Testicular Cancer: What’s New in Staging, Prognosis, and Therapy

ABSTRACT: Improvements in the clinical staging of testicular cancer may permit the identification of clinical stage I patients at low risk of harboring metastatic disease, who could be spared treatment and observed only. Both retrospective, single-institution studies and studies of unselected, consecutive patients have confirmed that vascular invasion, lymphatic invasion, and percentage of embryonal carcinoma are predictive of metastasis in patients with low-stage nonseminoma. Whether patients with these risk factors have a worse outcome if managed with surveillance, rather than with aggressive therapy, is unclear. Low MIB-1 staining (which identifies the Ki-67 antigen) in conjunction with a low percentage of embryonal carcinoma in the testicular specimen appears to be predictive of a low probability of metastasis. Computed tomography (CT) is a useful staging tool. A new prognostic classification system for seminomas and nonseminomas was recently developed by an international consensus conference. Laparoscopic retroperitoneal lymphadenectomy appears to be a feasible staging tool with acceptable short-term morbidity. Whether laparoscopic lymph node dissection is equivalent to the open procedure when used as a therapeutic modality is not yet known. At present, laparoscopy should be used only in selected patients in a study setting. Primary chemotherapy is not recommended currently because it has not yet been proven to be superior in patients with high-risk clinical stage I nonseminoma and can cause significant long-term sequelae.[ONCOLOGY 13(12):1689-1694, 1999]

Introduction

The treatment of testicular cancer continues to evolve. Several treatment alternatives are available that afford an excellent chance for cure in patients with low-stage seminoma or nonseminoma. Current issues in low-stage disease relate to minimization of the morbidity of therapy and maximization of the patient’s psychological and physiologic well-being. In addition, cost constraints are important issues in low-stage testicular cancer.

With respect to good- or intermediate-risk patients with high-stage disease, minimization of treatment-related morbidity is being actively studied. Another very pertinent issue in high-stage disease is the treatment of patients with poor-risk features.

The current article is not meant to be an exhaustive review of clinical studies of staging, prognosis,
and treatment. Rather, the intent is to update the clinician on recent advances in these three aspects of testis cancer management.

**Staging**

**Low-Stage Disease**

Patients with clinical stage I or II nonseminoma have approximately a 95% to 99% chance of being cured. These patients are treated primarily with either nerve-sparing retroperitoneal lymphadenectomy, surveillance, or primary chemotherapy. Reported outcomes using these treatment strategies in patients with clinical stage I or II nonseminoma are approximately equal, at least over the short term. Therefore, improvements in clinical staging are unlikely to change the prognosis of the patient but may, by identifying metastasis earlier, allow for selection of the single most effective method of management in an individual patient.

What, then, is to be gained from improvements in the clinical staging of these patients? Since approximately 70% of clinical stage I patients, in fact, do not develop metastatic disease, identification of this low-risk group of patients would allow such patients to be observed without any treatment.

Pro and con arguments can be made regarding the treatment-related morbidities of surgery, surveillance, and primary chemotherapy in patients with clinical stage I disease, but no clinician would be likely to oppose a strategy of observation alone if a group of clinical stage I patients with an extremely low risk of metastasis could be identified. Treatment-related morbidity would be minimized, costs would likely be decreased, and the anxiety patients experience over whether or not occult metastatic disease exists would also be lessened. Therefore, an excellent rationale exists for identifying patients at extremely low risk for metastasis.

Many excellent studies of staging have been performed in patients with low-stage testis cancer. Most of these studies have attempted to identify patients at high risk for metastatic disease in order to appropriately institute therapy earlier in the course of the disease.[1,2] Most of the studies were retrospective, single-institution studies, with a mixture of pathologic stage I and II patients that does not conform to the expected mixture of these two stages (ie, 70%, pathologic stage I; 30%, pathologic stage II). However, some very well-designed, well-conducted studies have addressed clinical staging issues in consecutive groups of patients, usually in multi-institution format. This article will review selected studies of the former type, as well as selected studies in consecutive patients.

**Histologic Factors**

- **Single-Institution Studies**—Among the most frequently studied parameters predictive of pathologic stage are histologic factors, such as the presence of vascular invasion and lymphatic invasion. [3,4] These and other studies, such as the study by Dunphy et al, also identified the presence of embryonal carcinoma as another factor associated with relapse if patients were managed on a surveillance protocol. [5] In addition, studies performed by Freedman et al[3] and Hoskin et al[4] found the absence of yolk sac elements in the tumor to be associated with an increased risk of recurrence among patients managed by surveillance.

More recently, Moul et al showed that the combination of percentage embryonal carcinoma and vascular invasion was predictive of pathologic stage II disease in a group of 92 clinical stage I patients—all of whom underwent retroperitoneal lymphadenectomy. [6] The presence of these two factors predicted stage 85.9% of the time in this selected population of patients.

Similarly, Wishnow et al demonstrated a greater likelihood of a higher pathologic stage if the orchiectomy specimen exhibited a high percentage of embryonal carcinoma and vascular invasion. [7] In this study, a cohort of low-risk patients who had no vascular invasion, less than 80% embryonal carcinoma, and an alpha-fetoprotein level less than 80 ng/mL experienced no relapses when managed by surveillance.

In general, other single-institution studies have supported the prognostic importance of extent of embryonal carcinoma, vascular invasion, and lymphatic invasion.

- **Studies in Consecutive Patients**—Studies performed in consecutive, unselected patients have corroborated the predictive ability of these parameters. A prospective study of surveillance conducted by the Medical Research Council (MRC) in the United Kingdom showed that vascular invasion, lymphatic invasion, the presence of embryonal carcinoma, and the absence of yolk sac elements are predictive of recurrence. [1] Patients with three or four of these risk factors had a
relapse-free rate of 53%. This study confirmed the previous findings of the MRC in an independent data set.

A prospective, multicenter, Scandinavian study by Klepp et al showed the importance of vascular invasion as a predictor of metastasis.[8] Similarly, Sesterhenn et al reviewed the histology of the orchiectomy specimens in the Testicular Cancer Intergroup study.[9] Vascular invasion and percentage of embryonal carcinoma in the tumor were predictive of stage in these patients, who were managed by retroperitoneal lymph node dissection.

• **Unanswered Questions**—Thus, significant evidence confirms that vascular invasion, lymphatic invasion, and percentage of embryonal carcinoma are predictive of metastasis in patients with low-stage nonseminoma. What is unclear from these studies is whether or not patients with such risk factors necessarily have a poor outcome if they are managed aggressively at diagnosis with either retroperitoneal lymphadenectomy or chemotherapy, as compared with their outcome if they are managed by surveillance.

In other words, if secondary issues (e.g., morbidity, psychological issues, or economic issues) are set aside, is it essential for increased survival that such patients be managed proactively when “high risk” is defined at orchiectomy? Does managing high-risk patients with surveillance necessarily lead to a lower chance for cure? Based on the evidence from several surveillance series, this does not seem to be the case.

**Immunohistochemical and Flow Cytometric Parameters**

Immunohistochemical and flow cytometric parameters also have been studied in an effort to improve clinical staging. In a retrospective analysis of a selected group of patients, DeReese et al found that proliferative parameters (as measured by flow cytometry) were predictive of pathologic stage II disease in patients managed with retroperitoneal lymphadenectomy.[10] However, Moul et al found that such parameters were predictive in a univariate but not a multivariate analysis.[11]

Albers et al subsequently studied these same parameters in a group of 105 consecutive patients.[12] In a multivariate analysis, proliferative parameters (as defined by flow cytometry) were the most predictive of pathologic stage. In contrast, Fossa et al found that these proliferative parameters were not helpful in predicting metastasis.[13]

Immunohistochemical parameters that correlate with cell division also have been assessed in an attempt to predict metastasis. Albers et al showed that low MIB-1 staining (which identifies the Ki-67 antigen) in conjunction with low volumes of embryonal carcinoma predicts those patients managed with retroperitoneal lymphadenectomy who are at a low probability of having pathologic stage II disease.[14] This finding was subsequently confirmed in an independent group of German patients.[15]

The use of other immunohistochemical markers, such as proliferative cell nuclear antigen (PCNA) and p53 staining, have been investigated in many other studies and have shown no definite ability to predict pathologic stage.[16] Various investigators have examined the use of isochromosome 12P, a common chromosomal abnormality in testicular germ-cell tumors.[17] These studies have shown no definite correlation between this chromosomal abnormality and metastasis. Biological markers, such as HST-1 and ras mutation, similarly have shown no definite usefulness in the prediction of metastasis in low-stage disease.

**CT Findings**

Computed tomographic (CT) criteria for the diagnosis of abnormal lymph nodes in the retroperitoneum are also evolving. Traditionally, lymph nodes ≤ 1 cm in diameter were considered to be normal in the staging of testicular cancer. Moul[18] and Leibovitch et al[19] found that by decreasing the limits for the diagnosis of abnormal lymph nodes to below 1 cm, the sensitivity of clinical staging was improved.

In a subsequent study of consecutive patients, by combining such new CT-based criteria with MIB immunostaining and the volume of embryonal carcinoma in the testicular specimen, Leibovitch et al were able to identify a group of 41 patients felt to be at low risk for metastatic disease.[20] Of these 41 patients, 40 actually proved to have pathologic stage I disease at retroperitoneal lymphadenectomy. This group of 41 patients constituted 45% of the overall population of clinical stage I patients in this study. In addition, this study was performed in a group of consecutive patients.

**Summary**
Therefore, several studies have identified new predictors of pathologic stage in patients with low-stage nonseminomatous testis cancer. Many of these studies have limitations, in that the populations studied were selected and the parameters used to predict metastasis may suffer from interobserver variability (eg, CT scan reading and immunohistochemical staining). If the goal is to accurately define a paradigm that is more useful in the prediction of pathologic stage, a prospective study comparing consecutive, unselected patients managed by retroperitoneal lymphadenectomy vs surveillance is needed. The cooperative groups have been planning such a study for some time. Hopefully, this study will be approved shortly and will be completed expeditiously in a multi-institution, prospective format.

**Prognosis in Advanced Disease**

In 1997, an international consensus conference was convened to address the multiplicity of prognostic systems and to attempt to develop a system that would serve as a unified approach to assigning risk to patients with disseminated germ-cell tumors.[21] Many large institutions from throughout Europe and the United States pooled patient information in this effort. Over 6,000 cases were analyzed, and several themes emerged from this analysis.

First, mediastinal nonseminomatous germ-cell tumors were clearly associated with a poor outcome. The presence of nonpulmonary visceral disease was a commonly accepted adverse feature. The issue of the prognostic impact of marker elevation was less clear, but it seemed possible to augment the prognostication based on anatomic distribution and levels of alpha-fetoprotein, human chorionic gonadotropin, and lactic dehydrogenase. TABLE 1

<table>
<thead>
<tr>
<th>New International Germ Cell Consensus Prognostic Classification System for Testicular Cancer</th>
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<tbody>
<tr>
<td><strong>GOOD PROGNOSIS</strong></td>
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<tr>
<td>No mediastinal nonseminomatous germ-cell tumor</td>
</tr>
<tr>
<td>No pulmonary metastasis</td>
</tr>
<tr>
<td>Serum markers not elevated</td>
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<tr>
<td><strong>INTERMEDIATE PROGNOSIS</strong></td>
</tr>
<tr>
<td>Mediastinal nonseminomatous germ-cell tumor</td>
</tr>
<tr>
<td>Pulmonary metastasis</td>
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<tr>
<td>Serum markers elevated</td>
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<tr>
<td><strong>POOR PROGNOSIS</strong></td>
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<tr>
<td>Mediastinal nonseminomatous germ-cell tumor</td>
</tr>
<tr>
<td>Pulmonary metastasis</td>
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<td>Serum markers elevated</td>
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This new prognostic classification system—the International Germ Cell Consensus Classification—is shown in Table 1. This model divides patients into three tiers—those with good, intermediate, or poor prognosis.

A recent report from Memorial Sloan-Kettering by Bajorin and colleagues confirms most of the tenets of the International Germ Cell Consensus Group.[22] Reviewing data accumulated from 796 patients from 1975 to 1990, these investigators found mediastinal primary tumor, metastasis to nonpulmonary, visceral sites, and high pretreatment levels of human chorionic gonadotropin and lactic dehydrogenase to be independently significant predictors of poor outcome. Like the International Germ Cell Consensus Group, the Sloan-Kettering investigators developed a three-tiered model that predicted complete response rates of 92%, 76%, and 39% in good,
intermediate-, and poor-prognosis patients, respectively. The primary difference between the two models is that the Memorial model did not find alpha-fetoprotein elevation to be an independent prognostic factor, although their study may have been hampered by small size, compared to the International Germ Cell Consensus Group study.

**Therapy**

**Laparoscopy**

The rationale for using retroperitoneal lymph node dissection in clinical stage I nonseminoma is twofold: Retroperitoneal lymphadenectomy effectively determines whether or not the patient falls into the 30% of clinical stage I patients who have pathologic stage II disease. Also, by removing metastatic nodes in the retroperitoneum, lymphadenectomy affords the patient a chance for cure with surgery alone.

Testis cancer is a very unique disease in that surgical cure is possible even after lymphatic metastasis has been discovered and removed.[23,24] Depending on the volume of retroperitoneal disease, the likelihood of cure ranges between 50% and 70%. Because surveillance has worked well in patients with clinical stage I disease, the importance of retroperitoneal lymphadenectomy as a staging tool has diminished somewhat, but it remains important in treatment.

Several series reporting on laparoscopic retroperitoneal lymphadenectomy in clinical stage I disease have been published.[25-27] These series have shown that there is a learning curve in mastering this procedure. The early patients in these series were more prone to serious complications and conversion to open surgery because of bleeding. With more experience, the complications and necessity for converting to open surgery have diminished. Therefore, these series showed that laparoscopic retroperitoneal lymphadenectomy appears to be feasible with acceptable short-term morbidity. Whether or not the patients in these series were subselected from the general population of clinical stage I patients is unclear, however.

Moreover, these series did not employ retroperitoneal lymphadenectomy as a therapeutic tool. In fact, if metastatic disease was discovered at laparoscopic retroperitoneal lymphadenectomy in some series, the operation was terminated without complete removal of all lymphatic tissue and chemotherapy was given. Even if a complete retroperitoneal lymphadenectomy was performed in a patient with pathologic stage II disease, chemotherapy was routinely administered postoperatively. Most series employed two or three courses of bleomycin (Blenoxane), etoposide, and cisplatin (Platinol).

Not unexpectedly, overall survival was excellent in these series. Essentially what was done is that systemic chemotherapy, as given for good-risk metastatic disease, was administered to these patients with presumed retroperitoneal-only low-volume metastasis.

Therefore, laparoscopy has been used only as a staging tool. Since deferred treatment of patients with pathologic stage II disease is usually successful, as employed in surveillance series, one wonders whether or not discovering retroperitoneal disease earlier via laparoscopy is worth the cost and morbidity. In other words, if the intent is to treat retroperitoneal-only disease with chemotherapy, why not simply enter the patient into a surveillance protocol and treat him with systemic chemotherapy at the time of clinical relapse?

- **Which Patients Might Benefit From Laparoscopic Management?**—It is conceivable that selected patients may be best managed laparoscopically. For instance, a noncompliant patient (who would not adhere to adequate follow-up on a surveillance protocol) who is interested in treating his metastatic disease with chemotherapy and is willing to undergo laparoscopic retroperitoneal lymphadenectomy to stage his disease earlier may be a reasonable candidate.

Currently, for laparoscopic retroperitoneal lymphadenectomy to supplant open lymphadenectomy, it must be shown that the two are therapeutically equivalent. If this hypothesis is tested, and if laparoscopic retroperitoneal lymphadenectomy proves to be equivalent to the open procedure, local recurrences should be extremely rare. Similarly, any such patient who agrees to test this hypothesis must provide informed consent after being given adequate information about other management options for clinical stage I disease.

Laparoscopy has also been employed in patients who have residual retroperitoneal tumor after systemic chemotherapy for disseminated disease.[28] These patients were highly selected, but in small numbers of such patients, the procedure has been performed with acceptable morbidity. It is entirely conceivable that laparoscopic removal of low-volume teratoma after chemotherapy may be therapeutically equivalent to open retroperitoneal lymphadenectomy. However, patient selection is very important, since it is difficult for the surgeon to predict the amount of scarring and reaction in
the retroperitoneum based on a preoperative CT scan. Similarly, for laparoscopic post-chemotherapy retroperitoneal lymphadenectomy to show equivalence to open post-chemotherapy retroperitoneal lymphadenectomy, the local recurrence rate in the retroperitoneum would have to be extremely low. It is incumbent upon surgeons performing laparoscopic retroperitoneal lymphadenectomy in nonseminomatous testis cancer to clearly state the rationale for performing this procedure in clinical stage I patients and in post-chemotherapy patients. Selection criteria for each of these procedures must be clearly defined, and such surgeons should determine whether or not they are willing to test the therapeutic capability of laparoscopic retroperitoneal lymphadenectomy. Reports of such series should employ both short- and long-term follow-up, as there is some evidence that inadequately resected retroperitoneal disease, even if treated subsequently with chemotherapy, is sometimes prone to late recurrence.[29]

**FIGURE 1**

![Suggested Approach to Managing State I Nonseminoma](image)

**Summary**—Laparoscopic lymphadenectomy, as practiced currently, represents nothing more than an expensive staging tool. If a patient is compliant and is comfortable with treating any metastatic disease with chemotherapy, surveillance has been shown to be an effective method of management, with an overall survival essentially equal to open retroperitoneal lymphadenectomy (Figure 1). If chemotherapeutic treatment of any metastatic disease is chosen, pathologic staging at the time of diagnosis is not as important. That is, surveillance studies have shown that the effectiveness of chemotherapy in treating metastatic disease when it is eventually discovered radiographically or serologically is equivalent to treating microscopic disease, assuming that adequate doses and schedules of chemotherapy are given. Therefore, in the absence of proof of the therapeutic capability of retroperitoneal laparoscopic lymphadenectomy, it is difficult to justify its recommendation as a standard method of management.

**Primary Chemotherapy for High-Risk Stage I Nonseminoma**

The efficacy and safety of chemotherapy for patients with good-risk metastatic disease and the near-perfect results of two cycles of chemotherapy in the setting of fully resected stage II disease have prompted investigators to consider the use of primary chemotherapy in patients with high-risk clinical stage I disease. Several small series using this approach have reported excellent short-term survival.[30,31] More recently, the British Medical Research Council reported the use of two cycles of bleomycin, vincristine, and cisplatin as adjuvant therapy for patients with high-risk clinical stage I disease (defined by the presence of vascular invasion).[2] In this study of 115 patients, chemotherapy was well tolerated, but there have been two relapses and one death with a median follow-up of 4 years. Primary chemotherapy is incompletely investigated and has the potential for producing significantly more long-term consequences. Although favorable initial reports suggested near-universal cure with two cycles of chemotherapy in patients with poor-risk, early-stage disease, these studies have shown deaths from treatment and progressive disease. The studies were seriously underpowered to be definitive, especially when one considers that ≥ 50% of similar patients have been cured with orchectomy alone.

In addition, it is not unusual to find patients with grossly involved lymph nodes at the time of surgery despite a negative abdominal CT scan. These patients are at risk for undertreatment with abbreviated chemotherapy. Such patients ultimately may require significantly more treatment than would have been needed if nonchemotherapeutic approaches had been used. Also, these patients may be at increased risk of developing drug-resistant disease and suffering treatment failure. Until more accurate discriminators of risk are available, we do not favor exposing patients to chemotherapy, with its attendant risks of fatal neutropenic sepsis, second malignancies, and endocrinologic consequences, when effective nonchemotherapeutic approaches are readily
available.
Finally, in patients with clinical stage I disease, surveillance and open retroperitoneal
lymphadenectomy have “raised the bar” quite high in terms of overall chance for cure and
minimization of long-term morbidity and late recurrence. If laparoscopy and/or primary
chemotherapy are to be widely employed in patients with high-risk disease, they must meet these
high standards.

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