ABSTRACT

Most urologists perform adjuvant radiation therapy for stage 1 (T1 N0 M0) testicular seminoma after orchiectomy, although the majority of patients with clinical stage 1 seminoma do not have occult metastases and therefore do not require elective nodal irradiation. However, there are currently no clinical or histological parameters that can be used to distinguish patients who need radiation therapy from those who do not. We reported previously that estimates of volume-weighted mean nuclear volume (MNV) were a better predictor of the prognosis of prostate cancer and renal cell carcinoma than subjective histological grading. Here, we examined the usefulness of estimation of MNV for predicting the prognosis of primary testicular seminoma. A retrospective study of 57 patients with testicular seminoma diagnosed between April 1981 and March 1997 at Kobe City General Hospital was performed. Unbiased estimates of MNV data were compared for prognostic value with the level of β-human chorionic gonadotropin (β-HCG), α-fetoprotein (AFP), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Fifty patients were stage 1 (T1 N0 M0), and 7 patients were stage 2 (T2 N0 M0). All patients received orchiectomy, followed by radiation therapy. Estimates of MNV of stage 2 patients were significantly larger than that of stage 1 patients (P = 0.0142). Although the LDH level was also significantly higher in stage 2 (P = 0.001), there were no significant differences between stages 1 and 2 with respect to β-HCG (P = 0.997), ALP (P = 0.226), and AFP (P = 0.467). Multivariate logistic regression analysis revealed that the estimate of MNV was the only variable predicting lymph node metastasis (P = 0.0315). In stage 1 patients, only the estimate of MNV was significantly correlated with progression-free survival (P = 0.0118). These findings indicate that the estimate of MNV may be an important prognostic indicator for testicular seminoma. Estimates of MNV may also be useful for excluding patients from surveillance protocols.

INTRODUCTION

Remarkable improvement in the prognosis of testicular tumors has recently been achieved. Metastatic disease can be cured in the majority of patients by multiagent systemic chemotherapy after orchiectomy (1, 2). Patients with clinical stage 1 seminoma are treated by orchiectomy plus external radiation to the retroperitoneal lymph nodes at risk of harboring subclinical micrometastases (the ipsilateral pelvic and para-aortic nodes), and this approach has achieved long-term cure rates of greater than 90–95% (3, 4). It is generally accepted that approximately 10–20% of clinical stage 1 seminoma patients have occult disease in the abdomen (5). Therefore, this policy of elective adjuvant regional nodal irradiation means that ~85% of patients are being treated unnecessarily (6). If it were possible to more accurately stage seminoma, many patients could avoid the side effects of radiation therapy, and medical costs would also be decreased. However, conventional histopathological findings cannot be used to identify patients with occult retroperitoneal metastases (7).
Multivariate logistic regression analysis was performed using SPSS software (Statistical Package for the Social Sciences; SPSS, Inc., Chicago, IL) to determine the variables that were correlated independently with the prognosis. Comparisons between group means were done using the Mann-Whitney test. More than two groups were analyzed by the nonparametric Kruskal-Wallis test. The limit of significance for all tests was \( P < 0.05 \).

**RESULTS**

**Lymph Node Metastasis.** The mean estimate of MNV calculated for stage 2 patients was 891.4 \( \mu m^3 \), whereas that of stage 1 patients was 626.2 \( \mu m^3 \). Therefore, the MNV was significantly larger in stage 2 than in stage 1 (\( P = 0.0142 \), Table 1). Although the LDH level was significantly higher in stage 2 than in stage 1 (\( P = 0.001 \)), there were no significant differences between the two stages with regard to the levels of \( \beta \)-HCG (\( P = 0.997 \)), ALP (\( P = 0.226 \)), and AFP (\( P = 0.467 \), Table 1). Multivariate logistic regression analysis revealed that estimates of MNV were the only prognostic factor predicting lymph node metastasis (\( P = 0.0315 \), Table 2).

**Progression-free Survival.** Factors predicting disease progression were analyzed for the stage 1 patients. Five stage 1 patients showed disease progression during the follow-up period, with four developing mediastinal lymph node metastasis and one developing inguinal lymph node metastasis. Fifty stage 1 patients were classified by their MNV values, which ranged from 259.4 to 1066.7 \( \mu m^3 \), with a median of 620 \( \mu m^3 \). Progression-free survival curves are shown in Fig. 1. The prognosis of the MNV \( \geq 620 \mu m^3 \) group was significantly worse than that of the MNV < 620 \( \mu m^3 \) group (\( P = 0.0118 \)). LDH (\( P = 0.3274 \)), \( \beta \)-HCG (\( P = 0.3424 \)), ALP (\( P = 0.1210 \)), and AFP (\( P = 0.9870 \)) were of no prognostic value.

**DISCUSSION**

The prognosis of testicular tumors has improved remarkably with the development of techniques for imaging the retroperitoneum, as well as introduction of new chemotherapy agents and identification of sensitive tumor markers (7). Many seminoma patients can be cured by radiation therapy and platinum-based chemotherapy, even when they have distant metastases (1–4). On the other hand, most urologists irradiate the retroperitoneal lymph nodes after orchiectomy for clinically localized (stage 1) seminoma. In fact, the majority of stage 1 seminomas can be cured by orchiectomy alone; therefore it would be desirable to spare patients the unpleasant side effects of irradiation, such as gastrointestinal disturbance, reduced fertility, a risk of secondary retroperitoneal tumors, and anxiety. In a recent study performed in England, 7 of 52 patients (13%) with clinical stage 1 seminoma managed by surveillance after orchiectomy developed recurrence during a follow-up period of 12–41 months (5). Unfortunately, computed tomographic scans cannot identify micrometastases, and conventional histopathological findings cannot identify the patients who have occult retroperitoneal metastases (6, 7). Pathological assessment remains difficult and is subject to interobserver variation. Nativ et al. (7) reported on the importance of the nuclear DNA ploidy pattern in seminoma, whereas Hititma et al. (17) stated that a diploid seminoma on flow cytometry is most likely associated with extensive lymphatic infiltration. The present study focused on whether accurate prediction of the malignant potential of seminoma was possible by using ordinary histological slides.

An estimate of MNV is the only method by which an unbiased estimate of three-dimensional parameters can be obtained from a single two-dimensional histological section (8). This parameter was developed by Gunderson and Jensen (9, 10) and is based on a stereological method. It has been proven by Sørensen et al. (18), Baak et al. (19), Nielsen et al. (20), and ourselves (21) to be highly reproducible. Since Weibel (22) discussed the application of stereology to cancer research, the value of MNV as a prognostic factor has been demonstrated for several tumors (11–16, 23–25). We reported previously that MNV was a better predictor of the prognosis of prostate cancer (11–14) and renal cell carcinoma (15) than subjective histological grading. Sørensen and Muller (26) reported that the MNV of testicular carcinoma in situ was significantly larger than that of morphologically normal spermatogonia, but no previous study has assessed the relationship between estimates of MNV and the prognosis of seminoma.

When we analyzed the relationship between lymph node metastasis and several prognostic factors, multivariate analysis showed that the estimate of MNV was the only factor predicting lymph node metastasis. It would have been better to study a group of pathologically staged cancer patients, but unfortunately, this is not possible in clinical practice. Despite this limitation, our findings revealed a clear trend. Furthermore, no stage 1 patient with a small estimate of MNV showed disease progression during the follow-up period. These findings suggest that patients with a small MNV and no apparent lymph
node metastasis on computed tomographic scans may be candidates for surveillance rather than radiotherapy.

Several problems remain to be solved before clinical use of estimates of MNV will become possible. The cut-off value that best reflects the biological characteristics of seminoma needs to be determined. Although we used the median as the cut-off value in the present study, further investigation of a larger number of patients at multiple institutions will be required to provide a more definitive answer. There have been no objective criteria for predicting the outcome of patients with seminoma. However, the present study suggested the possibility that MNV might be one such criterion; therefore, additional studies must be performed to assess the reproducibility of this finding.

In conclusion, estimates of MNV may be prognostically important for seminoma. No special training is needed to measure MNV; only a projector and microscope are required, and evaluation can be performed in 10–15 min with excellent reproducibility. Taking this into account, we recommend MNV estimation for predicting the outcome of patients with seminoma. MNV may also be a useful criterion for excluding patients from surveillance.

ACKNOWLEDGMENTS

We thank Dr. Sørensen, Stereological Research Laboratory, and University Institute of Pathology, Aarhus Kommunehospital, University of Aarhus, Denmark, for technical assistance.

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