New Treatments for Stage I Testicular Cancer

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Abstract Clinical stage I represents the most frequent presentation of both seminoma and nonseminoma testicular cancer. Despite a survival rate of close to 100%, the management of patients with this disease stage is controversial. The recurrence rate is 10% to 20% for patients with stage I seminoma and 15% to 50% for those with stage I nonseminoma. A highly sensitive and specific biomarker of relapse that is applicable to both seminoma and nonseminoma, and able to drive a definitive risk-adapted management of the patients, still is not available. Lymphovascular invasion (LVI) in the orchiectomy specimen has been used as a risk factor in patients with stage I nonseminoma. However, with a risk of recurrence of 50% for LVI-positive patients and 15% for LVI-negative patients, the discriminative power of LVI is modest at best. Various management options exist. In the absence of a predictive biomarker for recurrence, active surveillance avoids overtreatment in 50% to 85% of patients, with no risk of long-term side effects in nonrelapsing patients and a preserved overall survival of almost 100% after specific treatment for recurrent disease. However, although active surveillance has been accepted as the preferred option for stage I seminoma and low-risk stage I nonseminoma, its role in high-risk stage I nonseminoma remains controversial.

Introduction

Testicular cancer is a paradigm of the curable tumor. Although it is considered rare, testicular cancer is the most frequent solid tumor in men between 15 and 40 years. Given the young age of patients, testicular cancer affects both economic productivity and fertility.[1] The incidence of this type of cancer has increased significantly over the last decades, for reasons that are not entirely clear.[2,3] Clinical stage I is the most common presentation of testicular cancer, and approximately 75% of all patients are diagnosed at this stage.[4,5] By definition, stage I is characterized by negative tumor markers and no evidence of metastases after orchiectomy for the primary tumor. Despite the excellent survival rate—close to 100%—several adjuvant strategies have been proposed to reduce the relapse rate of stage I

seminoma and nonseminoma. These strategies were once preferred over active surveillance, and some patients continue to prefer receiving treatment.[6,7] However, better understanding of the biologic behavior of seminoma and nonseminoma—information regarding location and time of relapse, as well as increasing knowledge of late effects associated with chemotherapy and radiation—have prompted a shift from an active treatment approach to management with active surveillance. This review analyzes the various strategies proposed to manage patients with stage I seminoma and nonseminoma, discusses the pros and cons associated with each strategy, and explores potential new tools for patient selection.

Stage I Seminoma

Seminoma is characterized by a slower proliferation rate and more indolent biology than nonseminoma. Almost 80% of patients with seminoma are diagnosed at stage I. The relapse rate after orchiectomy is approximately 10% to 20%, and no biomarkers are currently available to reliably identify patients with a high risk of relapse who could potentially be selected for adjuvant treatment.[8] Tumor volume of 4 cm or more and invasion of rete testis have been proposed as negative prognostic factors. Warde and colleagues reported a 5-year relapse rate for stage I seminoma of 31.5% in the presence of 1 of these risk factors and 15.9% in the presence of both of these risk factors. A 4% relapse rate was observed in patients without either of these risk factors.[9] Validation of this classification in an independent data set failed, although tumor size as a linear variable was correlated with an increased risk of relapse.[10] For these reasons, the use of these prognostic factors to select candidates for adjuvant treatment or active surveillance has been abandoned. Three options are available for the management of patients with stage I seminoma: surveillance, chemotherapy, and radiation therapy.

Surveillance

Despite a relapse rate of 10% to 20%, the survival of patients with stage I seminoma approaches 100% because nearly all relapsed patients are cured by chemotherapy, radiation therapy, or surgery. Hence, all guidelines—including those from Canada, the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN)—recommend active surveillance as the preferred choice for the management of patients with stage I seminoma.[11,12]

In the largest published study to date, Kollmannsberger and colleagues retrospectively analyzed the pattern of relapse and the clinical outcomes of 1344 patients with stage I seminoma managed with active surveillance.[13] In line with previous reports, a relapse rate of 13% was observed, with a median time to relapse of 14 months. Ninety-two percent of recurrences were observed within the first 3 years. All relapsed patients were cured with either chemotherapy or radiation therapy, with 99% of patients alive after a median follow-up of 52 months. Interestingly, there was no difference in prognosis and response to chemotherapy in the patients whose disease relapsed beyond the third year of surveillance. The vast majority of relapses were detected by abdominal computed tomography (CT) scan. Only a few relapses (4%) were detected by an increase in beta-human chorionic gonadotropin (β-HCG). These data support the use of surveillance as the preferred choice for the management of patients with stage I seminoma.

Although nonadherence is frequently used as an argument against active surveillance, survival rates with active surveillance for stage I seminoma have consistently been greater than 97%, regardless of the degree of adherence in these studies. No standard surveillance schedule exists, but the number of CT scans necessary has decreased significantly over the past decade. In addition, because the pattern of metastases of testicular cancer is extremely conservative and predictably limited to the retroperitoneal lymph nodes, CT or magnetic resonance imaging of the abdomen alone is sufficient to detect the vast majority of relapses.[13,14]

Chemotherapy

Adjuvant chemotherapy has been proposed as an alternative to radiation therapy for stage I seminoma. In a large randomized trial, Oliver and colleagues demonstrated that a single cycle of carboplatin at a dose of 7 times the area under the curve (AUC 7) reduced the risk of relapse from 15% to 5%, a result comparable to that with radiation therapy.[15] Using the Warde risk factors for stage I seminoma, Aparicio and colleagues assigned high-risk patients (with both tumor volume ≥4 cm and rete testis involvement) to 2 cycles of AUC 7 carboplatin, whereas patients with no or 1 risk factor were managed by active surveillance. The study confirmed a lower relapse rate in high-risk patients on carboplatin than in low-risk patients on surveillance (1.4% vs 9.8%, respectively).[16] Overall survival was 100% regardless of the management option offered to the patients. Moreover, in some patients with borderline retroperitoneal lymphadenopathies, the use of carboplatin may be deleterious. Patients who have metastatic disease require etoposide, cisplatin, and bleomycin (BEP) rather than carboplatin monotherapy in order to achieve a cure.[17] In the large, population-based SWENOTECA (Swedish and Norwegian Testicular Cancer Group) study, the risk of relapse was only modestly decreased after adjuvant carboplatin, with a 9% recurrence rate in patients with larger primary

tumors. In addition, adjuvant chemotherapy represents overtreatment for the 80% to 85% of patients who are cured by surgery alone. Finally, the follow-up of patients with stage I seminoma treated with 1 to 2 cycles of carboplatin is not long enough to rule out potentially significant long-term side effects, and some authors have already pointed out a possible association with late cerebrovascular events.[18]

Radiation Therapy

In the past 20 years, a dramatic reduction in the use of radiation therapy has been observed for patients with stage I seminoma. Because of the high radiosensitivity, radiation is a very active treatment for seminoma that reduces the relapse rate from 10% or more to 4%.[19] However, despite the progressive reduction in the radiation dose and field to minimize the side effects,[20] the risk of long-term sequelae remains high. As a result, radiation therapy is no longer considered a recommended strategy for the management of stage I seminoma. Radiation-associated long-term toxicity includes the risk of second malignancies (kidney cancer, colorectal cancer, sarcoma, and some leukemias) and cardiovascular disease, both of which are highly relevant for this young patient population with a normal life expectancy.[21,22]

Stage I Nonseminoma

After orchiectomy, the expected relapse rate for stage I nonseminoma is between 10% and 50%. The rate of relapse in the primary tumor is 50% in the presence of lymphovascular invasion (LVI) and 15% in LVI-negative patients.[23] LVI positivity has only modest discriminative power because 50% of LVI-positive patients are cured by orchiectomy alone. Three management options exist for patients with stage I nonseminoma: surveillance, chemotherapy, and retroperitoneal lymph node dissection (RPLND). Overall survival for patients with stage I nonseminoma exceeds 98% in experienced centers regardless of the treatment chosen. No consensus exists for the management of LVI-positive patients, who are considered high risk, whereas most guidelines recommend active surveillance for LVI-negative patients.[11,12,24]

Surveillance

Active surveillance is recommended by most guidelines for the management of LVI-negative stage I nonseminoma. Recommendations for LVI-positive stage I nonseminoma differ among guidelines. Whereas the Canadian guidelines recommend surveillance as the preferred choice, both the ESMO and NCCN guidelines endorse adjuvant chemotherapy and surveillance as options. The NCCN guidelines are less focused on risk stratification based on LVI status, and recommend surveillance, chemotherapy, or RPLND as equivalent therapeutic options.[11,12,25]

Based on the data of patients with stage I nonseminoma on surveillance, the expected relapse rate is approximately 50% for LVI-positive patients and 15% for LVI-negative patients. The median time to relapse is 4 months for LVI-positive patients and slightly longer (8 months) for LVI-negative patients. Most patients relapse within the first 2 years, and only 1% of patients relapse after 3 years. Overall survival for patients with stage I nonseminoma is very high (98%) regardless of the management strategy because these patients are cured with either chemotherapy or RPLND.

Tumor marker increase is frequently used to detect relapse. This measurement represents the first sign of relapsed disease in 61% of LVI-positive patients and 41% of LVI-negative patients.[13] Based on this pattern and the timing of relapse, a CT scan of the abdomen should be done earlier and more often than in patients with stage I seminoma, especially during the first year of follow-up. As suggested earlier for stage I seminoma, follow-up should be more intense during the first 2 years, when the risk of relapse is highest. The timing and frequency of CT scans remains controversial in stage I nonseminoma. The results of a randomized trial did not show any difference in survival of patients assigned to receive 2 CT scans (at 3 and 12 months) or 5 CT scans (at 2, 6, 9, 12, and 24 months).[26] However, as Kollmannsberger and colleagues have demonstrated, almost 28% of patients with low-risk stage I nonseminoma relapse beyond year 1, and the approach of using 2 CT scans at 3 and 12 months would not be adequate to identify those patients.[13]

Chemotherapy

The risk of relapse is approximately 15% in patients without LVI, but increases to 50% if LVI is present. As reported by Chevreau and colleagues, adjuvant treatment of patients with high-risk stage I nonseminoma with 2 cycles of BEP significantly reduced the risk of relapse, from 50% to 2%.[27] These data have been confirmed by Maroto and colleagues.[28] The results of this trial showed that 17% of patients with LVI-negative disease and 55% of those with LVI-positive disease relapsed after 40 months of follow-up, but only 1.3% of those with LVI-positive disease who were treated with 2 cycles of chemotherapy relapsed in the same period. The patients who relapsed were cured with other treatment, however, and the disease-specific mortality rate was only 1.4%. This finding underscores the fact that overall outcomes remain excellent regardless of the management option used.[28]

More recently, several studies have demonstrated a similar reduction in relapse risk with 1 cycle of BEP. Tandstad and colleagues found no difference between 1

and 2 cycles of BEP for high-risk patients. Moreover, they also have compared surveillance with 1 cycle of BEP in LVI-negative patients, confirming that either strategy can be used in these patients with the same results.[29] Huddart and colleagues presented the results of the 111 study (A Single-Arm Trial Evaluating One Cycle of BEP as Adjuvant Chemotherapy in High-Risk, Stage 1 Non-Seminomatous or Combined Germ Cell Tumors of the Testis), again demonstrating that 1 cycle of BEP leads to a significant reduction in relapse rates.[30] Therefore, only 1 cycle of BEP should be given as adjuvant therapy.

Even if patients are selected based on LVI status, 50% of them will be overtreated and may experience significant long-term effects from chemotherapy, including cardiovascular disease, chronic peripheral neuropathy, tinnitus, infertility, and second tumors, even after 1 cycle.[31] On the other hand, 50% of the high-risk patients will need 3 cycles of BEP at relapse rather than 1 cycle proposed as adjuvant therapy. There is a risk of undertreatment for the patients with early metastatic disease and borderline lymph nodes, who may receive 1 or 2 cycles of chemotherapy instead of 3 cycles.

RPLND

RPLND was the only treatment choice for patients with stage I nonseminoma prior to the introduction of cisplatin-based chemotherapy in 1977.[32] Primary RPLND is now recommended only for patients who refuse and/or are not suitable candidates for either chemotherapy or active surveillance. Pathological metastatic retroperitoneal lymph nodes are expected in 15% to 35% of patients with stage I disease. The cure rate with primary RPLND is 84.1% for patients with pathologically confirmed stage I disease, but only 68.3% for patients with pathologically confirmed metastatic disease. After RPLND, the chest represents the first site of relapse in 70% of cases.[33]

The risk-adapted model based on the LVI has diminished the role of RPLND in the management of patients with stage I disease. In a European study, adjuvant chemotherapy was superior to primary RPLND. Of note, the relapse and complication rates increased significantly outside of expert surgical centers.[34,35] Moreover, as demonstrated in an Italian study by Nicolai and colleagues, 16% of patients need chemotherapy after RPLND to eradicate the disease.[33]

Management of the 15% to 35% of patients with stage II disease revealed by RPLND remains controversial. Although adjuvant chemotherapy with 2 cycles of BEP reduces the risk of relapse,[36] phase 3 clinical trials have not shown any advantage in survival benefit from adjuvant chemotherapy.[37] Outcomes of primary RPLND significantly depend on the expertise of the treating center.[38] For these reasons, primary RPLND usually is recommended only in referral centers with a high level of expertise, and for patients who do not want and/or are not suitable for chemotherapy or active surveillance.

Biomarkers for Risk-Adapted Management of Stage I Testicular Cancer

Despite the excellent outcomes, some aspects of treatment of patients with stage I testicular cancer are controversial. Concern about the overtreatment of a young patient population and the risk of potentially significant long-term toxicity make surveillance the most attractive management option for these patients. Therefore, the development of a reliable predictive biomarker remains a priority. LVI predicts outcomes correctly in only 50% of patients with nonseminoma. No reliable biomarker exists for stage I seminoma. Only tumor volume as a continuous variable has been confirmed as a risk factor, and it only modestly discriminates between high-risk and low-risk patients.[10] Unfortunately, no new biomarkers have been identified at this stage. The association between a high percentage of embryonal carcinoma in the primary tumor and low expression of C-X-C motif chemokine ligand 12 (CXCL12) has been proposed in addition to LVI for the risk stratification of patients with stage I nonseminoma.[39] Patients classified as being low-risk, moderate-risk, or high-risk according to those risk factors had respective relapse rates of 10%, 30% to 40%, and 70%. Although interesting, these data need to be validated in larger prospective studies.

Circulating micro-RNAs (miRNAs) have been evaluated in the metastatic setting. Some miRNA clusters, in particular miR-371-373 and miR-302-367, are overexpressed in testicular cancer and negative in normal tissue, teratoma, and other cancers.[40] Moreover, their ubiquitous expression among the various histologies, patient ages, and anatomic sites make them potential universal biomarkers for both seminoma and nonseminoma. The levels of these miRNAs correlate with tumor burden and are decreased after surgery and/or chemotherapy.[41-44] Moreover, as demonstrated by Murray and colleagues in a pediatric population of patients with testicular cancer, the miRNA levels also correlated with disease recurrence.[45]

Testicular cancer is characterized by a low mutation rate compared with other highly mutated tumors (eg, bladder or pancreatic cancer). However, recent data have shown that a high mutation rate correlates with reduced sensitivity to cisplatin and poor prognosis.[46] The gene profile analysis of tumor tissue—or even better, of circulating tumor DNA—could represent another tool by which to identify patients with aggressive disease and intensify therapy accordingly, while sparing patients who do not need treatment from receiving it.

The Role of the Patient in the Decision-Making Process

Because different management options are available for the treatment of stage I testicular cancer, the risks and benefits of each option should be communicated carefully to patients. The way in which this information is explained, along with the psychological and personality characteristics of each patient, are variables that affect shared decision-making regarding the optimal treatment option. The role of the patient in this process has been analyzed. Using a standard communication approach based on the definition of the problem, a discussion of pros and cons, the endorsement of patient preferences, and an explanation of the options, Palmieri and colleagues observed that most patients choose chemotherapy over surveillance.[47] These results suggest that the shared decision-making process is affected by both patients' and doctors' perceptions of the safest approach, and that communication between patients and health care providers should be improved to avoid biases.

Conclusions

Clinical stage I testicular cancer is a highly curable disease, with a survival rate of 99% to 100%. Despite this impressive rate, some aspects in the management of patients with stage I disease remain controversial. The survival rate approaches 100% regardless of the type of treatment. As a result, efforts over the past decade have focused on maintaining cure rates while minimizing treatment-related long-term toxicity. Both the patient and the physician are important in the decision-making process, and management can be tailored to the individual patient's needs and wishes.

Disclosures

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