Controversies in the Management of Stage I Seminoma

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Current controversies in the treatment of stage I seminoma center on the relative roles of surveillance, adjuvant radiotherapy (RT), and adjuvant single-agent chemotherapy. Surveillance has been studied in over 800 patients,

Introduction

In the United States, an estimated 7,200 new cases of testicular cancer were diagnosed in 1997, but only 340 deaths were attributable to this cancer.[1] Seminoma represents about 50% of all germ-cell tumors and is the most common histologic type of testicular cancer. Seminoma has long been recognized as a radiosensitive and chemosensitive neoplasm.

Stage I testicular cancer includes all patients without lymph node involvement or distant metastatic spread (T1-4 N0 M0) and represents 70% of all cases of seminoma.[2] A new staging system for testicular cancer now includes the presence of vascular lymphatic invasion and marker elevation, as shown in Table 1. The stage groupings have also been modified in this new system.

The management of stage I testicular cancer has followed the lead of other successfully treated cancers, including Hodgkin’s disease and various pediatric malignancies. The primary end point of many ongoing studies in these tumors is not to improve efficacy, but rather, to lessen toxicity from equally effective therapies. Several older studies have shown that the mediastinum can be omitted from the treatment volume of irradiated patients, even those with stage IIA disease, thus eliminating the potential toxicity associated with thoracic radiotherapy (RT).

The management of stage I seminoma continues to evolve. Currently, there are significant controversies regarding the relative roles of adjuvant RT, surveillance, and adjuvant single-agent chemotherapy. This review focuses on the changing management of this very curable neoplasm and addresses the results and toxicity of standard-volume RT, reduced-volume RT, surveillance, and adjuvant single-agent chemotherapy after orchiectomy. Potential salvage therapies for rare primary treatment failures are also discussed.

Standard Adjuvant Therapy: Para-aortic and Pelvic RT

Standard therapy for all patients with early-stage seminoma includes radical inguinal orchiectomy with high ligation of the spermatic cord. Scrotal violation has never been shown to compromise survival, but may preclude patients from the option of postoperative surveillance and may alter RT volumes, leading to the delivery of unnecessary dose to normal tissues, including the remaining testicle. Any additional therapy besides orchiectomy in stage I seminoma is adjuvant in nature and is designed to treat subclinical nodal or micrometastatic spread.

Radiation therapy has been a standard adjuvant treatment for early-stage seminoma. The patterns of dissemination include progressive spread from the retroperitoneum to the mediastinum and supraclavicular lymph nodes. This was the rationale for extended-field RT in early-stage seminoma, which often included elective treatment of the mediastinum and supraclavicular lymph nodes. Prior to the advent of cisplatin (Platinol), extensive-field RT cured a significant number of patients, even those with lymphadenopathy.

Hanks et al found that 27% of patients with clinical stage I seminoma treated in the US Patterns of Care Study received supradiaphragmatic RT, and more than half received subdiaphragmatic doses > 30 Gy.[3] In the Norwegian Radium Hospital series (1970 to 1982), radiation was delivered to a median dose of 40 Gy prior to 1980, with only one field treated each day.[4] Since current RT doses
and volumes are much lower, interpretation of the toxicity data from series with the longest follow-up must take this into account.

**Efficacy**

Table 2 summarizes the relapse-free survival rates of stage I seminoma patients treated with standard ipsilateral pelvic and para-aortic RT in several studies.[3-11] Many of these reports included some patients treated in the 1950s and ‘60s. Overall, about 95% to 97% of patients were relapse-free after standard adjuvant RT. Most of the deaths from seminoma in these series occurred in the platin era. The patterns of failure after RT indicated that seminoma is a very radiosensitive neoplasm.

Dosmann et al found no recurrences in the treatment field in 282 patients with stage I seminoma treated with adjuvant RT.[5] Similar results have been seen in other institutions.[7]

**Toxicity**

Delayed toxicity after RT, although generally occurring at a low frequency, is important given the high likelihood of disease control. Toxic events related to RT include infertility, cardiotoxicity, gastrointestinal toxicity, second neoplasms, and immunosuppression.

**Infertility** is an important issue for many men with seminoma. The average patient with seminoma is approximately 35 years old. Whether infertility is the result of surgery, adjuvant therapy, a coexisting testicular abnormality, or a combination of all of these factors is unknown.

Southwest Oncology Group (SWOG) trial 8711 prospectively followed 53 patients treated with orchiectomy and adjuvant pelvic and para-aortic irradiation.[12] Over half (54%) of the patients with baseline sperm counts were subfertile. Lower testicular doses (< 0.79 Gy) were achieved when testicular shields were used, and this protection was associated with beneficial effects on 1-year sperm counts. Sperm count recovered 1 year after RT in the low-testicular-dose group but was delayed in patients who received higher doses. Similar changes were seen in serum follicle-stimulating hormone (FSH) concentration but not in serum testosterone level.

**Cardiotoxicity**—Elective mediastinal RT was associated with an excessive number of cardiac deaths in the Patterns of Care series.[13] The cardiac toxicity of mediastinal RT was subsequently confirmed in Hodgkin’s disease.

Elective mediastinal therapy has no role in stage I seminoma, as relapse-free survival is excellent without it.[6] Only about 1.9% of patients with clinical stage I seminoma treated with standard pelvic and para-aortic RT will develop disease recurrence in the mediastinum or supraclavicular lymph nodes.[14] In stage II seminoma, the risk of mediastinal recurrence depends on the size of the para-aortic metastasis. In general, mediastinal therapy has been abandoned in patients with retroperitoneal tumors < 5 cm in favor of preservation of bone marrow for salvage chemotherapy, and in order to avoid late cardiac toxicity.

**Gastrointestinal Toxicity**—Late gastrointestinal toxicity has been reported after irradiation to the abdomen. In 365 stage I seminoma patients receiving relatively high doses of adjuvant RT, Fosså et al described 9 patients who developed gastric ulceration and 16 who experienced dyspepsia.[4] The median mid-plane dose in this study was 40 Gy. More conventional regimens, such as 25.5 Gy in 17 fractions, should have significantly lower rates of gastrointestinal toxicity.

**Second Neoplasms**—Much of the data on second malignancy after pelvic and para-aortic irradiation comes from large population registries or much smaller single-institution reports. Unfortunately, since many of the larger studies lack details on treatment, the relative contribution of RT is difficult to determine. Data are often combined for seminoma and other types of germ-cell tumors.

These limitations notwithstanding, the long-term toxicity data indicate that patients who have been irradiated for seminoma have a higher rate of second malignancy than age-matched controls. Second testicular tumors are probably not related to treatment, but rather, stem from a
predisposition to germ-cell neoplasms. This phenomenon has been readily observed in patients with cryptorchid testes and has also been confirmed by large population studies.

Wanderås et al updated the Norwegian Radium Hospital experience with second germ-cell tumors, including 2,201 patients with primary germ-cell tumors.[15] In 1,135 patients with seminoma, the cumulative risk of a second germ-cell tumor was 3.4% at 15 years (relative risk [RR], 27.7). Age may be an important risk factor for posttherapeutic neoplasia. Patients diagnosed with a germ-cell tumor when they were under 30 years of age had a cumulative risk of 7.8% at 15 years.

Hanks et al found 14 second tumors among 387 patients treated with RT for stage I and II seminoma.[13] This corresponded to an 8% risk at 15 years (RR, 3.4). Of the 14 second malignancies, 2 were leukemias, 1 was an in-field melanoma, and 1 was a second testicular tumor. All of the remaining malignancies were marginal or out-of-field tumors.

A large, population-based study from Denmark included 3,256 patients with seminoma treated from 1943 to 1987 with various modalities.[16] For all second malignancy sites, the overall relative risk was 1.5 compared to the expected incidence in the overall population. A statistically significant increased risk was seen for cancers of the stomach (RR, 1.9), colon (RR, 1.7), pancreas (RR, 2.1), kidney (RR, 2.2), and bladder (RR, 2.1); nonmelanoma skin cancer (RR, 1.8); and leukemia (RR, 2.3). Only 1 of the 13 patients who developed leukemia had received chemotherapy.

What cannot be ascertained from these studies is whether RT causes a higher rate of second tumors, or whether seminoma patients are predisposed to developing second tumors even without RT. Three studies have compared the rate of second malignancy in patients who did and did not receive RT.

In a large, population-based study of second non-germ-cell tumors in patients from Norway, Wanderås et al found a relative risk of 1.58 (95% confidence interval [CI], 1.3 to 1.9) in patients who received RT without chemotherapy, 3.54 (95% CI, 2.0 to 5.8) in patients who received RT and chemotherapy, and 1.31 (95% CI, 0.4 to 3.4) in patients who received neither RT nor chemotherapy.[17] Even when second germ-cell tumors were excluded in this study, the relative risk of secondary malignancy was still greater than 1 in patients treated with surgery alone, possibly indicating that these patients are at an increased risk of second tumors even without cytotoxic therapy, (although the 95% CI included 1).

The Connecticut Tumor Registry data combined with the Surveillance, Epidemiology, and End Results (SEER) data of the National Cancer Institute (NCI) included 9,739 patients with testicular tumors (all histologies).[18] Ten-year survivors of seminoma were at increased risk for cancers of the pancreas (RR, 3.23), kidney (RR, 3.22), and bladder (RR, 2.94), as well as acute nonlymphocytic leukemia (RR, 5.77). This study confirmed the findings of the Norwegian population study that excess second tumors occur at a higher rate in patients treated with surgery alone (RR, 1.40).

Testicular cancer patients undergoing RT in the Netherlands had a relative risk of 4.4 for a second gastric cancer.[19] No increased risk was seen in patients who were treated with surgery alone, but since there were so few cases of gastric cancer, the 95% confidence intervals overlapped significantly. The relative risk of gastric cancer did increase with follow-up interval, suggesting that RT had some role in causation.

Unfortunately, follow-up from the more recent prospective surveillance studies is not long enough for an accurate assessment of second malignancies to be made. It is interesting to note that some of the tumors ascribed to RT, such as gastric cancer, have been seen in surveillance patients as well.[20]

Immunosuppression—Total lymphoid irradiation, as used in Hodgkin’s disease, is chronically immunosuppressive.[21] Alterations in CD4+ lymphocyte counts have been described in this setting. Similar changes may occur after para-aortic and pelvic RT for seminoma. Any role this potential immunosuppression may play in the pathogenesis of second malignancies is unknown.
The availability of successful salvage therapy for seminoma has called into question the need for routine adjuvant therapy. Cisplatin-based chemotherapy has been remarkably successful in the treatment of advanced testicular tumors, curing 70% to 80% of patients who present with advanced disease. Relapse-free survival using single-agent carboplatin (Paraplatin) for the treatment of advanced seminoma is 77%. Seminoma is an exceptional neoplasm in that even a significant number of patients with brain metastases can be cured. Cisplatin has also been successful as a salvage treatment in patients with stage II seminoma who do not respond to primary RT and in the few patients with stage I disease whose disease recurs after adjuvant RT.

An older surgical series suggested that only 8% of clinical stage I seminoma patients have pathologic involvement of the para-aortic lymph nodes. Based on surveillance studies in nonseminomatous germ-cell tumors and these surgical data in seminoma, several institutions have begun to explore surveillance after radical inguinal orchietomy to better evaluate the natural history of stage I seminoma.

Although a randomized trial comparing surveillance and standard adjuvant therapy has never been performed, early single-arm trials have had encouraging results. These studies generally employed an aggressive follow-up regimen to facilitate early detection of recurrence. Some of the studies included both computed tomography (CT) and lymphangiography as staging modalities.

The results of these studies of surveillance regimens are summarized in Table 3. Actuarial results are given when available, as well as crude failure rates. Not all of these studies represent unselected series, as some considered patient preference and logistical factors in the selection of therapy. Also, in some studies, selected patients thought to be at a higher risk for recurrence underwent RT.

Overall, more than 800 patients undergoing surveillance have been reported with varying lengths of follow-up, 17.1% (145/850) of whom have relapsed. The largest single report comes from the Danish Testicular Carcinoma (DATECA) Study Group, which followed 261 patients for a median of 48 months. The 4-year actuarial relapse-free survival rate was 80%. Long-term follow-up from these studies will provide information regarding the patterns of failure and the relative risk of second malignancy in surgically treated patients with seminoma.

**Risk Factors for Relapse**

Identification of prognostic factors for relapse after radical inguinal orchietomy alone would enable the selection of appropriate patients for adjuvant therapy rather than salvage therapy. Patients without these risk factors could be spared adjuvant therapy and might not need an aggressive surveillance regimen.

The surveillance series with the most data on recurrence after surgery is also the DATECA study. The 4-year actuarial rate of relapse was 20% after orchietomy alone. Univariate analysis revealed tumor size, histologic subtype, presence of necrosis, and invasion of the rete testes to be predictive of recurrence, but only tumor size was a statistically significant predictor on multivariate analysis. The 4-year relapse-free survival rate was 6% for tumors < 3 cm, 18% for tumors 3 to 6 cm, and 36% for tumors > 6 cm. The largest tumors (> 6 cm) represented about 25% of the study population.

In a study from London, Horwich et al found that patients with both lymphatic and vascular invasion are at an increased risk for failure after orchietomy alone. Failures occurred in 4 of 42 patients with neither lymphatic nor vascular invasion and 9 of 53 patients with either risk factor, as compared with 3 of 8 patients with both lymphatic and vascular invasion (P = .05). A nonstatistically significant trend toward worse relapse-free survival was seen in patients with either lymphatic or vascular invasion.

A retrospective study by Marks et al from Duke University showed that lymphatic vascular invasion predicted for clinical stage II or greater disease on multivariate analysis. Nativ et al from the Mayo Clinic found that tumor ploidy was strongly associated with stage. None of the surveillance studies has evaluated this prognostic factor. Dosmann et al have suggested that an elevated beta-human chorionic gonadotropin (beta-HCG) level after orchietomy is equivalent to
"biochemical" stage II disease.\cite{5}

The relative merit of each of these factors is unclear, but certainly patients with a confirmed, elevated beta-HCG after orchiectomy should not be offered surveillance. In addition, the DATECA Study Group concluded that adjuvant RT should be offered to patients with tumors > 6 cm.\cite{20}

**Economic Impact of Surveillance**

The optimal postorchiectomy surveillance regimen is unknown, and therefore its economic impact is also unclear. At present, there is no evidence for a decrease in survival when surveillance is used, if compliance with follow-up is ensured. Salvage therapy with radiation or chemotherapy occurs in almost all patients. As shown in Table 3, only 4\% (6/145) of patients who relapsed eventually died from seminoma. This represents fewer than 1\% of all patients who underwent surveillance. It is conceivable that the death rate may be higher with longer follow-up, as some patients develop several recurrences before ultimately dying of their disease.

Most recurrences are asymptomatic, and the optimal method and frequency of diagnostic evaluation are unclear. The economic impact of surveillance obviously depends on the follow-up regimen employed. At least two analyses have been performed to assess the economic impact of surveillance.

Warde et al at Princess Margaret Hospital evaluated a surveillance protocol of abdominopelvic CT at 4-month intervals for 3 years, then every 6 months for 4 years, and every 12 months for 3 years.\cite{26} Including the cost of salvage treatment and the diagnostic evaluation as outlined, surveillance was more expensive, with an average cost of $262 (Canadian) per year for 10 years. A less intensive follow-up surveillance regimen may be less costly, but the efficacy of salvage therapy may also be lower if treatment is delayed until symptoms develop.

Sharda et al assumed an equivalent clinical outcome with surveillance and adjuvant RT and used a cost-minimization model.\cite{36} Costs were analyzed from the perspective of the payor. In the surveillance regimen, follow-up constituted 91\% of all costs, and salvage chemotherapy comprised only 9\%. The higher ongoing costs associated with surveillance surpassed the upfront cost of adjuvant RT after 2.5 years. Using University of Wisconsin reimbursement rates, surveillance cost $20,487 (1994 dollars) over a 5-year period, as compared with $14,722 for adjuvant RT.

Several factors can confound economic analyses comparing surveillance and various adjuvant strategies. First, cost varies with the length of intensive follow-up, and the optimal duration of surveillance follow-up is unclear. Most recurrences occur within 2 to 3 years, but cases of very late recurrences after treatment have been documented. In the report by Blanke et al, a patient developed a recurrence 21 years after therapy.\cite{37} In the Toronto surveillance study, 4 of the 23 relapses occurred after 4 years.\cite{38}

Second, the optimal RT dose and fractionation scheme are unknown. A dose of 20 Gy in 8 or 10 fractions may be as effective as 30 Gy in 15 fractions, as discussed below, but the costs of the two regimens are very different.

Third, if adjuvant chemotherapy is to be used, how many cycles and which drugs are needed? The current Medical Research Council (MRC) trial is allowing the use of either adjuvant cisplatin or carboplatin because of questions regarding the relative efficacies of these regimens in the setting of advanced seminoma.\cite{39}

**Other Problems Associated With Surveillance**

Surveillance has other potential problems. Despite attempts to closely follow patients, Horwich et al found that 4 of 17 relapses were moderately bulky.\cite{25} All of these patients underwent successful salvage therapy, but more advanced disease has the potential to compromise the efficacy of salvage therapy.

Unlike nonseminomatous tumors, seminoma does not have a reliable tumor marker to aid in the
early detection of recurrent disease. A large prospective trial from Germany found that the combined sensitivity of beta-HCG, lactic dehydrogenase (LDH), and placental alkaline phosphatase (PLAP) was 84%.[40]

Placental alkaline phosphatase was the most sensitive marker for detecting metastatic disease, but 49% of patients with known metastatic disease did not have an elevated level. Placental alkaline phosphatase also was the most sensitive indicator of relapse, but its specificity was low because of a false elevation in smokers.

Beta-HCG can also be falsely elevated in patients successfully treated for seminoma and, thus, should not be used as the sole indicator of relapse without confirmation.[41]

**Omission of the Pelvic Radiation Field**

Omission of the pelvic field has been proposed as a possible strategy to lessen the long-term morbidity of adjuvant RT. An example of a para-aortic-only radiation treatment field is shown in Figure 1 and is contrasted with the standard portal.

**Data on Patterns of Failure**

The best data on the patterns of failure come from the DATECA surveillance study.[20] Of the 49 recurrences, most were in the para-aortic lymph nodes (41), followed by the pelvic nodes (5), inguinal nodes (2), and lungs (1). Since the inguinal nodes may or may not be in the irradiated field, only 5 to 7 of the total 261 patients would have derived an advantage from elective pelvic RT.

Kiricuta et al reported the results of 86 patients with stage I (T1-2 N0 M0 only) seminoma treated with adjuvant para-aortic RT (L1-L5) to a median dose of 30 Gy.[42] The pelvic field was omitted in all patients. Staging included either a lymphangiogram or pelvic CT. No patient underwent prior orchiopexy, inguinal hernia repair, or pelvic surgery.

With a median follow-up of 63 months, the 5-year disease-free survival rate was 95.3%; no patient died of seminoma. Four patients relapsed, with one failure occurring in the ipsilateral pelvic lymph nodes and one in the inguinal scar. One of these patients was salvaged with 36 Gy of RT alone (2.6 years of follow-up), while the second patient was successfully salvaged with chemotherapy (7.7 years of follow-up).

Since standard RT portals may or may not cover the entire inguinal scar, only one or two patients in this series would have potentially benefited from adjuvant pelvic RT. Both were apparently successfully salvaged. There was no discussion of gastrointestinal toxicity or fertility in the report. Furthermore, as highlighted in an accompanying editorial, an additional 31 patients whose superior treatment border was T12 rather than L1 were excluded from the analysis. It is unknown whether the rate of recurrence was higher in this subset of patients.

The MRC and European Organization for Research and Treatment of Cancer (EORTC) performed a phase III trial evaluating the role of adjuvant pelvic RT in 478 men with T1-3 N0 M0 seminoma who had not undergone previous inguinal surgery prior to orchiectomy.[43] These patients were randomized to para-aortic RT alone or para-aortic and ipsilateral pelvic RT. Both arms employed the same dose: 30 Gy delivered over 3 weeks. The RT volume in the para-aortic arm was larger than that used by Kiricuta et al and included T11 to L5.

After a median follow-up of 36 months, the relapse-free survival rate was 96% in patients given para-aortic-only treatment and 97% in those who underwent para-aortic and ipsilateral pelvic therapy ($P = .97$). Of the 18 relapses, 4 were in the pelvis, and no patient who received adjuvant pelvic RT developed a pelvic failure.

Rates of grade 2 or higher myelotoxicity and gastrointestinal toxicity appeared to be lower in the group who received para-aortic-only treatment. In addition, 9 to 18 months after therapy, 31% of patients who received para-aortic-only treatment were azoospermic, as compared with 18% of those
who received pelvic RT (P = .02).

Thus, the MRC trial results suggest that the addition of the pelvic field may decrease the rate of pelvic failures but does not have a major impact on relapse-free survival. A reduction in RT volume seems to decrease the risk of toxicity without increasing the risk of mortality. Follow-up is too short to assess whether the smaller volume irradiated is associated with fewer second neoplasms. Further follow-up since presentation of the abstract has not altered the conclusions of this study.[D. Fosså, personal communication, 1997]

Jacobsen et al used in vivo and phantom measurements of testicular radiation doses to compare para-aortic and ipsilateral pelvic RT with para-aortic-alone RT, as employed in the MRC/EORTC trial.[44] External gonadal shielding was used in patients who received pelvic RT but not in those treated with para-aortic-only therapy. A higher mean testicular dose was seen with para-aortic and pelvic RT than with para-aortic-alone treatment (32 vs 9 cGy). This difference correlated with an increase in FSH concentrations for all patients and a drop in sperm count for those with a pretreatment sperm count \( \geq 10 \times 10^6/mL \) who received pelvic RT. Patients treated with para-aortic-alone RT did not have significant changes in sperm count.

Advantages and Disadvantages of Omitting the Pelvic Field

There are many potential advantages of omitting the pelvic field from the RT volume. Less scatter dose to the remaining testicle allows for potentially better fertility and fewer endocrine sequelae. Smaller volumes should be better tolerated acutely, and late gastrointestinal toxicity may be less frequent, although the reported incidence of small bowel toxicity is very low with the modest doses required to sterilize microscopic seminoma. In addition, patients who require salvage chemotherapy may tolerate aggressive treatment better if the pelvic field is eliminated.

Omission of the pelvic field does have potential disadvantages, however. First, it is unclear whether all patients should undergo surveillance pelvic CT scans during routine follow-up. If so, how long should pelvic CT be continued? Kiricuta et al found no treatment failures after 2 years, but late recurrences have been described in other series.[42]

Also, surveillance has both psychological and economic implications, as discussed above. Caution should be exercised when considering surveillance in patients with prior pelvic, inguinal, or scrotal surgery, as lymphatic channels may have become disrupted; patients with prior surgery were not eligible for reduced-volume RT in the MRC study.

Furthermore, it is unknown whether the pelvic field can be safely omitted in patients with a history of undescended testes. Mason et al evaluated the risk factors for clinical inguinal or iliac nodal disease in 1,191 patients with germ-cell tumors of the testes. They found that bulky para-aortic nodes, a history of maldescent, or orchiopexy increased the risk of inguinal or iliac nodal spread.[45]

Finally, the results of adjuvant stage I para-aortic RT should not be extrapolated to the treatment of stage IIA seminoma without further study. Although surgical series have shown an increased risk of pelvic nodal involvement when there is known para-aortic disease, a recent multicenter report of stage II seminoma found that the lower RT border could be placed at the top of the acetabulum.[46]

Reducing the Adjuvant RT Dose

A review of the patterns of care of patients treated in the United States from 1973 to 1974 indicated that only 10% of patients with stage I seminoma received \( \leq 25 \) Gy of subdiaphragmatic RT and that 20% received > 35 Gy.[13] Seminoma is very sensitive to ionizing radiation; gross stage II disease has been controlled with moderate doses, such as 30 to 35 Gy.[5] The optimal dose to control microscopic disease is unknown, but is probably < 30 Gy in 15 fractions, as in-field failures are extremely rare.

The MRC is currently conducting a phase III study evaluating RT dose. Patients are being randomized to 30 or 20 Gy of para-aortic RT. Neither group is receiving pelvic RT. The hypothesis under study is
that a reduction in dose will not significantly compromise relapse-free survival but will result in fewer late effects. This hypothesis is supported by the large retrospective experience in the Patterns of Care series in which high radiation doses were associated with an increased risk of late gastrointestinal toxicity after infradiaphragmatic RT.[47]

**Adjuvant Chemotherapy**

**Efficacy and Toxicity**

The success of chemotherapy in advanced seminoma has led to the potential expansion of its use in the adjuvant setting. Several phase II and single-institution noncontrolled studies have evaluated adjuvant carboplatin chemotherapy in stage I seminoma (Table 4).[10,48-50] In the total of 300 patients treated with either one or two cycles of adjuvant chemotherapy, there were only four failures, for a crude relapse-free survival rate of 98.7%. Thus, the efficacy of this approach compares favorably to that of adjuvant radiation. The acute toxicity of adjuvant chemotherapy is generally mild and consists of nausea, which can be medically controlled, low-grade hematologic toxicity, and fatigue.

Dieckmann et al evaluated the endocrine and gonadal toxicity of adjuvant carboplatin therapy by obtaining serial measurements of serum FSH in a subset of patients.[48] Only mild elevations of serum FSH were seen, and two patients were able to father children. A retrospective comparison of the quality of life of patients undergoing adjuvant RT or chemotherapy revealed only minor differences, but did find that patients who received only a single course of carboplatin returned to work earlier than those who received two courses.

**Second Neoplasms**—Whether or not adjuvant chemotherapy has an effect on the rate of second testicular neoplasms is unclear. Oliver et al reported no cases of second testicular tumors in 78 patients who received adjuvant chemotherapy, as compared with three second testicular tumors in 67 patients who were observed.[10]

In a study 2,201 Norwegian men with primary germ-cell tumors, Wanderås et al did not find that previous use of cytotoxic chemotherapy decreased the risk of second germ-cell tumors.[15] Of the nine patients with second germ-cell tumors who had previously received cytotoxic chemotherapy, seven had been treated with cisplatin-based regimens.

Single-agent chemotherapy may have a small risk of leukemia induction, as both single agent cisplatin and carboplatin have been implicated in case reports of acute promyelocytic leukemia.[29,51]

**Economic Impact of Adjuvant Chemotherapy**

The cost to treat a patient with a single course of carboplatin includes the cost of the drug, mixing and preparation by the pharmacy, nursing care during drug delivery, physician fees, and other hospital costs, including laboratory fees. Carboplatin (600 mg) costs the pharmacy at the University of Michigan about $775.[University of Michigan pharmacy, personal communication, 1998] Estimates for the costs of delivery of RT are more difficult to calculate than the actual charges to a patient. Nevertheless, a single cycle of carboplatin should have a favorable cost compared to even abbreviated RT regimens, such as 20 Gy in 10 fractions.

Medical Research Council trial TE19 is an ongoing phase III study that is comparing adjuvant RT with adjuvant carboplatin for stage I seminoma.[T. Oliver, personal communication, 1998] The study is designed to determine whether a single cycle of carboplatin is equivalent to adjuvant RT. A total of 800 patients are expected to be enrolled over 4 years, which gives the study 94% power to detect a 4% difference in recurrence rates (one-sided t-test, P = .05). Quality of life is a secondary end point. Follow-up from this study will provide information on the relative efficacy of adjuvant RT and single-agent chemotherapy, as well as the long-term toxicity. This study has been amended to permit the administration of either cisplatin or carboplatin.[39]
Conclusions

Stage I seminoma can be successfully treated with adjuvant RT with very few deaths. The current challenge is to minimize morbidity, as serious toxicity occurs late after treatment.

The use of surveillance after orchiectomy eliminates certain types of treatment-related morbidity but must be done carefully and only in properly selected patients who are committed to appropriate follow-up.

Data from a European randomized trial indicate that omission of the pelvic portion of the standard RT portal should be considered. Whether follow-up imaging studies should be modified to include pelvic CT in patients so treated is unclear, however.

Early studies of adjuvant, single-agent chemotherapy demonstrate efficacy and relatively modest toxicity. Further follow-up from these studies, as well as the ongoing MRC randomized trial, will better define the role of adjuvant chemotherapy in stage I seminoma.

The relative economic impact of each of these management strategies remains to be determined, but such information will undoubtedly influence the management of stage I seminoma.

References:


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