Staging Laparotomy in the Management of Hodgkin’s Disease: Is it Still Necessary?

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ABSTRACT
Approximately 3,500 cases of stage I and II Hodgkin’s disease are diagnosed each year in the United States. Traditionally, those patients who are considered candidates for primary radiation therapy undergo staging laparotomy (pathologic staging) to rule out definitively the presence of occult subdiaphragmatic disease. An appreciation of the risks of laparotomy and a recognition of the effectiveness of salvage chemotherapy in patients who fail primary radiation therapy have permitted the increased use of clinical staging as the basis for treatment of these patients. This article summarizes the literature regarding the need for staging laparotomy in early stage Hodgkin’s disease and suggests alternative approaches to the management of these patients based on clinical criteria and prognostic factors.

INTRODUCTION
Advances in the treatment of Hodgkin’s disease have transformed a once fatal disease into a highly curable one. At present, virtually all patients given the diagnosis of Hodgkin’s disease have a chance for cure, with at least 75% of newly diagnosed patients expecting long-term survival [1]. As the cure rate for Hodgkin’s disease improves, the implications of long-term complications of therapy become a paramount consideration in making therapeutic decisions. Disease stage remains the principle determinant of therapy [2], with early stage patients (I-II) treated primarily with radiotherapy and advanced stage patients (III-IV) receiving combination chemotherapy or combined-modality therapy. This discussion will focus on early stage disease, which comprises about 40%-50% of all new Hodgkin’s disease cases, or about 3,000-4,000 expected patients in 1996 [3].

Controversy exists regarding the proper staging and management approach to this cohort of patients. Traditionally, these patients undergo staging laparotomy to define precisely any subdiaphragmatic involvement by Hodgkin’s disease, and decisions to proceed with initial radiation therapy or chemotherapy are based on these results. Recent data indicate that the majority of patients with early stage disease who relapse after primary radiation can be effectively salvaged with chemotherapy, suggesting that the decision to proceed with primary radiation therapy need not be made on the basis of pathologic criteria. In addition, staging laparotomy, radiation therapy and chemotherapy all have side effects that need to be considered in the selection of therapy. This review will consider whether surgical staging retains a valid role in the evaluation of early stage patients, or whether pathologic staging may be supplanted by an enhanced appreciation of the merits of clinical staging.

INITIAL EVALUATION OF PATIENTS WITH HODGKIN’S DISEASE
Clinicians have been grappling with Hodgkin’s disease since Thomas Hodgkin published his paper “On Some Morbid Appearances of the Absorbent Glands and Spleen” in 1832 [4]. Only in the last half-century were biologic aspects of the disease elucidated, with the realization that Hodgkin’s disease almost always arises in the lymph nodes and spreads along contiguous lymph node chains. As such, the most likely sites of microscopic disease spread are in anatomically adjacent sites [1, 5]. Since radiotherapy to visibly involved sites causes tumor regression, broadening the treatment field should provide more effective therapy [6].

As a result, determining the extent of tumor involvement becomes critical in deciding which patients can be treated with radiation therapy alone and which require systemic chemotherapy. As most Hodgkin’s disease cases present above the diaphragm (fewer than 10% of patients present with...
disease confined to subdiaphragmatic sites [7, 8]), defining the extent of disease below the diaphragm ordinarily determines which patients have localized disease. In the late 1960s, staging laparotomy with splenectomy, wedge liver biopsy and para-aortic lymph node sampling was introduced as the standard method of acquiring this information [9, 10]. In step with this advance in cancer detection came refinements in staging, with the introduction of the Ann Arbor staging system [11]. This system incorporated the finding that splenic involvement could be determined reliably only via surgical exploration of the abdomen and pathologic examination of the spleen. A corollary to this assertion was the introduction of a second stage, the “pathologic stage,” determined only after laparotomy [12, 13]. A modification to the Ann Arbor staging system was proposed after it became clear that distinctions were required beyond the anatomic distribution of disease. The Cotswolds classification added the variable of tumor bulk, particularly massive mediastinal involvement, a finding that warranted the use of chemotherapy in addition to radiation therapy despite otherwise apparent early stage disease, thus creating the term “unfavorable” early stage disease [12]. Large mediastinal adenopathy became one of many such aspects of presentation, ranging from symptoms to laboratory findings to histology, bearing important prognostic information.

Modern staging methods attempt to generate a detailed risk profile for a patient to determine the extent of disease, and the presence or absence of adverse prognostic factors predictive of a greater relapse risk. An appropriate goal during the initial evaluation should be to search for valid reasons to include chemotherapy in the treatment program, since radiation therapy alone succeeds only in properly selected patients [14]. If the decision is made early to proceed with chemotherapy, then the rationale for the use of staging laparotomy effectively vanishes. Caution must persist regarding the inappropriate use of chemotherapy, since there are both short- and long-term side effects of therapy, and since its initial use may undermine the subsequent use of chemotherapy in the event of relapse [15, 16].

The initial evaluation includes a thorough history, physical examination and radiologic evaluation, beginning with the chest radiograph [12]. Chest computerized tomography (CT) demonstrates new disease as well as disproves suspected disease in a significant number of patients with abnormal chest radiographs, especially in the regions of the hilar and subcarinal nodes, and in extranodal areas including the chest wall, pleura and pericardium. These latter extranodal areas appear to portend higher local relapse rates and thus warrant the use of initial chemotherapy in the treatment program [17].

Gallium scanning also has been utilized in the evaluation of disease stage [18, 19]. This radionuclide study has a low sensitivity when used in untreated patients (64%), but a high specificity (98%). Thus, a positive study is highly predictive of active disease, but a negative study is not definitive. Both chest CT and gallium scanning have been employed to assess mediastinal disease, at initial presentation and in follow-up [18-22]. Radiographic abnormalities of the mediastinum may persist in greater than two-thirds of patients post-therapy, especially those with initial bulky mediastinal disease. This finding may be accepted as indicating a complete response with residual fibrotic tissue, provided that a negative gallium scan is obtained. This represents one of the few instances where the sensitivity of gallium scanning is relatively high [18, 23, 24].

Lymphangiography also was once included in the initial workup, but few centers still practice this technique, instead relying on abdominal CT as the modality of choice to assess disease below the diaphragm. Lymphangiography excels at excluding tumor involvement of the para-aortic and iliac nodal regions because it can detect architectural abnormalities within normal-sized lymph nodes [25]. Reported figures for sensitivity in these nodal regions range from 80% to 85%, and for specificity from 91% to 100%. Lymphangiography is much less accurate at identifying pathology of the spleen or the splenic hilar, mesenteric and upper retroperitoneal lymph node regions (those superior to the renal vessels) in comparison to CT [25-27]. Abdominal CT better identifies disease involving the splenic, portal, mesenteric and superior retroperitoneal lymph node regions, albeit with a low sensitivity. Its sensitivity for identifying splenic and liver involvement is on the order of 15%-20% [1, 25, 28, 29]. Despite some utility, the discomfort and the risk of potential complications of lymphangiography have caused its use to decline, and abdominal CT scanning has become the default imaging modality.

After a thorough history, physical examination and chest radiograph, 80%-90% of patients will be clinical stage I-II (CS I-II) [27]. Following further radiographic studies, about 30% of these patients will be upstaged [1]. After complete pathologic staging with laparotomy, an additional 25%-30% will have advanced stage disease, thus leaving only 40%-50% of the original cohort with pathologic early stage disease [1, 25, 27, 30-37].

**THE ROLE OF STAGING LAPAROTOMY IN HODGKIN’S DISEASE**

Staging laparotomy remains the gold standard for evaluating microscopic disease in the abdomen, including the spleen and liver [33]. From its introduction, staging laparotomy was intended only for patients in whom radiation therapy potentially could be the sole therapeutic modality [13]. Surgical staging allows treatment to be chosen with specific knowledge regarding the extent of disease [27]. Patients
who prove to have pathologic early stage disease in the absence of bulky mediastinal adenopathy may be treated safely with radiation alone with an anticipated disease-free survival (DFS) of greater than 75% for pathologic stage IA and IIA (PS IA-IIA) disease [38-44]. Furthermore, pathologic staging may permit the use of smaller radiation fields. In a group of patients with pathologic early stage disease and other favorable prognostic factors (such as young age or nodular sclerosis or lymphocyte predominant histology), mantle field irradiation alone may be sufficient [14, 40, 45, 46]. In those patients who still require subdiaphragmatic irradiation after laparotomy, splenectomy allows delivery of a smaller dose to the abdomen without jeopardizing the left kidney and lung base [6, 9, 10, 47].

Despite these attractive advantages, compelling reasons exist to avoid surgical staging (Table 1). A laparotomy delays by at least two to three weeks the implementation of therapy, as the patient recuperates after a five- to seven-day hospitalization. While laparoscopic splenectomy may shorten the recuperative period, this procedure does not afford the full nodal examination that can be obtained with the open procedure [48-52]. Staging laparotomy has associated morbidity and mortality. Published mortality rates range from 0.3% to 1%, but should not represent a major concern at most centers [27, 33, 34]. Morbidity poses the greater threat. Major complications include cardiac arrest, wound infection or dehiscence, postoperative hemorrhage, subphrenic abscess, pulmonary embolism, pneumonia, sepsis and small bowel obstruction from adhesions. Minor complications include postoperative atelectasis, urinary tract infections, urinary retention and prolonged ileus. Published incidence rates for major complications range from 3% to 18% and for minor complications, from 6% to 19% [27, 33-36, 53, 54]. The higher figures tend to come from older published series. Nevertheless, further therapy delay occurs in 5%-10% of patients due to one or more of these complications.

In addition, the loss of the spleen carries its own lifetime risks. Foremost among these is the risk of overwhelming sepsis from encapsulated bacteria, with a case fatality rate as high as 20%-30%. Published series place the risk of bacterial sepsis at anywhere from 1.5% to 9% [34, 55, 56]. The higher risk is present in children, especially in those undergoing splenectomy prior to age ten, and in all patients undergoing aggressive chemotherapy with or without radiation [56]. The routine use of bacterial polysaccharide vaccines may curtail this risk, although vaccination needs to be performed before chemotherapy commences and, ideally, prior to splenectomy. Unfortunately, antibody levels tend to fall rapidly after therapy begins, which is the time of highest risk [57]. Routine antibiotic prophylaxis with penicillins or cephalosporins has been advocated to reduce the risk of sepsis with encapsulated organisms [54, 58-60]. Finally, recent literature suggests that splenectomy is associated with a greater lifetime risk of leukemia (relative risk 2-3.6) [61, 62].

Because pathologic staging incurs so many risks, and yet provides valuable information about treatment choice, the major current controversy in Hodgkin’s disease management involves the selection of patients who can avoid staging laparotomy without jeopardizing outcome. These patients would either be at such low risk of abdominal disease as not to justify the risks of exploratory laparotomy or at such high risk of abdominal involvement, or in need of systemic chemotherapy because of disease-related prognostic factors, that surgical staging also would do little to influence treatment.

**Clinical Management of Early Stage Hodgkin’s Disease**

Many investigators have sought to define groups of early stage patients for whom the results of staging laparotomy will not alter management. For example, patients with large mediastinal adenopathy, even if they have otherwise pathologic early stage disease, comprise a separate category of patients with higher relapse rates [63]. To distinguish these patients from the 60% or more of patients who will have some degree of mediastinal involvement at presentation [5, 64], many discriminant functions were developed, but the one used most commonly is the mediastinal-thoracic (MT)

<table>
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<th>Table 1. Potential risks and benefits of staging laparotomy</th>
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<tr>
<td><strong>Pro</strong></td>
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<td>More accurate staging</td>
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<td>Avoidance of chemotherapy if possible</td>
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<tr>
<td>Possibility of mantle radiation therapy alone for PS IA-IIIA disease</td>
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<tr>
<td>Appropriate use of chemotherapy for patients upstaged to advanced stage disease</td>
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<tr>
<td>Surgical minor morbidity (6%-19%):</td>
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<tr>
<td>• postoperative atelectasis</td>
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<tr>
<td>• urinary tract infection</td>
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<td>• urinary retention</td>
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<td>• prolonged ileus</td>
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ratio, a ratio between the largest transverse diameter of the mediastinal mass and the transverse diameter of the thorax at T5-6 on a standard standing postero-anterior chest radiograph [65]. Those patients with a ratio greater than 0.35, comprising 15%-20% of pathologic early stage patients [63, 65-67], have DFS rates ranging from 39%-55%, compared to 72%-92% for patients with smaller or no mediastinal involvement when treated with extended field (mantle and para-aortic fields) radiotherapy alone [38, 64-75]. Of note, most relapses in these patients are intrathoracic failures [38, 63-68, 70]. The addition of chemotherapy to the initial treatment regimen significantly decreases relapse risk, increasing the DFS rate from 73% to 92%. Overall survival (OS) appears unchanged, except in one early study [65]. This discrepancy between improved DFS but not OS with initial combined-modality therapy has been attributed to the added toxicity of this approach, and the efficacy of salvage chemotherapy at inducing complete remission in radiation failures [38, 64, 66-71, 73, 74, 76]. Nevertheless, the high relapse rate with radiation alone has been considered unacceptable, and most authorities advocate initial treatment with combined-modality therapy, thereby obviating the need for surgical staging in patients with large mediastinal adenopathy [38, 77, 78].

Other investigators have also tried to describe other subgroups for whom treatment decisions could be made safely without the need for laparotomy. However, early attempts to identify these patients only proved the value of pathologic staging. In the “new series” of the Collaborative Clinical Trial, 117 CS and PS I-II patients without mediastinal disease were randomized to either involved field or extended field (including the upper abdomen) radiotherapy. Clinically staged patients treated with extended field therapy had a higher nine-year survival than those given limited field therapy (80% versus 56%, respectively), although this result did not reach statistical significance. In the pathologically staged patients, there was no significant difference in 10-year OS between those patients receiving extended field and limited field radiation (100% versus 93%, respectively), although there were significant differences in 10-year DFS (77% versus 44%, respectively). Of greater importance to this discussion is the finding that both pathologically staged groups had higher survival rates than the clinically staged group treated with extended field therapy [72]. Thus, even eliminating patients with mediastinal disease from consideration, pathologic staging appeared necessary to identify early stage patients who would do well with radiation therapy alone.

Several other studies have failed to show a difference in OS in patients who are clinically staged compared to those who are pathologically staged. A retrospective review from the Princess Margaret Hospital (PMH) compared its series of 780 CS IA-IIB and IIIA patients to a surgically staged cohort treated at Stanford over the same time period of 1968 to 1977. Both cohorts received radiation therapy alone. After 10 years of follow-up, relapse-free survival (RFS) was higher in the Stanford group (66.8%), compared to the PMH group (48.9%), although no difference was observed in OS [79].

The British National Lymphoma Investigation (BNLI) reported on 610 CS and PS IA-IIA patients, treated either with involved or regional field radiotherapy. Involved field radiotherapy consisted of 4000 cGy to the 5 cm margin around the involved nodes. Regional field therapy also included 3500 cGy to immediately adjacent areas such as the contralateral cervical region, ipsilateral axilla and mediastinum [80]. A report after nine years of follow-up showed a RFS of 53% for the group undergoing laparotomy and 37% for the clinically staged group, a statistically significant difference. No statistical differences were found in OS (88% versus 72%, respectively), although subgroup analysis did find a survival advantage with laparotomy in male patients over 45 years of age [81]. Another report was published after 12 years of follow-up. By this time no statistically significant differences were observed in RFS or OS [82]. This study suffered from a methodological flaw in that patients were not randomized prospectively to treatment arms based on clinical or pathologic staging. Field sizes also were small and inadequate by today’s standards, and regional fields comprised less area than a typical mantle field [80]. This would explain the overall lower DFS results compared to other studies [6]. Hence, in these three early reports, clinically staged patients appeared to fare relatively poorly, at least in early follow-up, when treated with radiation therapy alone.

The European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group has conducted several trials since 1964 in an attempt to define subgroups of patients who would do well with radiation therapy alone and to determine whether these patients could be identified clinically. These trials are summarized in Table 2. In an initial trial, EORTC-H1, 288 CS I-II patients were randomized prospectively to mantle (or inverted “Y”) radiotherapy (4000 cGy) with or without the addition of single agent chemotherapy, consisting of weekly vinblastine (10 mg for white count greater than 5000/mm$^3$; 5 mg for white count between 3000/mm$^3$ and 5000/mm$^3$). No prophylactic radiation was given to the other side of the diaphragm. Results showed a dismal 15-year DFS and OS for patients treated with radiotherapy alone (38% and 58%, respectively). The addition of single agent chemotherapy improved the DFS (60% at 15 years; $p < 0.001$), but OS remained unchanged (65% at 15 years; $p = 0.15$). Relapse rates in the para-aortic region were high, especially in those patients receiving radiotherapy alone [14, 83-85]. More aggressive initial
chemotherapy, more extensive radiation therapy or more aggressive staging practices obviously were needed in these clinically staged patients, as those patients who are PS I-II can be expected to fare much better with radiation therapy alone.

Subsequent EORTC trials began to provide evidence that clinical staging is not associated with inferior outcome. The EORTC-H2 trial examined more extensive radiotherapy techniques, addressing the questions of whether splenic irradiation could be substituted for splenectomy and whether splenectomy had prognostic significance. This trial involved 300 CS I-II patients with supradiaphragmatic disease. All patients received mantle and para-aortic radiation (40 Gy to mantle field, with an additional 5 Gy to slowly responding masses, and 40 Gy to para-aortic lymph nodes), and were randomized to receive splenectomy or splenic irradiation. Those patients with mixed-cellularity or lymphocyte-depleted histology also were randomized to receive chemotherapy with vinblastine (6 mg/m² for white count greater than 4000, 3 mg/m² for white count between 2000 and 4000) with or without procarbazine (150 mg/m²/day for white count greater than 4000 and platelet count greater than 150,000) [85, 86]. Subdiaphragmatic radiotherapy greatly improved DFS and OS, with no significant difference between radiated and surgically staged patients (DFS: 68% versus 76%, respectively; p = 0.18; OS: 77% versus 79%, respectively; p = 0.38). The 37 patients with a positive laparotomy (stage IIIA) out of the total 144 who underwent laparotomy had a higher relapse rate, especially in extranodal sites and non-irradiated areas. Their DFS was 56% at 12 years, compared to the patients with a negative laparotomy who had an 83% DFS. Importantly, no difference was seen in OS for this cohort because of the effectiveness of salvage chemotherapy [14, 85].

### Table 2: Treatment and outcomes in the major trials of clinical staging

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th># Patients</th>
<th>DFS (%) p</th>
<th>OS (%) p</th>
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<tbody>
<tr>
<td>Collaborative Clinical Trial [72]</td>
<td>CS IA-IIA involved field RT</td>
<td>21a</td>
<td>23</td>
<td>0.03</td>
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<tr>
<td></td>
<td>CS IA-IIA extended field RT</td>
<td>30</td>
<td>60</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>PS IA-IIA involved field RT</td>
<td>27</td>
<td>44</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>PS IA-IIA extended field RT</td>
<td>39</td>
<td>77</td>
<td>100</td>
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<tr>
<td>BNLI [82]</td>
<td>CS IA-IIA involved field RT</td>
<td>114</td>
<td>40</td>
<td>NS</td>
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<tr>
<td></td>
<td>CS IA-IIA extended field RT</td>
<td>95</td>
<td>42</td>
<td>NS</td>
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<tr>
<td></td>
<td>PS IA-IIA involved field RT</td>
<td>147</td>
<td>50</td>
<td>NS</td>
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<tr>
<td></td>
<td>PS IA-IIA extended field RT</td>
<td>181</td>
<td>48</td>
<td>NS</td>
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<tr>
<td>EORTC-H1 [14]</td>
<td>Mantle or Inverted Y RT + vinblastine</td>
<td>152</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RT + vinblastine</td>
<td>136</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>EORTC-H2 [14]</td>
<td>STNI ± CT, no laparotomy</td>
<td>156</td>
<td>68</td>
<td>NS</td>
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<tr>
<td></td>
<td>STNI ± CT, laparotomy</td>
<td>144</td>
<td>76</td>
<td>NS</td>
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<tr>
<td></td>
<td>positive laparotomy</td>
<td>37</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>negative laparotomy</td>
<td>107</td>
<td>83</td>
<td>&lt;0.001</td>
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<tr>
<td>EORTC-H5 [14]</td>
<td>Favorable (negative laparotomy)</td>
<td>100</td>
<td>69</td>
<td>NS</td>
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<tr>
<td></td>
<td>STNI</td>
<td>98</td>
<td>70</td>
<td>NS</td>
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<tr>
<td></td>
<td>Unfavorable (positive laparotomy or no laparotomy)</td>
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<tr>
<td></td>
<td>CMT</td>
<td>144</td>
<td>83</td>
<td>&lt;0.001</td>
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<td></td>
<td>TNI</td>
<td>152</td>
<td>66</td>
<td>NS</td>
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<tr>
<td>EORTC-H6 [14, 130]</td>
<td>Favorable</td>
<td></td>
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<tr>
<td></td>
<td>No laparotomy with STNI</td>
<td>118</td>
<td>80</td>
<td>NS</td>
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<tr>
<td></td>
<td>negative laparotomy with mantle RT</td>
<td>114</td>
<td>84</td>
<td>NS</td>
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<td>or positive laparotomy with CMT</td>
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<td></td>
<td>CMT with MOPP</td>
<td>139</td>
<td>79</td>
<td>0.02</td>
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<td></td>
<td>CMT with ABVD</td>
<td>126</td>
<td>90</td>
<td>NS</td>
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OS: Overall survival; DFS: Disease-free survival; RT: Radiation therapy; STNI: Subtotal nodal irradiation; TNI: Total nodal irradiation; CT: Combination chemotherapy; CMT: Combined modality therapy; NS: Not significant; aFigures given for new series patients only
Further extending these findings, several studies considered initial treatment with chemotherapy alone in patients with early stage disease. This approach, using MOPP or ChlVPP regimens, has proven successful in children with Hodgkin’s disease [87]. A 1991 study by the National Cancer Institute compared radiation therapy to MOPP chemotherapy in 136 patients with early stage disease (including stage II A1). After 7.5 years of median follow-up, when patients with massive mediastinal disease and stage III A1 disease were excluded, there were no significant differences in projected 10-year DFS (67% for radiation therapy versus 82% for MOPP), and OS (85% versus 90%, respectively) [88]. Other studies also showed early equivalency in DFS and OS when MOPP was compared to radiotherapy in early stage patients [16, 42, 43]. However, with longer follow-up, survival in the chemotherapy arm of these studies declined because of impaired survival in those patients who relapsed after receiving initial chemotherapy [16, 42, 43, 89]. Similar studies have compared initial combined-modality therapy to radiotherapy alone. In these studies, initial DFS favored combined-modality chemotherapy, but OS did not differ [82, 85, 90-96]. The radiation field sizes varied considerably in these studies, making it difficult to draw conclusions about whether adding chemotherapy permits treatment with smaller field sizes. Nevertheless, two studies do suggest that the addition of chemotherapy allows treatment with only supradiaphragmatic radiation and the omission of abdominal irradiation [17, 97].

A common finding in these studies is that differences in DFS usually do not lead to differences in OS. It is possible that follow-up has not been long enough or that trials have not been large enough to demonstrate small differences in OS [6]. More important is the observation that patients relapsing after radiotherapy alone achieve a second remission with salvage chemotherapy more easily than patients whose initial treatment included chemotherapy. After salvage chemotherapy, the latter group only achieves freedom from second relapse (FFSR) rates of 25%-38% after five years [15, 16, 42, 43, 93, 94, 98], compared to a 58% 10-year FFSR rate for the former group [99, 100]. Importantly, the cohort that does not relapse after radiation therapy alone is spared the potential short- and long-term toxicities of additional chemotherapy. These toxicities include a 2% to 6% 10- to 15-year risk of developing acute leukemia [6, 61, 62, 79, 93, 101-115], as well as infertility [116-118] and cardiac and pulmonary toxicity [119-123].

**Identification of Prognostic Factors in Clinically Staged Patients with Hodgkin’s Disease**

Based on the early trials, one could conclude that staging laparotomy allows one to make more accurate predictions of relapse risk for patients and allows therapy to be tailored accordingly. An alternative approach involves determining whether one can predict the results of laparotomy based on clinical factors alone. Many retrospective analyses have attempted to delineate clinical prognostic factors that may be used to identify patients at high and low risk for relapse, as well as those patients with a greater risk of harboring clinically occult subdiaphragmatic disease. Prospective trials have then been designed to test the value of these factors in determining appropriate therapy without surgical staging.

Factors found to be predictive of a positive staging laparotomy in clinically staged patients include the number of involved nodal sites, mixed-cellularity or lymphocyte-depleted histology, age, sex, and presence and number of B symptoms [10, 27, 30, 31, 33, 124]. Surprisingly, mediastinal involvement correlates with a significantly lower risk for occult abdominal disease [30]. Low-risk subgroups include CS IA females, and CS IA males with favorable histology (lymphocyte predominant of nodular sclerosis), who have a 5%-14% risk of a positive staging laparotomy [27, 30, 31, 33]. In contrast, high-risk groups include symptomatic males with unfavorable histology (mixed-cellularity or lymphocyte-depleted) or symptomatic males with more than four sites of involvement, with an expected positive laparotomy rate of 69% to 81%, or up to 93% if all these factors are present [30, 31]. This latter figure is so high that one could reasonably assume the presence of occult abdominal disease without surgical confirmation and include chemotherapy in the initial treatment plan.

Researchers also have sought to identify prognostic factors in clinically staged patients that would be predictive for relapse or survival (Table 3). Many factors that fail to predict for relapse or survival in pathologically staged patients may be important in clinically staged patients, because they relate to a patient’s risk for occult abdominal involvement [6]. These factors predictive for relapse and survival include male sex [14, 82, 125], age (usually greater than 40 to 50 years) [14, 82, 125-127], number of involved sites (usually greater than four) [14, 125, 127], unfavorable histology (mixed-cellularity or lymphocyte-depleted) [14, 70, 82, 126], and an elevated erythrocyte sedimentation rate (ESR) with or without systemic symptoms (e.g., ESR >30 with symptoms or >50 without symptoms) [14, 82, 125, 126, 128]. Two factors more predictive for relapse than for survival are treatment with involved field radiation alone [126] or presentation with massive mediastinal adenopathy [70, 127].

More detailed analyses of some of these factors derive from a consideration of pathologically staged patients. A retrospective analysis of data compiled from PS IB-IIB patients showed that patients with night sweats alone and no other B symptoms had a prognosis no different from PS IA-IIA patients. Fevers and weight loss were independent risk
factors for survival, and their presence together conferred a significantly worse freedom from relapse and survival compared to patients with only one of these symptoms [69, 129]. Assembling these clinical criteria for high, intermediate, and low-risk groups, large-scale trials have been conducted in an attempt to identify optimal treatment plans for the different groups. Several investigators have eliminated the practice of staging laparotomy. Instead, they delineate groups of clinically staged patients based on prospectively derived prognostic variables and tailor therapy based on the specific risk of relapse. Patients with favorable prognostic factors received radiotherapy (either mantle or extended field) alone, while all others received combined-modality therapy (chemotherapy with involved or regional radiation) [6, 14]. The early EORTC trials included surgical staging for certain subgroups, but other ongoing trials have eliminated surgical staging altogether [14, 85, 131].

The EORTC-H5 trial divided a cohort of 494 CS I-II patients without mediastinal involvement into two groups, labeled “favorable” and “unfavorable.” The favorable group consisted of patients aged less than 40 years with favorable histology and ESR <70. All favorable patients underwent laparotomy. Those that had a negative laparotomy were randomized between mantle or mantle and para-aortic radiation. Favorable patients with a positive laparotomy, as well as all unfavorable patients (who did not undergo laparotomy), were randomized between total nodal radiation or mantle radiation sandwiched between two sets of three cycles of MOPP chemotherapy [131].

Initially 237 patients were considered favorable, but 39 (16%) had positive laparotomies. The unfavorable group numbered 296 patients. Among the favorable group patients, there was no difference in DFS and OS between the mantle alone and extended field radiotherapy groups (DFS: 69% versus 70%; p > 0.50; OS: 94% versus 91%; p > 0.50) at nine years. In the unfavorable group, the patients in the combined-modality therapy arm fared much better with regard to DFS than those in the total-nodal irradiation group (DFS: 83% versus 66%; p < 0.001), and there was a trend toward greater OS, but this did not reach statistical significance at nine years (88% versus 73%; p = 0.06) [14, 131]. Of note is that those in the unfavorable group, comprising 52% of early clinical stage patients, were treated with excellent results without the use of surgical staging.

The EORTC-H6 trial built upon these findings, taking 497 CS I-II patients and again subdividing them into two groups, “favorable” and “unfavorable.” The favorable group consisted of patients with one or two involved lymph node regions, and either the combination of no symptoms and an ESR <50, or B symptoms and an ESR <30. This group then was randomized to undergo further surgical staging or no surgical staging. Those patients that were surgically staged and had a negative laparotomy received mantle radiotherapy alone if they had favorable histology, or extended field radiotherapy if they had unfavorable histology. Patients with a positive laparotomy were treated similarly to the unfavorable group of patients, as in the H5 trial, receiving combined-modality therapy (mantle irradiation sandwiched

### Table 3. Clinical prognostic factors in early stage Hodgkin’s disease

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<tr>
<td>Sex</td>
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<td>Survival</td>
<td>NS</td>
<td>Relapse Survival</td>
<td>NS</td>
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<tr>
<td>Age</td>
<td>≥50: Relapse Survival</td>
<td>Survival</td>
<td>≥45: Relapse Survival</td>
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<td>Number of involved sites</td>
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<td>Survival</td>
<td>≥3: Relapse</td>
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<td>ESR and/or B symptoms</td>
<td>Relapse Survival</td>
<td>B symptoms: NS</td>
<td>≥50 and A or ≥30 and B: Relapse</td>
<td>≥40: Relapse Survival</td>
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<td>Stage</td>
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<td>Large mediastinal involvement</td>
<td>Relapse Survival</td>
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<td>Involved field RT alone</td>
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Relapse: Indicates the study found the factor in question had a statistically significant impact on relapse risk
Survival: Indicates the study found the factor in question had a statistically significant impact on survival
NS: Indicates study found the factor in question did not have a statistically significant impact on survival or relapse risk
*Indicates study did not include the factor in question

Table 3: Clinical prognostic factors in early stage Hodgkin’s disease
between two sets of three cycles of either MOPP or ABVD). Those patients not undergoing laparotomy at all were treated with subtotal nodal irradiation, including mantle, para-aortic and splenic fields. The H2 trial had shown that splenic irradiation was equivalent to splenectomy for splenic disease.

The DFS was lower in the clinically staged group after four years of follow-up, but after six years, the difference was no longer statistically significant (80% versus 84%, respectively; \( p = 0.25 \)). OS did not differ (93% versus 89%, respectively; \( p = 0.24 \)), due to the effectiveness of salvage chemotherapy [14, 130]. These results show that in patients with a favorable risk profile, for whom one plans subtotal nodal irradiation alone, surgical staging can be avoided without jeopardizing DFS or OS. However, given that treatment-related toxicities, including secondary solid tumors, pulmonary toxicity and cardiotoxicity which may take greater than a decade to develop, OS figures remain subject to change.

An analysis of data pooled from all four EORTC trials that have been discussed attempted to refine the established prognostic groups. Patients in either the unfavorable subgroup or those who received chemotherapy as part of their initial treatment did not benefit clinically from the additional information obtained from staging laparotomy. The pooled data did demonstrate that the subset of patients in the favorable group with a positive laparotomy had a reduction in the risk of relapse by the addition of up-front chemotherapy, but further follow-up showed that the impact of initial chemotherapy on DFS did not translate into improved OS because of the efficacy of salvage chemotherapy [14].

A small subset of patients does exist for whom the initial inclusion of chemotherapy improves survival. This group consists of patients over 50 years of age, or between age 40 and 49 with four to five involved lymph node areas; or patients less than 40 years of age, who are male, have an elevated ESR, and have four or five involved lymph node areas. Their survival increases from 57% with radiation alone to 84% (with MOPP at 10 years) or 92% (with ABVD at four years), but this group only constitutes 11% of all CS I-II patients [14].

Similarly, there exists another small subset of patients of exceptionally favorable prognosis for whom mantle irradiation after a negative laparotomy, or subtotal nodal irradiation without surgical staging, promises excellent DFS and OS. This group contains those few CS I asymptomatic females with age less than 40, an ESR less than 50 and favorable histology. These patients constitute only 6% of all clinical early stage patients and can expect 10-year DFS rates of 83% to 89% with radiation alone, and OS rates of 83% to 100% [14].

**The Management of Early Stage Hodgkin’s Disease: Recent and On-Going Clinical Trials**

The vast middle ground of patients, who have neither an unfavorable nor a highly favorable diagnosis, continues to be the subject of debate regarding the need for surgical staging. In these patients, subtotal nodal irradiation can be delivered promptly with few acute toxicities and effective salvage can be administered if required. In contrast, initial combination chemotherapy reduces the risk of relapse at the expense of potential toxicity. The clinician’s and patient’s tolerances for relapse (in the absence of an impact on survival) will determine which patients will be placed in the unfavorable group, thereby receiving chemotherapy, and which patients will remain in the favorable group, receiving subtotal nodal radiation [14].

The goal of ongoing trials is to devise rational therapy for this middle ground. One option involves the identification of alternative chemotherapy regimens in an attempt to decrease toxicity by reducing exposure to alkylating agents, bleomycin and adriamycin. One such regimen is EBVP (epirubicin, bleomycin, vinblastine and prednisone), which has been proposed to have a lower side effect profile than MOPP and possibly ABVD [132-134]. The EORTC-H7 trial incorporated this regimen into its treatment of favorable and unfavorable patients. Because the trial has only been completed recently, few data have been published. Nevertheless, the trial design is revealing. A “very favorable” group was defined from data compiled from the previous EORTC trials. It consisted of asymptomatic CS I females younger than 40 years, with an ESR <50, favorable histology and an MT ratio less than 0.35. They would have an expected 10-year DFS of 53% and OS of 80% with radiation therapy without pathologic staging [14]. The “unfavorable” group consisted of patients with any one of the following characteristics: age greater than 50; either no symptoms with an ESR >50 or B symptoms with an ESR >30; CS II patients with more than four involved nodal areas; or MT ratio of greater than 0.35. These patients were randomized between six cycles of the hybrid regimen MOPP/ABV and six cycles of EBVP, with both arms followed by involved field radiotherapy. “Favorable” group patients (not meeting the very favorable or unfavorable criteria) were randomized between subtotal nodal irradiation and combined-modality therapy with six cycles of EBVP followed by involved field radiation.

Another novel chemotherapeutic regimen involves VBM (vinblastine, methotrexate and bleomycin). One study randomized PS IIA-IIB and IIIA patients to subtotal or total lymph node irradiation alone, or six cycles of VBM with involved field radiation. After approximately three years of median follow-up, the freedom from progression was higher in the VBM and involved field therapy group than in the radiation alone group (95% versus 70%, respectively), but this result was not yet statistically significant (\( p = 0.10 \)). The OS did not differ (100% versus 97%, respectively). The side effects of VBM, particularly the impact on fertility, appeared
decreased when compared to MOPP [135]. Although this trial did not address directly the utility of clinical staging, further development of the VBM regimen may prove useful.

The VBM regimen has been used also in a small uncontrolled trial conducted by the BNLI group involving 30 CS IA-IIA patients at intermediate risk of relapse (projected DFS of 55% and OS of 88% at five years). These patients had nodular sclerosis grade I histology and ESR >10; or grade II histology and ESR <60; or mixed-cellularity histology and a lymphocyte count less than 1500). Patients were treated with two cycles of VBM, then with involved field radiotherapy, followed by four additional cycles of VBM. Response rates were excellent, with 27 complete remissions, but pulmonary toxicity (14 patients symptomatic, seven reported severe functional limitation) and myelotoxicity (three episodes of neutropenic sepsis with one death) were observed, leading the BNLI to abandon this regimen in favor of a methotrexate, vinblastine and prednisolone combination [136].

Yet another alternative chemotherapy regimen under consideration is EVA (VP-16, adriamycin and vinblastine). The EVA regimen yielded a response rate of 73% in patients with previously treated, relapsed advanced stage Hodgkin’s disease, with a toxicity profile notable for myelosuppression and the absence of pulmonary toxicity [137]. The Cancer and Leukemia Group B (CALGB) completed a study in patients with CS IA-IIIB disease with large mediastinal adenopathy, PS IIb or IIIA, CS or PS IA-IIIA with two or more negative prognostic factors, or PS IB with one risk factor. All patients received three cycles of EVA followed by radiation therapy to mantle and para-aortic fields (with splenic irradiation). Results of this trial are awaited.

In a current Southwest Oncology Group (SWOG) and CALGB trial, patients with CS IA-IIIA disease are randomized to undergo therapy with subtotal nodal radiation (3600-4000 cGy) or three cycles of chemotherapy with doxorubicin and vinblastine followed by subtotal nodal radiation. The EORTC presently is conducting a randomized trial (EORTC-H8), which incorporates modifications of standard chemotherapy regimens into its treatment protocols. Patients in the “very favorable” group (CS I females with age <40, no symptoms with ESR <50, favorable histology and MT ratio less than 0.35) receive mantle radiation alone. Patients in the “unfavorable” group (age 50 or greater; or no symptoms and ESR >50; or B symptoms and ESR >30; or CS II with >4 involved nodal areas or MT ratio of 0.35 or greater) are randomized between three arms: six cycles of MOPP/ABV and involved field radiotherapy versus four cycles of MOPP/ABV, and involved field radiotherapy versus four cycles of MOPP/ABV and subtotal nodal irradiation. Patients in the “favorable” group (CS I-II patients not meeting criteria for either group) receive either subtotal nodal irradiation alone or three cycles of MOPP/ABV and involved field radiation. These newer trials will define further the optimal strategy for clinically staged patients.

**Recommendation for Management of CS I-II Patients**

We strongly recommend that early stage patients be referred for participation in ongoing clinical investigations targeted at devising an appropriate therapy for their disease. In the absence of availability of these trials, and as clinical data from earlier trials mature, one can derive several principles for the management of early stage Hodgkin’s disease. Based on the EORTC trials, a short list of prognostic factors can define two groups of clinically staged patients, those at very low risk and high risk of subdiaphragmatic disease or relapse, for whom therapeutic decisions require little deliberation. The latter group consists of patients over age 50, or younger patients with extensive lymph node involvement (including massive mediastinal involvement) or multiple B symptoms. This group, consisting of about 10%-20% of patients [14], merits either chemotherapy or combined-modality therapy, thereby obviating the need for staging laparotomy. Most, if not all, patients with clinical stage IIB disease can be treated rationally with up-front chemotherapy with or without consolidative radiotherapy based on the bulk of disease.

Similarly, a small group of patients, about 6%, consisting of CS I asymptomatic, young females with favorable histology and a low ESR can be treated with subtotal nodal irradiation alone. Conceivably, a negative staging laparotomy would permit an even smaller subset of these patients to be treated with mantle irradiation alone, but the risks of laparotomy may outweigh the risks of an expanded radiation field [40, 41]. Indeed, the EORTC-H7 and H8 trials will confirm whether mantle field radiotherapy can be used on the basis of clinical staging alone.

What should be the recommended therapeutic approach to the remaining 75% of patients with CS I-II disease? The simple answer would be to continue with surgical staging and offer chemotherapy to those patients with positive laparotomies, and subtotal nodal irradiation to those patients with negative laparotomies. Clinicians who favor continuing with surgical staging argue that the use of prognostic factors alone is sufficient only to identify the very high- and low-risk patients who definitely do or do not require chemotherapy as part of their initial management. They further argue that 80% of patients would receive chemotherapy, when at least half of these patients could be managed adequately with radiation therapy alone.

Nevertheless, the risks of surgical staging cannot be ignored. This conservative management strategy requires that the entire CS I-II cohort be subjected to the considerable
morbid risk and up to 1% mortality risk of exploratory laparotomy, even though more than two-thirds of the patients will derive no clinical benefit from its information. Again, the simplest approach would be to stage patients clinically and either give everyone combined-modality therapy to minimize relapse risk, or give every one subtotal nodal radiotherapy to preserve optimal salvage therapy options.

In the absence of laparotomy, the toxicities of the various therapies require careful examination. As has been discussed, chemotherapy, particularly with the MOPP regimen, has been associated with a 2% to 6% 10- to 15-year risk of developing acute leukemia [6, 61, 62, 79, 93, 101-115]. If preleukemic cytogenetic abnormalities are included, then the 10-year risk climbs to 13% [138]. The ABVD chemotherapy regimen appears to carry a much lower risk of secondary malignancy [114, 130, 139-141], but has the potential of long-term cardiac and pulmonary toxicity [119-123]. Chemotherapy also is associated with temporary or permanent infertility [116-118].

Also to be considered are the potential long-term side effects of radiation therapy. With extended follow-up, radiation therapy has been associated with second malignancies, specifically non-Hodgkin’s lymphoma (NHL) and solid tumors. The 10- to 15-year cumulative risk of developing NHL has been reported to be 2%-6%, and this risk does not plateau but appears to increase indefinitely [62, 102, 110, 111, 142-144]. The risk appears to be the same in those patients receiving radiotherapy and those receiving combined-modality therapy, although some studies have found the risk to be higher in the latter group [62, 143]. Likewise, there is an increased risk of solid tumors, with up to a 13% risk at 15 years after radiotherapy [111]. Lung cancer alone accounts for nearly half of this risk [62], but many other tumor types are also seen with increased frequency, such as head and neck tumors, breast cancer, soft tissue sarcomas, thyroid and GI malignancies [62, 102, 110, 111, 140, 142, 145-147].

Radiation therapy also has a potential impact on the subsequent development of coronary artery disease [108, 148, 149], and has been associated with pulmonary fibrosis [123, 150].

In addition to the untoward effects of laparotomy, radiation therapy and chemotherapy, other intangible factors require consideration as the treatment decision is made for a CS I-II patient. While some patients may be willing to tolerate an increased risk of relapse in order to avoid laparotomy and chemotherapy, other patients may have difficulty dealing emotionally with recurrent disease and may desire a more aggressive first-line approach at the cost of potential delayed toxicities of therapy.

Based on the data in this article, it is our opinion that the practicing clinician can safely avoid recommending laparotomy for this large middle ground of patients. At the very least, the decision to proceed with staging laparotomy no longer should be a reflex reaction. Figures 1A and 1B demonstrate the equivalent OS results that can be obtained in clinically and pathologically staged patients. These results are derived from survival estimates drawn from several published series. While PS I and II patients have high OS rates with radiation therapy alone, clinically staged patients can achieve equivalent outcomes with the use of primary radiation therapy and salvage chemotherapy at the time of relapse or with the
use of up-front combined-modality therapy. For the 25% of patients who are upstaged with staging laparotomy (PS III-IV), radiation therapy is not offered as a single therapeutic modality and the patients are spared a high relapse risk. However, the OS of this latter group probably cannot be distinguished from that of the CS I-II patients with occult subdiaphragmatic disease who are managed with the use of clinically derived prognostic factors. Any small advantage to laparotomy in these patients will be difficult, if not impossible, to discern.

Thus, by discussing the patient’s prognostic factors and estimating the risk of subdiaphragmatic disease, the clinician can use the data that we have summarized from the available literature to inform the patient about the expected DFS and OS with initial radiation therapy, salvage chemotherapy in the event of radiation therapy failure, or combined-modality therapy without laparotomy. The effectiveness of salvage chemotherapy in patients relapsing after primary radiation therapy often should outweigh the additional information to be acquired from surgical staging. Informed patients should be able to participate in the decision-making process, and we believe that many would elect to avoid a staging laparotomy on the basis of available clinical information. Results of ongoing clinical trials that will be available in the next decade should validate the rationale of this approach.

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REFERENCES


