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ABSTRACT

Experience at various institutions has shown staging laparotomy to be an important procedure to define a subset of patients who may be treated with radiation therapy alone. Available clinical tests without staging laparotomy understage patients in approximately one-third of the time. Since the majority of pathologic stage III patients are probably best treated with combination chemotherapy, initial treatment with radiation therapy without staging laparotomy may be suboptimal. The patients with clinical stage I and II Hodgkin’s disease who present for therapy should be treated with a regimen that maximizes the chances for cure the first time around. The group of patients which fails initial radiation therapy after clinical staging may experience toxicities of both full-dose radiation therapy and salvage chemotherapy without survival benefit. Staging laparotomy has acceptable morbidity, and it continues to provide crucial data for effective treatment planning.

There are many ways to treat patients with Hodgkin’s disease, and there are solid arguments for most forms of treatment options. Thus, determining the appropriate treatment plan can be confusing. Staging for Hodgkin’s disease is anatomically based and within each staging category there is a wide range of tumor burden. Many oncologists prefer radiotherapy for early-stage disease and combination chemotherapy for advanced-stage disease. Both controlled and uncontrolled data indicate that stage III patients are probably best treated with combination chemotherapy [1, 2]. In selected situations, as in bulky mediastinal disease, both chemotherapy and radiotherapy are usually recommended [3-7]. A recent review in this journal made the case for avoiding staging laparotomy for supradiaphragmatic, non-bulky clinical stage I or II patients [8]. We believe that an alternative point of view also deserves consideration.

Routine use of staging laparotomy for early-stage Hodgkin’s disease began in the late 1960s at Stanford University Medical Center [9, 10]. Laparotomy was introduced to clarify equivocal clinical staging, and it served as the “gold standard” for other clinical evaluations. Currently there is still no better way to make treatment decisions that address specific anatomic considerations in individual patients.

It is naive and erroneous to assume that radiotherapy for Hodgkin’s disease is identical for all patients within certain stages. The radiation oncologist must often consider whether to treat the liver or make other modifications to the “standard” field. Although staging laparotomy remains an elective procedure, we believe it is still an integral step for those patients with early stage (I or II) disease with good performance status in a reasonable age range (15-60) for whom radiotherapy alone is a reasonable treatment plan. We also believe that patients within the clinical stage II disease with more than four sites of involvement are unfavorable for radiation therapy alone and thus should not go to laparotomy but rather to chemotherapy.

Experience at various institutions has shown staging laparotomy to be an important tool to define a subset of patients who may best be treated with radiation therapy alone. It is also clear that clinical staging tools including CT scans, lymphangiogram and laboratory tests have finite limitations in their abilities to detect disease below the diaphragm. The
most common infradiaphragmatic sites of Hodgkin’s disease involvement are the spleen and left upper quadrant [9-12]. However, these particular sites are not easily diagnosed with conventional radiologic techniques, and the staging laparotomy has resulted in recognition of pathologic splenic involvement in about one-third of patients who were otherwise clinically thought to have stage I or II supradiaphragmatic disease. This was and is an important revelation, as advanced stage patients are better treated with chemotherapy.

The utility of staging for Hodgkin’s disease has been debated over the past 30 years, and it is again the issue of debate in the recent scholarly publication by Multani and Grossbard [8]. The necessity of staging laparotomy is again questioned. A major argument for omission of staging laparotomy relies on the important observation that patients who fail initial treatment with radiation therapy are often successfully salvaged with the addition of chemotherapy [1, 2, 12-15]. Approximately 75%-95% of the relapsed patients can achieve complete response with salvage chemotherapy [1, 16, 17]. However, the long-term salvage of such patients who fail radiation treatment after clinical staging is not 100%; most large series show long-term salvage rates of less than 70% of relapses after radiation [16-18]. This is certainly an improvement over the past, however failure is still a major problem. The salvage of second-line treatment is certainly better than in previous eras, but no one can make a realistic case that relapses after treatment are “good” events. Obviously, they should be avoided to the maximum degree that can be achieved safely. Hence, we believe optimal treatment depends on defining the problem in enough anatomic detail to plan the treatment to the individual patient’s presentation. We are concerned about many patients who may initially undergo suboptimal therapy in hopes of successful salvage chemotherapy. These patients will experience toxicities of both radiotherapy and chemotherapy without significant survival benefit. The combined toxicities of both chemotherapy and radiotherapy may even potentially shorten the chance for long-term survival.

It is clear that either chemotherapy or radiation therapy can cure patients who have early stage Hodgkin’s disease with good expectations and probabilities. It seems to us that there is no need to cure patients twice on a routine basis; one modality should be sufficient. Some investigators seek an optimal mix of low-dose radiation and safe nontoxic chemotherapy but, to prove the utility of such a regimen, they devise research protocols. Other practitioners, anxious to avoid toxicities at all cost, take established regimens and either lower the cyclic doses of agents or give only two or three cycles. These individuals frequently fail to understand that when they arbitrarily make such alterations, they are unintentionally doing “research” also. They do not seem to appreciate that they are in “uncharted waters,” and they are exploiting patients who are clearly potentially curable. Such practitioners should have patients sign a very complex informed consent form, for they are actually risking a major lawsuit if the outcome turns out to be unfavorable.

Long-term data from radiation therapy without staging laparotomy remain uncertain. The heterogeneous mixture of patients treated after various clinical staging protocols makes the data harder to interpret. In the randomized European Organization for Research and Treatment of Cancer H-6 trial [12] (so highly regarded by Multani and Grossbard), radiation therapy alone was used in a group of favorable patients after clinical staging; lymphangiography (LAG) was required as a part of the initial work-up. In addition, thoracic CT scans were obtained in only 52% of favorable patients, and abdominal CT scans were obtained in only 68% of patients. If there was evidence of abdominal disease after the initial clinical staging, patients were placed into the “unfavorable” group and received combined chemotherapy and radiation therapy. Even in such a highly selected remaining group of favorable patients, 30% were still upstaged to stage III and 3% to stage IV after staging laparotomy! Most of the upstaging was due to the splenic involvement undetected by LAG and CT scans. Thus, patients who were upstaged after staging laparotomy were treated differently than originally planned. It is painfully evident from this often-referenced study that our ability to accurately predict the disease below the diaphragm leaves much to be desired. Eleven percent of patients relapsed in the staging laparotomy arm after negative pathologic finding after laparotomy and 19% in the clinical staging arm. The six-year freedom-from-progression rates were 83% in the laparotomy arm and 78% in the clinical staging arm ($p = 0.27$). It might have been more interesting (and certainly more revealing) to analyze the data with long-term outcomes of patients based on the original randomization. That is, what would be the difference in disease-free survival and overall survival if the 30% of patients who were upstaged after laparotomy were treated on the favorable protocol without chemotherapy? The staging laparotomy still succeeded in selecting out 30% of patients whose treatments were altered based upon the pathologic findings! We must await further follow-up of these patients.

From early experiences, it became evident that LAG and CT scans were complementary. LAG detected disease in the lower para-aortic and iliac lymph nodes better than CT scans [19-21]. LAG was able to detect tumor involvement within normal-sized lymph nodes and benign changes in enlarged nodes. It also gave the precise location of the lymph nodes for radiation treatment planning [22]. The high para-aortic nodes (above L2) were better visualized by abdominal CT scans. Unfortunately, LAG is falling into disuse in the United States. The CT scan became the preferred study by default because of less time required to perform it.
and its ability to visualize more sites. CT scans and LAG remain poor in their ability to detect spleen and liver involvement. For nodal interpretation CT scans rely only on size; size is the singular CT criterion for abnormality. If one categorizes that all lymph nodes greater than 1.5 cm are positive on CT scans, what kind of confidence does one have for nodes at the threshold of abnormality? The answer is not much. These cases cannot be settled easily and may need laparotomy in selected cases to better define the staging. This is even more important today when LAG, which not only utilizes size but also internal nodal architecture in the interpretive process, is generally unavailable to clinicians.

Staging laparotomy, unfortunately, has its own set of complications including a mortality rate of less than 1% in most centers [23, 24]. It also has other significant side effects as well, including a small but definite risk of overwhelming postsplenectomy sepsis. However, in a recent review Jockovich [23] reported none of the 25 patients who received pneumococcal vaccine before splenectomy developed overwhelming sepsis and none died due to surgical complications. The continued use of vaccination before splenectomy may significantly reduce or even eliminate the frequency of postsplenectomy sepsis reported in older literature. The use of vaccination about a week prior to splenectomy (the spleen appears necessary to opsonize the antigen) and/or low dose penicillin can certainly help to reduce the possibility of such a catastrophic event.

Probably the most important thing the physician can do is to educate the patient about the potential risk of sepsis postsplenectomy and its continuous risk. The patient must be educated to demand physician attention when he or she becomes febrile, etc.; appropriate antibiotics against pneumococcus, hemophilus and neisseria are indicated even before the return of cultures in the postsplenectomy patient.

Multani and Grossbard discuss various factors leading to treatment-related complications. However, some additional comments are needed to address the potential side effects of overtreating and undertreating clinically staged patients. Patients who receive extended field irradiation to the spleen, left kidney, small bowel and stomach are at significant risk for treatment-related toxicities. The left kidney, in particular, may be irreparably damaged from irradiation administered. Clinically staged patients usually receive larger-sized portals than patients treated after staging laparotomy [12, 25]. Moreover, there may be additional risk of further serious complications due to superimposed salvage treatments. Valagussa [26] reported 15.5% cumulative actuarial incidence of leukemia if patients were treated with radiotherapy first and salvaged with MOPP chemotherapy. In addition, the actuarial risk of leukemia was 2.2% among patients treated with MOPP and supradiaphragmatic radiotherapy, but 9.1% for those who received subtotal or total lymphoid irradiation with MOPP. This suggests there may be a volume effect of radiotherapy in patients who develop leukemia. Moreover, the cardiopulmonary toxicities of ABVD [27] may possibly offset the benefits of a decrease in the risk of presumably treatment-induced leukemia related to MOPP.

With an upstaging rate of 30% in even the “favorable” group of patients, it is not surprising to observe an increased relapse rate with radiotherapy after clinical staging. The arguments against laparotomy often quote the same overall survival percentages as justification for initial radiotherapy without laparotomy. However, we continue to find it hard to justify initial use of suboptimal therapy in anticipation of an effective salvage regimen. We believe that the patient should be initially offered a definitive treatment. Such patients treated with salvage therapy after suboptimal radiotherapy planning may have significant increases in both acute and long-term morbidities.

It is clear that some patients can avoid laparotomy based on multiple poor prognostic factors, while others with an extremely good prognosis avoid laparotomy because it would not add meaningful data. However, our responsibilities lie with the individual patients confronting us; those individual patients with supradiaphragmatic clinical stage I or II either have a 0% or 100% chance of infradiaphragmatic involvement. We recognize that we do overtreat some patients; our problem is that we cannot identify them reliably. We agree that every effort should be made to enroll patients in protocols to help define the treatments for the future. Staging laparotomy remains a valuable tool for patients who present with not so clearly defined prognostic factors. This category includes those with nonbulky supradiaphragmatic stage I and II patients with supracavicular lymph node presentation of virtually any histologic subtype and equivocal CT scans of the abdomen and pelvis. In fact the majority of patients with Hodgkin’s disease will present with mixed prognostic factors. An unremarkable CT scan of the abdomen is not, in our opinion, an indication to avoid laparotomy. Patients with grossly abnormal CT scans of the abdomen and pelvis, on the other hand, may avoid laparotomy and proceed to combination chemotherapy. Patients can avoid laparotomy if they: 1) present with more than four sites of disease, 2) have bulky disease, 3) desire chemotherapy, or 4) have medical contraindications for surgery. It is our opinion that modern surgical techniques combined with prophylactic vaccination have decreased the rate of complications to a more than acceptable level. We do not think overtreating or undertreating purposely is necessarily an advancement in treatment of Hodgkin’s disease.
A final issue on laparotomy has to do with excluding patients from laparotomy on the basis of data reported from large series. There are some problems with this. First of all, certain aspects, including pathology, are not always reproducible [28]. Data need confirmation from other sources. We view the situation as analogous to a pinch hitter in baseball who comes to bat in the ninth inning against the best relief pitcher in the game with two outs and the potential winning run on third base. The odds are against him, but he will still take his swings at bat. Moreover, from time to time he will be successful and defy the odds. No one knows when. That is exactly the point; no one "knows" in any individual patient when the findings will force rethinking of the initial consideration of treatment; past performance cannot always serve as an accurate basis for future projections in all instances.

The situation in which the patients with early stage Hodgkin’s disease have a high probability of a long-term survival leads to an important consideration of the long-term morbidity of each therapeutic modality. Both radiation and chemotherapy, regardless of the specific agents used, have potentially significant long-term toxicities inasmuch as both modalities depend on their effects on nucleic acids. Does the additional risk of up-front splenectomy and radiotherapy outweigh the subsequent risk in patients who receive salvage chemotherapy postirradiation, thus being exposed to combined toxicities? Since the upstaging of patients by staging laparotomy is significant in determining patients who are better chemotherapy candidates up front, we still believe that in anticipation of using radiation as a primary mode of treatment, staging laparotomy is beneficial, especially in the group of patients who have less well-defined prognostic factors. We recommend the decision tree below when considering early stage Hodgkin’s disease patients (Fig. 1).

<table>
<thead>
<tr>
<th>All untreated cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong> (± XRT in selected responses)</td>
</tr>
<tr>
<td><strong>Massive mediastinal disease</strong></td>
</tr>
<tr>
<td><strong>Combined modality</strong></td>
</tr>
<tr>
<td><strong>Clinical stage I, II</strong></td>
</tr>
<tr>
<td><strong>Stage I, axilla only</strong></td>
</tr>
<tr>
<td><strong>Stage I, high neck only</strong></td>
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<tr>
<td><strong>Ipsilateral scalene Node biopsy</strong></td>
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<td>(−)</td>
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<tr>
<td><strong>Mini-mantle XRT only</strong></td>
</tr>
<tr>
<td><strong>Staging laparotomy</strong></td>
</tr>
<tr>
<td>(+)</td>
</tr>
<tr>
<td>(−)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
</tr>
<tr>
<td><strong>Mantle + para-aortic</strong></td>
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</tbody>
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*Figure 1. All untreated cases.*
REFERENCES


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