Does Size Matter? Association Between Number of Patients Treated and Patient Outcome in Metastatic Testicular Cancer

Eric J. Feuer, Joel Sheinfeld, George J. Bosl

There is increasing evidence that, in the treatment of advanced testicular cancer, centers that do not treat a certain "critical mass" of patients may not achieve optimal treatment outcome. In this issue of the Journal, Collette et al. *(1)* further substantiate and extend past observation by finding that, in a large (n = 380) four-arm European Organization for Research and Treatment of Cancer/Medical Research Council (EORTC/MRC) trial for "poor-prognosis" metastatic nonseminomatous germ cell tumors (GCTs) *(2)*, patients treated at institutions accruing fewer than five patients to the trial had an inferior failure-free and overall survival compared with that among patients treated at institutions accruing five or more patients. These results are disconcerting, given the high cure rate of GCTs and the widespread knowledge of treatment success.

The first highly successful clinical trial for the treatment of advanced testicular cancer was initiated in 1974 *(3)*. Within 4 years after this trial was started, survival rates for patients with advanced testicular cancer in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)[1] population-based cancer registry program had improved dramatically *(4)*. The improvements that occurred from 1975 to 1978 abruptly plateaued, and subsequent survival has shown only modest improvements (Fig. 1). To determine the extent to which the plateaued survival rates in SEER match those of trials, we previously compared survival among patients diagnosed from 1978 through 1984 in SEER to that among a group of prognostically matched trial patients treated at the Memorial Sloan-Kettering Cancer Center *(5)*. Patients at the Memorial Sloan-Kettering Cancer Center with minimal/moderate metastatic disease had significantly better survival than those in SEER (95% versus 73% at 3 years; $P<.001$), whereas those with advanced disease showed smaller differences (52% versus 40% at 3 years; $P = .06$). Because most SEER patients were receiving cisplatin-based chemotherapy by 1978, lack of use of these new therapies could not explain the survival differences.

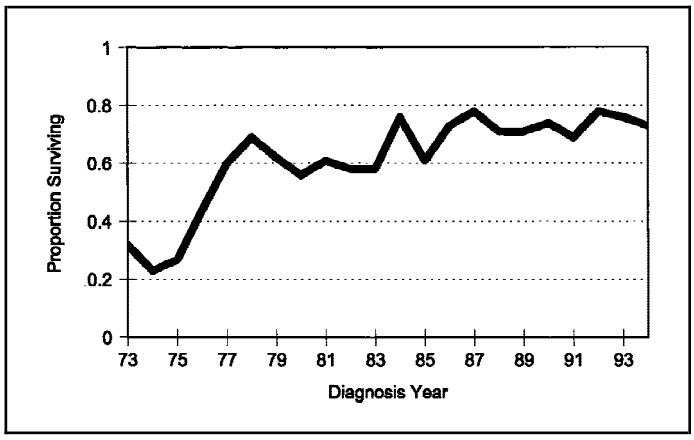

Fig. 1. Three-year overall survival by year of diagnosis for patients with advanced testicular cancer. Data from the Surveillance, Epidemiology, and End Results Program.

The results of the Swedish Norwegian Testicular Cancer Project *(6)* (from 1981 through 1986) showed a survival advantage for patients with large- and very-large-volume disease who were treated in a single large oncology unit compared with patients treated in smaller units (approximately 84% versus 60% at 3 years; $P = .01$). Similarly, a population-based audit of the management of patients with nonseminomatous GCTs in western Scotland from 1975 through 1989 *(7)* showed a survival advantage among patients treated in a large central unit compared with patients treated in one of four smaller outlying units (87% versus 73% at 5 years; $P<.001$). The survival advantage persisted after adjustment for prognostic factors and after restriction of the patient group to those who received protocol treatment. By comparison, Collette et al. *(1)* report 2-year overall survival rates of 77% and 62% at institutions that entered five or more patients and fewer than five patients, respectively ($P = .006$).

Retrospective audits, comparisons of trial and population-based data, and data-driven secondary results derived from trials must be interpreted with caution because they are all subject to biases of various types. Certainly, one must be concerned with self-selection bias with respect to who is informed, willing, and able to travel to a center that has experience in treating GCTs. This selection may be related to socioeconomic status, educational level, and unrelated disabilities that prevent patients from traveling to larger institutions. In testicular cancer, comorbidity is not a major consideration because the median age of patients at diagnosis is less than 35 years. Adequacy of diagnostic work-up may also bias results because, if institutions that have fewer patients also tend to have less extensive evaluations, then the disease in patients will tend to be down-staged relative to other institutions. The result in these institutions would be worse survival at every stage—the so-called "Will Rogers phenom-

Affiliations of authors: E. J. Feuer, Surveillance Modeling and Methods Section, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD; J. Sheinfeld (Urology Service, Department of Surgery), G. J. Bosl (Department of Medicine), Memorial Sloan-Kettering Cancer Center, New York, NY.

Correspondence to: Eric J. Feuer, Ph.D., National Cancer Institute, Executive Plaza North, Rm. 313, MSC 7344, Bethesda, MD 20892-7344 (e-mail: rf41u@nih.gov).

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enon" *(8).* In trial-based studies, one must also be concerned about selection bias with respect to who enters trials at different types of institutions and the role of competing protocols.

Both etoposide and cisplatin are mainstays of GCT therapy and have been used in the United States and Europe for 10–15 years. Despite widespread knowledge of the importance of optimal dosage of these drugs in the cure of GCT, the cumulative administered dose of both etoposide and cisplatin reported by Colette et al. *(1)* was less at institutions accruing fewer than five patients. The reduced cumulative dose of etoposide is difficult to understand because the schedules are well known and stipulated by protocol. The statistically significant attenuation of cisplatin dose is even more difficult to understand, given that a dose of 100–120 mg/m^2 per cycle of therapy has been well established in randomized clinical trials *(9)* and has been the standard of care in the combination chemotherapy for GCT for more than 15 years.

Deviations from standard chemotherapy may be due to physician-related or institution-related causes or patient compliance. In the study by Collette et al. *(1),* the number of delayed treatment cycles was not greater at institutions with fewer than five patients (in fact, the percentage was slightly less), suggesting that patients at both types of institutions were equally compliant. However, Collette et al. also suggest that longer treatment delays may explain the decreased dose intensity in institutions with fewer than five patients. There was a higher proportion of deaths from toxicity in the institutions accruing fewer than five patients (13% versus 6%; $P = .090$), and five institutions in the low-accrual group stopped recruitment 1 year before the end of the study after a patient died within 3 months after entry. This suggests that physicians at the institutions with lower accrual may not have felt comfortable with this protocol and the management of toxic events, leading to physician-directed dose attenuation and failure to adhere to the protocol.

Patient selection for omitting surgery after chemotherapy remains controversial. However, there is no doubt that leaving residual disease *in situ* has an adverse impact on outcome. It is surprising that only 40% (22 of 55) of patients in centers entering fewer than five patients and 53% (173 of 325) of patients in institutions entering five or more patients underwent surgery after chemotherapy. Moreover, 113 patients with residual masses did not undergo surgery: 48% (20 of 42) in centers entering fewer than five patients and 35% (93 of 266) in centers entering five or more patients.

Collette et al. *(1)* report a high postoperative mortality rate of 9% (two of 22) in institutions entering fewer than five patients compared with 2% (four of 173) in institutions entering five or more patients. Indiana University reported five deaths among 603 patients who underwent retroperitoneal lymph node dissection (RPLND) after chemotherapy *(10),* whereas the Memorial Sloan-Kettering Cancer Center has had no postoperative deaths in more than 385 consecutive patients who underwent surgery after chemotherapy (Sheinfeld J: personal data. MSKCC RPLND Database). A large volume of residual disease and desmoplastic reaction after chemotherapy increase the technical demands of the surgery. Furthermore, the routine use of bleomycin in patients on poor-risk protocols markedly increases the risk of serious pulmonary toxicity with injudicious perioperative fluid management.

Nonlethal surgical complications are not addressed in the article by Collette et al. *(1),* yet they may have had a possible impact on the end points of this study: overall survival and time to disease progression. Complications often delay and/or preclude the administration of postoperative chemotherapy (necessary when viable cancer is resected). Overall, 26 patients had viable cells resected: 23% (five of 22) in the group entering fewer than five patients and 12% (21 of 173) in the group entering five or more patients. Institutions with considerable experience in surgery after chemotherapy report an approximately 20% morbidity rate [*(10);* Sheinfeld J: personal data. MSKCC RPLND Database].

Despite potential biases, the accumulating evidence suggests that patients with GCT have improved outcome when they are treated at institutions with higher patient volume. The study by Collette et al. *(1)* focused on poor-risk patients with metastatic disease and found significant survival differences, whereas our study comparing GCT patient survival at Memorial Sloan-Kettering Cancer Center and SEER found larger differences in survival of good-risk patients with metastatic disease as opposed to poor-risk patients with metastatic disease (albeit with the use of a different staging scheme). Poor-prognosis patients have inherently resistant disease; some of these patients will not benefit even from the best treatment and proper protocol adherence. This finding suggests that differences found for poor-risk patients in the EORTC setting may persist also among good-risk patients. This has important implications for overall patient outcome because poor-risk patients, as described by the International Germ Cell Consensus Classification *(11),* account for only 16% of the patient population with advanced nonseminomatous GCT.

The survival advantage for patients at certain centers does not appear to be associated solely with the availability and use of state-of-the-art research protocols. In the United States, there is a growing political debate over access to centers of excellence. Are five patients the "cutoff" for experience in the treatment of GCT or is there a continuum? Collette et al. *(1)* show little difference in overall, failure-free, and progression-free survivals among those institutions accruing five or more patients. However, accrual of five patients over a 4-year period does not imply a high level of expertise unless physicians travel between institutions. Other studies have shown an association between patient outcome and volume in breast cancer *(12)* and operative mortality for major cancer surgery *(13).* In relatively rare cancers, such as GCTs, it is more difficult for centers to accrue the necessary "critical mass" of patients for physicians to become experts in the disease. Patients with GCT should be treated by experts to ensure the highest cure rate for these young patients who have their entire productive life ahead of them.

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NOTE

[1]*Editor's note:* SEER is set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.