</th>
<th>Chemotherapy</th>
<th>Cycles of chemotherapy</th>
<th>PET negative</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>571</td>
<td>ABVD</td>
<td>3</td>
<td>426</td>
<td>75 %</td>
</tr>
<tr>
<td>441</td>
<td>ABVD</td>
<td>2</td>
<td>381</td>
<td>86 %</td>
</tr>
<tr>
<td>221</td>
<td>ABVD</td>
<td>2</td>
<td>183</td>
<td>83 %</td>
</tr>
<tr>
<td>80</td>
<td>ABVD</td>
<td>2 - 4</td>
<td>70</td>
<td>87 %</td>
</tr>
</tbody>
</table>

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine
Table 7. Selected large studies reporting interim fluorodeoxyglucose positron emission tomography (PET) results in patients treated with six to eight cycles of ABVD for advanced stage Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>n</th>
<th>Cycles of chemotherapy before PET</th>
<th>Outcome by PET result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PET negative</td>
<td>PET positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>FFS % (years)</td>
</tr>
<tr>
<td>260</td>
<td>2</td>
<td>215 (83)</td>
<td>95 (3y)</td>
</tr>
<tr>
<td>260</td>
<td>2</td>
<td>210 (81)</td>
<td>95 (2y)</td>
</tr>
<tr>
<td>160</td>
<td>2</td>
<td>137 (86)</td>
<td>92 (2y)</td>
</tr>
<tr>
<td>77</td>
<td>2</td>
<td>61 (79)</td>
<td>96 (2y)</td>
</tr>
<tr>
<td>91</td>
<td>2</td>
<td>77 (85)</td>
<td>73 (3y)</td>
</tr>
</tbody>
</table>

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; FFS, failure free survival

** PET positive outcome not interpretable due to change in chemotherapy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Frequency</th>
<th>Effective interventions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced pulmonary function, major</td>
<td>~ 5 % to 10 %</td>
<td>omit bleomycin</td>
<td>(120, 121)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 50 %</td>
<td>~ 5 % to 10 %</td>
<td>omit doxorubicin; consider substitution with etoposide</td>
<td><a href="http://www.bccancer.bc.ca/NR/rdonlyres/30FDD508-96AC-4555-B682-294EA3635B06/71473/LYABVD_Protocol_1A">http://www.bccancer.bc.ca/NR/rdonlyres/30FDD508-96AC-4555-B682-294EA3635B06/71473/LYABVD_Protocol_1A</a> ug2014.pdf</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.2 %*</td>
<td>vigorous supportive care with appropriate antibiotics and neutrophil growth factors</td>
<td>(16, 17, 20-27)</td>
</tr>
<tr>
<td>Positive interim PET scan, limited stage disease</td>
<td>15 % - 20 %</td>
<td>involved field or involved nodal radiation</td>
<td>(99-102)</td>
</tr>
</tbody>
</table>

* Frequency with which the risk factor was encountered in a large sample (n = 1443) of consecutively diagnosed, unselected patients with Hodgkin lymphoma in British Columbia between 1998 and 2013.

HIV, human immunodeficiency virus
Figure 1. Complex interaction affecting risk of treatment failure for patients with newly diagnosed Hodgkin lymphoma. Green arrows show how the malignant Hodgkin Reed-Sternberg cells interact with pre-existing host factors including cancer predisposition, pharmacogenetics and acquired organ dysfunction, each of which may enhance malignant cell survival or interfere with effective treatment delivery. In addition the Hodgkin Reed-Sternberg cells manipulate cells in their micro-environment inducing release of growth enhancing and immune suppressing cytokines. Treatment (red arrows) reduces the risk of treatment failure by exerting direct cytotoxicity on the Hodgkin Reed-Sternberg cells, by interrupting the stimulation of tumor cell growth encouraged by micro-environmental cells and by restoring an effective immune response. Treatment effectiveness is modulated (orange arrow) by host factors with some (e.g. good performance status, young age) increasing host tolerance for higher dose treatment and therefore effectiveness and others (e.g. organ dysfunction, coincident HIV infection) diminishing treatment effectiveness.

Figure 2. Time to progression for 675 consecutive adult patients with advanced stage Hodgkin lymphoma treated with ABVD or equivalent chemotherapy at BCCA through 2009 by International Prognostic Factor Project score: Score 0, black solid n = 57; score 1, purple dashed, n = 185; score 2, green solid, n = 186; score 3, gray solid, n = 133; score 4, blue solid, n = 76; score 5-7, green, solid, n = 38.
Figure 2

Hodgkin lymphoma outcome
By IPFP score

Cum Survival

Time to progression (y)
Risk assessment in the management of newly diagnosed classical Hodgkin lymphoma

Joseph M. Connors