Stage I Seminoma: Adjuvant Treatment is Effective but is it Necessary?

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Over the past 40 years, the incidence of testicular cancer has increased in almost all populations worldwide, and it remains the most common solid malignancy in young men between the ages of 20 and 35 years. Primary germ cell tumors are the predominant histological type, with approximately 60% of germ cell tumors being pure seminoma, 30% being nonseminomatous germ cell tumors, and 10% being mixed tumors (1). In the United States, 8480 new diagnoses and 350 deaths from the disease have been projected for 2010 (2). Because 80%–85% of seminoma patients present with disease that is clinically confined to the testis, more than 50% of all patients with newly diagnosed testicular cancer have stage I seminoma.

Post-orchiectomy management in stage I seminoma includes surveillance, with treatment reserved for those who relapse, or adjuvant treatment with either radiation therapy or chemotherapy. Regardless of the management strategy used, nearly 100% of patients are ultimately cured. In this issue of the Journal, Mead et al. (3) report on the mature results of three large randomized trials (TE10, TE18, and TE19) of adjuvant therapy in patients with stage I seminoma. Results from these trials indicate that 1) if adjuvant radiation therapy is given, that a dose of 20 Gy in 10 fractions is all that is necessary; 2) if the para-aortic lymph nodes alone are treated, that the pelvic relapse rate is low (approximately 2%); and 3) both adjuvant radiation therapy and one course of carboplatin give a relapse rate of approximately 5%. The trials also provide extensive information about relapse sites and timing of relapse. The Medical Research Council investigators are to be congratulated for this major contribution to our body of knowledge about the management of stage I seminoma.

Although these trials address the relative merits of differing adjuvant therapy strategies, a key question is whether adjuvant therapy is necessary at all? Between 1950 and 1990, adjuvant radiation therapy was the standard treatment of stage I seminoma. However, during the past 20 years, mounting evidence has led to concern regarding the late effects of radiation therapy. The most important and worrisome late complication of radiation therapy is the risk of second nontesticular cancers. Since this increased risk is expressed more than 10–15 years after treatment, it is not apparent in most published series with shorter follow-up. Travis et al. (4) combined 14 population-based registries that included 10 534 patients with seminoma (all stages) treated with radiation therapy and estimated that for a 35-year-old patient with seminoma, the cumulative 40-year risk of a second malignancy if treated with radiation therapy was 36% compared with 23% in the normal population. A Dutch population-based study (5) of 2707 testicular cancer survivors with a median follow-up of 17.6 years showed that the rate of second nontesticular cancers was increased 2.6-fold among patients treated with radiation therapy compared with those treated with surgery alone. The increased risk associated with radiation therapy was similar to the increased cancer risk that is associated with smoking. Of additional concern was that those with second cancers had a median survival of only 1.4 years after that diagnosis.

There are now persuasive data to suggest that long-term survivors of testicular seminoma who are treated after orchiectomy with infradiaphragmatic radiation therapy are at a clinically important excess risk of cardiac disease (6,7). In the M.D. Anderson series of 453 patients who were treated between 1951 and 1999, the standardized cardiac mortality ratio for patients more than 15 years after infradiaphragmatic radiation therapy was 1.80 (95% confidence interval [CI] = 1.01 to 2.98) (7). Huddart et al. (6) reported a similar increase in cardiac events in a cohort of 992 patients who were treated at the Royal Marsden Hospital (risk ratio = 2.4, 95% CI = 1.04 to 5.45) among those who were treated with radiation therapy compared with those who were managed by surveillance. Recently published data from Norway indicate that long-term survivors of germ cell tumors that were treated with infradiaphragmatic radiation therapy have a fourfold increased risk of having a myocardial infarction compared with those who were managed with surgery alone (8).

The use of short-course carboplatin (one or two injections) as adjuvant therapy after orchiectomy has been investigated as an alternative strategy in stage I seminoma. Data from Mead et al. (3) on 537 patients who were treated with a single injection of carboplatin show a relapse rate of 5.35% (95% CI = 3.7% to 7.5%). The median follow-up was 6.5 years, and it is encouraging that only one relapse occurred after 3 years. Data from other single-institution series indicate that if adjuvant carboplatin is given in this setting, two courses of treatment may be necessary (9). However, if carboplatin dosing is based on an area under the curve of 7, as used by Mead et al. (typically approximately 15% greater than using a square meter dosing regimen), then a single course of treatment is likely all that is necessary (10). The major unanswered question about carboplatin chemotherapy in this setting is whether there are serious late effects of treatment. Although the total dose of the chemotherapy used in the treatment of stage I seminoma is low compared with the chemotherapy given for more advanced-stage disease, only long-term follow-up studies will inform us whether there are long-term health issues associated with one or two doses of carboplatin. Moreover, the use of adjuvant carboplatin in stage...
I seminoma will result in approximately 5% of patients who will receive two episodes of treatment, which may also increase the risk of late complications. The relapse pattern after adjuvant carboplatin treatment mandates that continued cross-sectional imaging of the retroperitoneal lymph nodes is required for a minimum of 3 years after treatment.

The success of surveillance in stage I nonseminomatous germ cell testis tumors as well as improvements in diagnostic imaging led to studies of surveillance in stage I seminoma. The data from numerous prospective nonrandomized studies on surveillance are now mature, and relapse rates have consistently been reported to be approximately 15% in unselected populations of patients with stage I disease (Table 1) (11–15). At relapse, most patients can be cured with retroperitoneal radiation therapy. A concern in the past regarding surveillance was the possibility of exposing these patients to an increased burden of treatment because of the need for combination chemotherapy that resulted from relapse with bulky retroperitoneal disease. However, data from Princess Margaret Hospital on 764 patients with stage I seminoma (484 on surveillance and 280 on adjuvant radiation therapy) showed that the 10-year actuarial risk of requiring chemotherapy was similar with both approaches (16). Patients managed with surveillance had an average of 0.16 episode of treatment with radiation therapy, chemotherapy, or surgery compared with 1.05 episodes for those treated with adjuvant radiation therapy.

A risk-adapted approach to management has been proposed by the Spanish Germ Cell Cancer Cooperative Study Group with surveillance reserved for low-risk patients and adjuvant therapy for intermediate- and high-risk patients (9). This strategy was based on a prognostic model of tumor size and rete testis invasion that has been shown in a pooled analysis of patients to predict relapse (17). However, a study that used an independent data set of 687 patients and median follow-up of 4 years has found that tumor size is the only factor that predicts relapse and that rete testis invasion is not of prognostic importance. Thus, risk-adapted management cannot be recommended because the prognostic model that it is based on has not been validated. In addition, even if correct, the model does not have sufficient discrimination to be clinically useful because even patients in the high-risk group have a greater than 65% chance of being relapse free on surveillance.

The optimal follow-up strategies need to be determined to minimize the effect of radiation exposure during follow-up because the use of repeated computed tomography scans of the abdomen likely increases the risk of induced cancer, given the young ages of many patients. Magnetic resonance imaging is currently being compared with computed tomography imaging in the TRISTT study (TE24), which is led by the National Cancer Research Institute in the United Kingdom. This study also addresses follow-up frequency by comparing three visits with seven visits over a 5-year period. An alternative approach is to use low-dose computed tomography, which considerably reduces the radiation exposure associated with standard dose computed tomography scans in patients with testicular germ cell tumors at the expense of slightly degraded image quality (18).

Cure without long-term sequelae of treatment is the goal of management in stage I seminoma, and there are increasingly persuasive data that adjuvant radiation therapy in this setting is associated with a small but definite increased risk of second malignancy and cardiovascular disease. Long-term toxicity data are not available for adjuvant carboplatin. The results from surveillance series have documented the safety of this approach, and in a compliant patient, surveillance should be considered the management option of choice and is recommended by the European, Canadian, and Societe Internationale d’Urologie consensus documents (19,20). It is disappointing to note that in a recent survey of Radiation Oncologists in the United States that more than 60% still routinely recommend adjuvant radiation therapy despite the clear risks associated with this strategy.

## References

the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). 


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