Dr. Raghavan is to be commended for a concise and comprehensive overview of the management of germ cell tumors. As he suggests, given the demographics of this relatively uncommon disease and the high cure rate that can be achieved with proper treatment and follow-up, it behooves us to maintain these excellent results, even while striving to reduce the toxicity of treatment. We will highlight a few additional points to complement this superb review.

Dr. Raghavan refers to the possibility of rigorous surveillance as opposed to adjuvant radiation for stage I seminoma. Published data would suggest that almost all patients with this disease are cured regardless of the management strategy selected after orchiectomy. This issue is important because the largest published study of long-term survivors of testicular cancer linked prior abdominal irradiation in seminoma patients with an excess risk of cancers of the stomach, bladder, and pancreas.[1]

One of the reasons for reluctance to adopt surveillance as a management option has been the lack of well-defined prognostic factors for disease relapse. A recent pooled analysis by Warde et al.[2] illuminates this issue. These authors analyzed the outcomes of 638 patients with stage I seminoma treated by orchiectomy followed by surveillance for a median of 7 years. The 5-year relapse-free survival rate for this patient cohort was 82%, and multivariate analysis revealed that primary tumor size greater than > 4 cm and rete testis invasion were predictive of relapse. Prospectively validated, these results could be used to select management for stage I seminoma—adjuvant therapy or observation—on the basis of individual risk of relapse.

Risk of Relapse

In stage IIA or IIB seminoma, current practice is to treat patients with para-aortic and ipsilateral pelvic node irradiation. However, retrospective studies report postirradiation relapse rates of 0% to 11% for stage IIA and 9% to 18% for stage IIB seminoma.[3-7] In an effort to further reduce the risk of relapse, Patterson et al.[8] recently reported their experience with a short course of chemotherapy prior to radiation therapy. Of 33 patients treated by this approach, 30 received a single course of carboplatin (Paraplatin) at a dose of 400 mg/m² or an area under the concentration-time curve (AUC) of 7 at 4 to 6 weeks prior to radiation, 2 received two courses of carboplatin, and 1 received a single course of carboplatin and etoposide. Outcomes for these patients were compared with historical controls treated with radiation alone at the same institution.

At a median follow-up of 4 years, 2 of the 33 chemotherapy-treated patients had relapsed, for a 5-year relapse-free survival of 97%. Among the radiation-alone controls with a median follow-up of 11 years, 15 of 80 patients had relapsed, for a 5-year relapse-free survival of 81%. Not surprisingly, the difference in relapse rates was more pronounced for patients with stage IIB disease, in whom 5-year relapse-free survival rates were 5.3% (vs 29%). Given the minimal toxicity associated with a single course of carboplatin, these interesting results warrant further study, particularly in patients with stage IIB disease.

NSGCT Treatment

Another issue that remains a topic for debate is the choice of chemotherapy regimen for patients
with good-prognosis nonseminomatous germ cell tumors (NSGCT). As detailed by Dr. Raghavan, BEP (bleomycin [Blenoxane], etoposide, cisplatin [Platinol]) was shown to be equivalent to PVB (cisplatin, vinblastine, bleomycin) with less toxicity. In addition, the number of cycles of BEP can safely be reduced from four to three in the good-risk patient cohort.

Further efforts concentrated on the omission of bleomycin, which is associated with significant pulmonary toxicity and Raynaud’s phenomenon. Although three cycles of EP was inferior to three of BEP,[9] four cycles of EP has never been directly compared to three of BEP. However, four cycles of EP (etoposide at 500 mg/ m² per cycle, cisplatin at 100 mg/m² per cycle) was equivalent to the Memorial Sloan-Kettering Cancer Center (MSKCC) VAB-6 regimen containing cisplatin and bleomycin as well as vinblastine, dactinomycin (Cosmegen), and cyclophosphamide (Cytoxan, Neosar).[10]

In addition, long-term follow-up of 142 patients classified as good risk according to the International Consensus Prognostic Classification[11] and treated with four cycles of EP at MSKCC revealed a complete response rate of 96% and a relapse rate of only 5%-results that are identical to those achieved with BEP for three cycles.[12] Consequently, the National Comprehensive Cancer Network Testicular Cancer Management Guidelines recommend four cycles of EP as an alternative to three cycles of BEP for good-risk patients.

Residual Masses

An area of continuing challenge is the management of patients with residual masses following chemotherapy. Although often useful in distinguishing malignant from benign lesions, positron-emission tomography (PET) imaging cannot reliably distinguish mature teratoma from viable malignant nonseminomatous elements in residual masses following chemotherapy for NSGCT.[13] Postchemotherapy masses are also common in bulky seminoma. While resection of these masses will usually reveal necrosis, surgery can be technically difficult due to intense desmoplastic reaction and fibrosis. Data from MSKCC indicate that the chance of persistent seminoma is 27% to 41% in masses greater than 3 cm in diameter, whereas the risk is only 3% for smaller residual masses. As a result, many centers reserve surgery for lesions greater than 3 cm.[14]

With improving technology, there is recent evidence that PET imaging may help distinguish residual seminoma from fibrosis/necrosis, although an earlier study was not encouraging.[15] De Santis et al[16] reported results from a prospective multicenter study of 33 seminoma patients with postchemotherapy masses. These patients had PET imaging 4 to 12 weeks after last chemotherapy and were managed with resection or clinical and radiologic surveillance for a median of 23 months. Negative PET scans of residual masses that contained no viable tumor on resection, or that decreased in size or remained stable radiologically for at least 2 years, were rated as true-negatives. Of 37 scans in 33 patients, there were 28 true-negative scans and 8 true-positives, all in lesions greater than 3 cm. There were no false-positive PET scans and one false-negative in a lesion less than 3 cm in size.

If the high sensitivity and specificity of PET imaging can be verified in larger studies, PET will become a standard tool in the decision to resect or observe residual masses greater than 3 cm following chemotherapy for seminoma.

Late Relapse

Finally, although the majority of germ cell tumor recurrences occur within the first 2 years following chemotherapy, long-term follow-up is required because of late relapse in approximately 3% of patients. In a multivariate analysis, Shahidi et al[17] recently analyzed the factors associated with tumor recurrence more than 5 years from initial presentation in a large series that included 586 patients followed for at least 10 years. The very late (> 5 years) relapse rate was 2.4%, with late relapses occurring in 14 patients, 12 of whom had been treated for metastatic NSGCT, 1 for metastatic seminoma, and 1 for stage I NSGCT.

Six late relapsing patients with nonseminoma had mature teratoma in resected postchemotherapy masses, whereas four had mature teratoma in prechemotherapy-resected primary tumors. Similar to the pattern of late relapse reported by the Indiana University Group,[18] elevation of alpha-fetoprotein (but not human chorionic gonadotropin) was commonly observed, teratoma was present in primary tumor or resected residual masses, and relapse was often confined to lymph nodes, particularly those in the para-aortic region.

Thus, although late recurrences of seminoma are rare regardless of initial stage, patients with metastatic NSGCT have a 2% to 3% risk of late relapse for which surgical resection is the mainstay of treatment. All patients with metastatic NSGCT require lifelong oncologic follow-up, with at least
yearly assessments after 5 years.

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