Tohoku J. Exp. Med., 2020, **252**, 219-224

Trends in Age and Histology of Testicular Cancer from 1980-2019: A Single-Center Study

Shinichi Yamashita,[1] Juntaro Koyama,[1] Takuro Goto,[1] Shinji Fujii,[1] Shigeyuki Yamada,[2] Yoshihide Kawasaki,[1] Naoki Kawamorita,[1] Koji Mitsuzuka,[1] Yoichi Arai[1,3] and Akihiro Ito[1]

[1]Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[2]Department of Urology, Tohoku Kosai Hospital, Sendai, Miyagi, Japan
[3]Department of Urology, Miyagi Cancer Center, Natori, Miyagi, Japan

Testicular cancer occurs in the testes of the male reproductive system and is the most common cancer in adolescent and young adult (AYA) men. However, recently, there have been more cases of testicular cancer in men older than 40 years. Therefore, trends of testicular cancer during the past 40 years were retrospectively examined, focusing on age and histology. Patients who were diagnosed with testicular cancer at our institution between 1980 and 2019 were enrolled in this study. The patients were divided into groups by the year of diagnosis (1980s, 1990s, 2000s, and 2010s), age at diagnosis (14, 15 to 39, and older than 40 years), and histological type (seminoma and non-seminoma). A total of 563 patients were diagnosed with testicular cancer over the 40-year period. The median age at diagnosis increased continuously, from 28 years to 31 years, 34 years, and 38 years in each period, respectively ($p < 0.001$). Moreover, most testicular cancer patients were of the AYA generation, whereas the ratio of patients older than 40 years increased significantly since 2000 ($p < 0.001$). The relative proportion of seminoma also increased more than 50% since 2000. In the seminoma group, median age increased from 31 years to 41 years during the 40-year period ($p < 0.001$). In conclusion, the age at diagnosis is rising for testicular cancer patients. Clinicians should recognize that testicular cancer affects not only the AYA generation, but there has been a shift to older than 40 years, especially in seminoma.

Keywords: age; histology; non-seminoma; seminoma; testicular cancer
Tohoku J. Exp. Med., 2020 November, **252** (3), 219-224.

Introduction

Testicular cancer (TC) can affect one or both testes, and most TCs develop in the male reproductive gland cells known as germ cells. Testicular germ cell tumors are histologically divided into two main types, seminoma and non-seminoma. TC is the most common cancer in adolescent and young adult (AYA) men (Katanoda et al. 2017), with an incidence of one to two cases per 100,000 males per year in Japan. In Western countries, its incidence is two to ten cases per 100,000, and it has been increasing (Trabert et al. 2015; Ylönen et al. 2018). The registry study by the Japanese Urological Association in 2005 and 2008 showed that 30.7% of TC patients had metastases at their initial medical examinations (Miki et al. 2014). However, treatment for TC has improved, and even patients with metastases could be expected to achieve long-term survival with appropriate chemotherapy, including multi-agent chemotherapy comprising bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide, and cisplatin (VIP), and/or residual tumor resection (Shintaku et al. 2008; Kojima et al. 2015). In Japan between 2000 and 2010, the 5-year overall survival of TC patients with intermediate and poor prognoses of the International Germ Cell Cancer Collaborative Group classification (IGCCC) (International Germ Cell Cancer Collaborative Group 1997) was 89% and 83%, respectively (Kojima et al. 2015).

Recently, we noted that the age of patients with TC and the ratio of seminoma cases were increasing in daily practice. However, to the best of our knowledge, there have

Received September 14, 2020; revised and accepted October 20, 2020. Published online November 3, 2020; doi: 10.1620/tjem.252.219.
Correspondence: Shinichi Yamashita, M.D., Ph.D., Department of Urology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: yamashita@uro.med.tohoku.ac.jp

been no reports of the long-term changes in the age of TC patients in Japan. This study therefore retrospectively examined trends over time in the age and histology of TC patients.

Materials and Methods

Patients diagnosed with TC at our institution between January 1980 and December 2019 were enrolled. Patients with extragonadal germ cell tumors were also included, because they received the same treatment as TC. However, it remains controversial whether extragonadal germ cell tumors represent metastases from undetected or regressed TC or tumors developed in extragonadal sites. Tumors were staged according to the Union for International Cancer Control TNM classification (Brierley et al. 2017). TC with metastases was classified as having a good, intermediate, or poor prognosis according to the IGCCC. The study protocol was approved by the Ethics Committee of Tohoku University Hospital (IRB No. 2017-1-1058).

The patients were divided into four groups according to the year of diagnosis: 1980 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2019. In addition, the patients were assigned to three age groups according to the age at diagnosis: 14 years or younger, 15 to 39 years (AYA generation), and 40 years or older. Ratios of age groups were calculated as age-adjusted ratios. Age adjustment was performed using the age distributions of the 1985, 1995, 2005, and 2015 male populations of Miyagi Prefecture, to reduce the differences between regions in Japan (Ministry of Internal Affairs and Communications 2020). The patients were divided by histological type into two groups: seminoma and non-seminoma.

Continuous variables are shown as medians (interquartile range, IQR). The Wilcoxon rank-sum test was used to compare the median ages of TC patients. Comparisons among groups were also performed using analysis of variance (ANOVA) and the chi-squared test. In addition, overall survival rates were estimated using the Kaplan-Meier method, and the log-rank test was used to compare data. A probability value of less than 0.05 was considered significant.

Results

A total of 563 patients were diagnosed with TC at our institution during the past 40 years. The median age was 34 years (IQR: 27-41 years). Overall, 263 patients (46.7%) had seminoma, and 300 (53.3%) had non-seminoma; 293 patients (52.0%) were stage I; and 126 (22.4%), 70 (12.4%), and 74 (13.1%) patients with metastases were categorized as having good, intermediate, and poor prognoses, respectively.

The median age at diagnosis increased continuously, from 28 years (IQR: 23-33 years, n = 54) to 31 years (IQR: 25-38 years, n = 136), 34 years (IQR: 27-40 years, n = 181) and 38 years (IQR: 29-44 years, n = 192) in each period, respectively (Fig. 1). The age increased obviously every ten years. In addition, most TC patients (80.1%) were of the AYA generation, but the ratio of patients older than 40 years increased significantly since 2000 ($p < 0.001$, Fig. 2a). Even when the age distribution was adjusted to the 1985 age profile of men in Miyagi Prefecture, the ratio of patients older than 40 years reached 28.8% in the past decade ($p = 0.019$, Fig. 2b), significantly different from 16.7% in the 1980s.

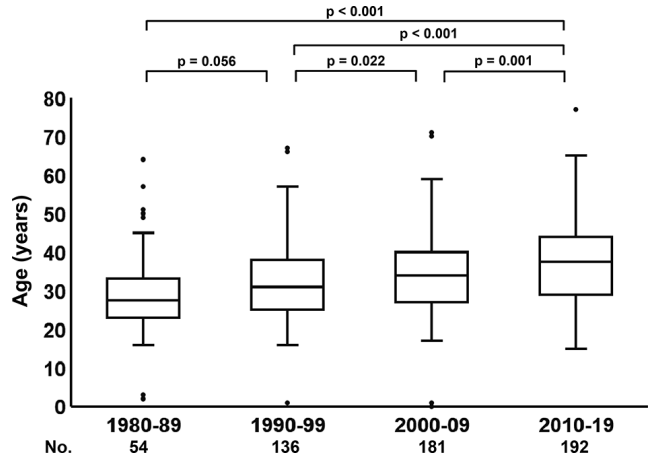

Fig. 1. Change in the median age at diagnosis of testicular cancer patients from 1980 to 2019.
Box plots show the 25th and 75th percentiles (bottom and top of the box, respectively), median (band within the box), 2.5th and 97.5th percentiles (whisker terminals), and outliers. The comparisons among groups were performed using the Wilcoxon rank-sum test.

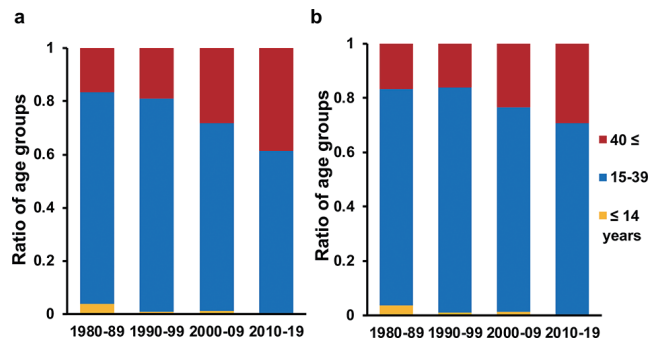

Fig. 2. Ratio of age groups in each period.
(a) Age distribution of the actual number; (b) age-adjusted distribution.

As to histological type, the numbers of both seminomas and non-seminomas increased (Fig. 3); in particular, the relative proportion of seminomas also increased from 37.0% to 39.7%, 51.4%, and 50.0% in each period, respectively. In the seminoma group, the median age increased constantly from 31 years (IQR: 27-43 years) to 34 years (IQR: 28-41 years), 36 years (IQR: 32-42 years), and 41 years (IQR: 36-46 years) in each period, respectively (Fig. 4a). The median age in the non-seminoma group also increased constantly from 26 years (IQR: 22-31 years) to 29 years (IQR: 23-36 years), 30 years (IQR: 25-39 years), and 33 years (IQR: 27-39 years) in each period, respec-

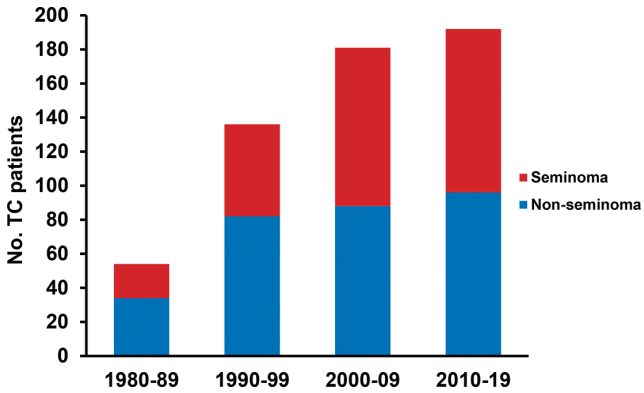

Fig. 3. Change in the number of testicular cancer patients by pathological type from 1980 to 2019.

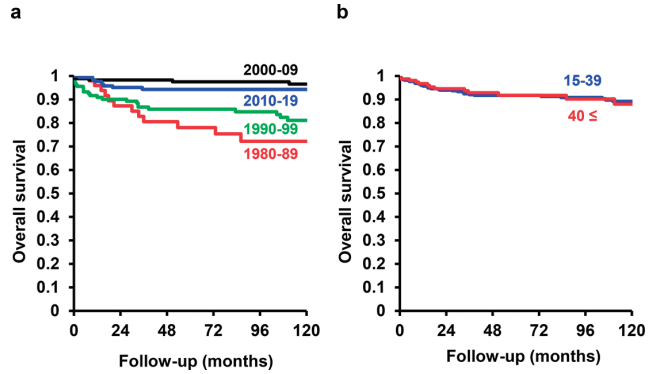

Fig. 6. Overall survival of testicular cancer patients.
(a) Overall survival of testicular cancer patients stratified by the year of diagnosis. (b) Overall survival according to the age at diagnosis.

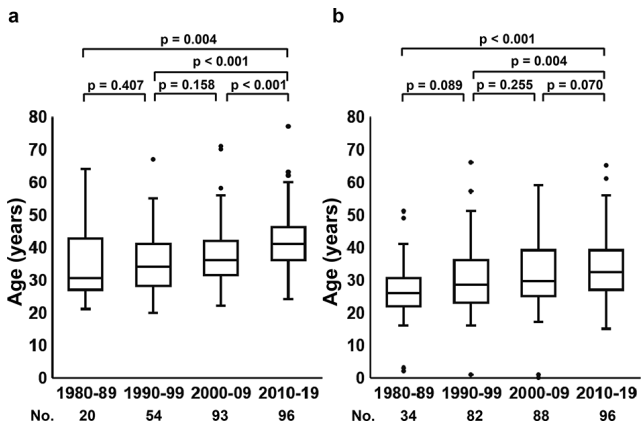

Fig. 4. Trends in age of testicular cancer patients by pathological type.
Shown are the changes in median age at diagnosis of patients with seminoma (a) and non-seminoma (b) from 1980 to 2019. Box plots show the 25th and 75th percentiles (bottom and top of the box), median (band within the box), 2.5th and 97.5th percentiles (whisker terminals), and outliers. The comparisons among groups were performed using the Wilcoxon rank-sum test.

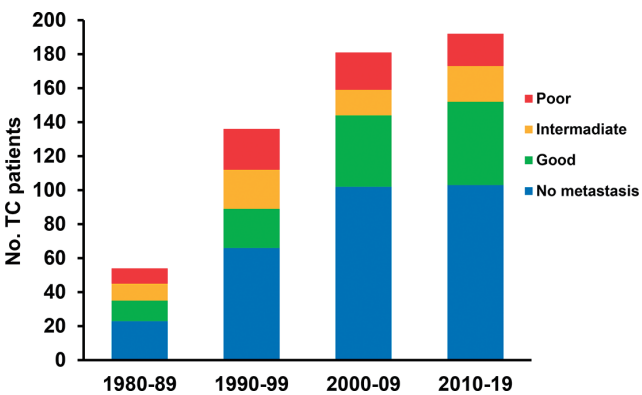

Fig. 5. Testicular cancer patients stratified by the International Germ Cell Cancer Collaborative Group classification in each period.

tively (Fig. 4b). The age of patients between 2010 and 2019 increased markedly compared with that before 2010, in both the seminoma and non-seminoma groups.

The number of good prognosis and no metastasis groups increased, and their ratios increased from 65% before 2000 to approximately 80% after 2000 (Fig. 5). Conversely, the proportion of the poor prognosis group decreased from 16.7% to 17.6%, 12.1%, and 9.9% in each period, respectively.

Regarding the laterality of TC, the right and left testes were involved in 276 (48.7%) and 258 (45.8%) patients, respectively. Seventeen (3%) patients developed TC in bilateral testes. Of 17 patients, 14 (82.4%) had metachronous bilateral TCs with a median age at first TC of 26 years (IQR: 23-34 years), and 3 (17.6%) had synchronous TCs with ages of 27, 39, and 48 years. In patients with metachronous TCs, the median age at the second TC was 38 years (IQR: 33-45 years), and the median interval between the 1st and 2nd TCs was 10 years (IQR: 8-13 years). Moreover, 12 patients (70.6%) had seminoma, and 5 (29.4%) had non-seminoma.

The median follow-up period was 75 months (IQR: 28-134 months). According to the year of diagnosis, the overall survival rates at 5 years were 78.1% for the 1980s, 85.9% for the 1990s, 97.6% for the 2000s, and 94.3% for the 2010s ($p < 0.001$) (Fig. 6a). Regarding the age at diagnosis, the overall survival rates were similar in the AYA generation and in patients older than 40 years (Fig. 6b). In addition, the overall survival rates at 5 years were 98.5% for the no metastasis group, 98.3% for the good prognosis group, 80.7% for the intermediate prognosis group, and 65.0% for the poor prognosis group ($p < 0.001$) (Fig. 7a). In particular, the overall survival rates were significantly higher for patients between 2000 and 2019 than for those between 1980 and 1999 in the intermediate ($p = 0.007$) and poor ($p = 0.004$) prognosis groups (Fig. 7b).

Discussion

In the current study, the age at diagnosis of TC patients

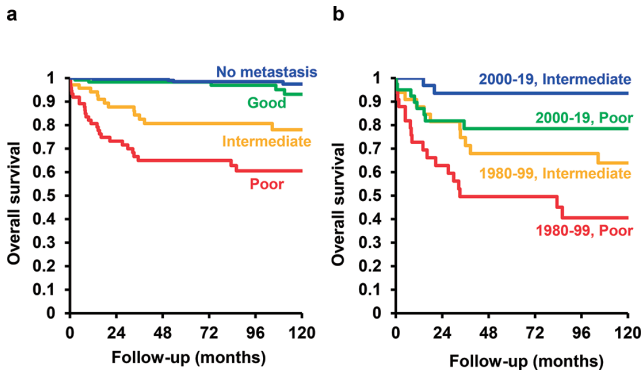

Fig. 7. Overall survival in the IGCCC groups.
(a) Overall survival of testicular cancer patients stratified by the International Germ Cell Cancer Collaborative Group classification (IGCCC). (b) Overall survival in the intermediate and poor prognosis groups of the IGCCC by the year of diagnosis: 1980 to 1999, and 2000 to 2019.

increased gradually from 28 years to 38 years over the past 40 years. In particular, the median age in the seminoma group reached 41 years in the 2010s. The ratio of seminoma also showed a clear increase. The trends were similar to those of the previous reports (Ruf et al. 2014; Drevinskaite et al. 2019). In Germany, the ratio of seminoma was 64.5%, and the median age of patients with seminoma was 40 years (Brandt et al. 2019). Interestingly, the ratio of patients older than 40 years increased from 16.7% in the 1980s to 28.8% in the 2010s, even when the age distribution was adjusted to the 1985 age distribution. Leveridge et al. (2018) reported that 32% of TC patients, especially 42% in the seminoma group, were older than 40 years in Ontario in the period of 2000-2010. Schaffar et al. (2019) also showed that the most substantial increase was observed in the 40-49 years age group of TC patients between 1970 and 2012, and the highest incidence rate was in the 30-39 years age group. Taking the recent reports of the trends of TC into consideration, TC patients older than 40 years might increase further in Japan.

The pathogenesis of these trends in TC remains unclear, but one possibility is a change in lifestyle. High intake of dairy products, particularly milk and cheese, has been reported to be associated with an increased risk of TC (Ganmaa et al. 2002; Garner et al. 2003). The dairy products contain estrogen, contributing potentially to affecting hormone balance. In addition, postnatal exposure to environmental toxins, including organochlorines, polychlorinated biphenyls, polyvinyl chlorides, and smoking might be resulting in TC (Meeks et al. 2012). Another possibility is prenatal exposure to maternal hormones, particularly estrogens (Weir et al. 2000). Further investigations are needed to clarify the pathogenesis of TC in the future.

The standard therapy for TC with metastasis currently is multi-agent chemotherapy. In the present study, 48% of TC patients had metastases. In the survey by the Japanese Urological Association, approximately 30% of TC patients had metastases at their initial medical examinations (Miki et al. 2014). Thus, many TC patients have a chance of being treated with chemotherapy. Their age should be considered when performing chemotherapy using the BEP regimen, since increased age at diagnosis is associated with the risk of pulmonary toxicity due to bleomycin (Simpson et al. 1998). The risk of bleomycin-induced pneumonitis, resulting in fatal toxicity, increases with age over 40 years, more particularly over 50 years, a cumulative dose of bleomycin of 300 mg or more, impaired renal function, and heavy cigarette smoking (Simpson et al. 1998; de Wit 2007). The favorable response rate and survival with BEP for advanced TC is similar to that with VIP (Nichols et al. 1998). However, VIP results in greater myelosuppression and genitourinary toxicities than BEP. Recently, long-acting granulocyte colony-stimulating factor has been used for severe neutropenia. This option is available for VIP, but not for BEP, which includes weekly injections of bleomycin. Moreover, antiemetic medications have also improved, and adverse events of VIP may be increasingly more manageable than before. Therefore, the patient's age should be kept in mind in the decision-making process leading to chemotherapy for TC.

The overall survival rates of TC patients have improved over time, and they reached approximately 95% since 2000 in the present study. The mortality of TC has decreased in most countries in Europe since the 1970s (Bosetti et al. 2011), because cisplatin-based therapies were introduced in the late 1970s. Moreover, the standard multi-agent chemotherapy for TC with metastasis was established in the 2000s in Japan. The decreased TC mortality in the present study was similar to the decreases seen in Europe. In addition, Fosså et al. (2011) reported that the mortality in TC patients older than 40 years was significantly higher than that in patients younger than 40 years. However, the mortality of TC patients older than 40 years was similar to that of the AYA generation in the present study. It is likely that the adverse events of multi-agent chemotherapy for TC might be manageable, as mentioned above.

During the last four decades, we treated 17 (3%) patients with bilateral TCs; 14 of them had metachronous bilateral TCs with a median interval between the 1st and 2nd TCs of 10 years. Bilateral TCs were reported to affect approximately 1-3% of TC patients (Ohyama et al. 2002; Zequi Sde et al. 2012; Kopp et al. 2017). The metachronous TCs had a median interval to 2nd TC of 73 months, with more than 25% being longer than 10 years after the 1st TC (Kopp et al. 2017). The interval between the 1st and 2nd TCs was longer than the 5-year follow-up period for relapse of TC recommended generally by the EAU guidelines on TC (Laguna et al. 2020). Moreover, Kopp et al. (2017) reported that the incidence of bilateral TCs increased over time, from 1.7% in 1989-1994 to 3.8% in 2010-2014. In Japan, the number of bilateral TCs might increase further with the increase of TC patients. Therefore, long-term follow-up has to be reconsidered after treatment for TC. If

their follow-up has finished, TC patients should be advised to perform regular self-checks during their lifetime.

The present study has several limitations. It was a retrospective, single-institutional study, and there might be a bias in the age of patients with TC because our institution is a high-volume center for its treatment. However, most patients with TC in our medical district were referred to our hospital. In fact, we treated more than 500 patients at our institution over 40 years, and 52% of the patients were classified as stage I. In the future, larger prospective trials are needed to confirm these findings. In addition, the Pacific coast of the south Tohoku region was exposed to low-dose radioactive materials following an earthquake (March 11, 2011). In the present study, the number of TC patients was 93 between 2002-2006, 88 between 2007-2011, and 96 between 2012-2016, respectively. However, radioactive contamination might have an effect on the incidence of TC in the future. Thus, a future study should examine if there is an additional increase of TC due to radioactive contamination in the Tohoku region.

In conclusion, the age at diagnosis is rising for patients with TC, and the age of TC patients may increase in the future. Thus, clinicians should recognize that the common age of TC is not only the AYA generation, but there is a shift to patients older than 40 years.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (18K09185).

Conflict of Interest

The authors declare no conflict of interest.

References

Bosetti, C., Bertuccio, P., Chatenoud, L., Negri, E., La Vecchia, C. & Levi, F. (2011) Trends in mortality from urologic cancers in Europe, 1970-2008. *Eur. Urol.*, **60**, 1-15.

Brandt, M.P., Gust, K.M., Bon, D., Tsaur, I., Thomas, C., Neisius, A., Haferkamp, A., Herrmann, E. & Bartsch, G. (2019) Trend analysis and regional tumor incidence in Germany for testicular cancer between 2003 and 2014. *Andrology*, **7**, 408-414.

Brierley, J.D., Gospodarowicz, M.K. & Wittekind, C. (2017) Testis. In *TNM Classification of Malignant Tumours 8th edition*, John Wiley & Sons, Ltd., Oxford, UK, pp. 195-198.

de Wit, R. (2007) Refining the optimal chemotherapy regimen in good prognosis germ cell cancer: interpretation of the current body of knowledge. *J. Clin. Oncol.*, **25**, 4346-4349.

Drevinskaite, M., Patasius, A., Kincius, M., Jievaltas, M. & Smailyte, G. (2019) A population-based analysis of incidence, mortality, and survival in testicular cancer patients in Lithuania. *Medicina* (*Kaunas*), **55**, 552.

Fosså, S.D., Cvancarova, M., Chen, L., Allan, A.L., Oldenburg, J., Peterson, D.R. & Travis, L.B. (2011) Adverse prognostic factors for testicular cancer-specific survival: a population-based study of 27,948 patients. *J. Clin. Oncol.*, **29**, 963-970.

Ganmaa, D., Li, X.M., Wang, J., Qin, L.Q., Wang, P.Y. & Sato, A. (2002) Incidence and mortality of testicular and prostatic cancers in relation to world dietary practices. *Int. J. Cancer.*, **98**, 262-267.

Garner, M.J., Birkett, N.J., Johnson, K.C., Shatenstein, B., Ghadirian, P. & Krewski, D.; Canadian Cancer Registries Epidemiology Research Group (2003) Dietary risk factors for testicular carcinoma. *Int. J. Cancer.*, **106**, 934-941.

International Germ Cell Cancer Collaborative Group (1997) International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J. Clin. Oncol.*, **15**, 594-603.

Katanoda, K., Shibata, A., Matsuda, T., Hori, M., Nakata, K., Narita, Y., Ogawa, C., Munakata, W., Kawai, A. & Nishimoto, H. (2017) Childhood, adolescent and young adult cancer incidence in Japan in 2009-2011. *Jpn. J. Clin. Oncol.*, **47**, 762-771.

Kojima, T., Kawai, K., Tsuchiya, K., Abe, T., Shinohara, N., Tanaka, T., Masumori, N., Yamada, S., Arai, Y., Narita, S., Tsuchiya, N., Habuchi, T. & Nishiyama, H. (2015) Identification of a subgroup with worse prognosis among patients with poor-risk testicular germ cell tumor. *Int. J. Urol.*, **22**, 923-927.

Kopp, R.P., Chevinsky, M., Bernstein, M., Bosl, G., Motzer, R., Bajorin, D., Feldman, D., Carver, B.S. & Sheinfeld, J. (2017) Bilateral testicular germ cell tumors in the era of multimodal therapy. *Urology*, **103**, 154-160.

Laguna, M.P., Albers, P., Algaba, F., Bokemeyer, C., Boormans, J.L., Fischer, K., Fizazi, K., Gremmels, H., Leao, R., Nicol, D., Nicolai, N., Oldenburg, J. & Tandstad, T. (2020) EAU guidelines: testicular cancer. http://uroweb.org/guideline/testicular-cancer/ [*Accessed*: July 15, 2020].

Leveridge, M.J., Siemens, D.R., Brennan, K., Izard, J.P., Karim, S., An, H., Mackillop, W.J. & Booth, C.M. (2018) Temporal trends in management and outcomes of testicular cancer: a population-based study. *Cancer*, **124**, 2724-2732.

Meeks, J.J., Sheinfeld, J. & Eggener, S.E. (2012) Environmental toxicology of testicular cancer. *Urol. Oncol.*, **30**, 212-215.

Miki, T., Kamoi, K., Fujimoto, H., Kanayama, H.O., Ohyama, C., Suzuki, K., Nishiyama, H., Eto, M., Naito, S., Fukumori, T., Kubota, Y., Takahashi, S., Mikami, K. & Homma, Y. (2014) Clinical characteristics and oncological outcomes of testicular cancer patients registered in 2005 and 2008: the first large-scale study from the Cancer Registration Committee of the Japanese Urological Association. *Int. J. Urol.*, **21**, S1-6.

Ministry of Internal Affairs and Communications (2020) Statistics Bureau. Population census. http://www.e-stat.go.jp/SG1/estat/GL02100104.do?tocd=00200521 [*Accessed*: July 15, 2020] (in Japanese).

Nichols, C.R., Catalano, P.J., Crawford, E.D., Vogelzang, N.J., Einhorn, L.H. & Loehrer, P.J. (1998) Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *J. Clin. Oncol.*, **16**, 1287-1293.

Ohyama, C., Kyan, A., Satoh, M., Saito, S., Nishimura, Y., Imai, Y., Oikawa, K., Yokoyama, J., Suzuki, K., Takeuchi, M., Hoshi, S. & Orikasa, S. (2002) Bilateral testicular tumors: a report of nine cases with long-term follow-up. *Int. J. Urol.*, **9**, 173-177.

Ruf, C.G., Isbarn, H., Wagner, W., Fisch, M., Matthies, C. & Dieckmann, K.P. (2014) Changes in epidemiologic features of testicular germ cell cancer: age at diagnosis and relative frequency of seminoma are constantly and significantly increasing. *Urol. Oncol.*, **32**, 33 e31-36.

Schaffar, R., Pant, S., Bouchardy, C., Schubert, H. & Rapiti, E. (2019) Testicular cancer in Geneva, Switzerland, 1970-2012: incidence trends, survival and risk of second cancer. *BMC Urol.*, **19**, 64.

Shintaku, I., Satoh, M., Okajima, E., Fujimoto, H., Kamoto, T., Ogawa, O., Kawai, K., Akaza, H., Tsukamoto, T., Naito, S., Miki, T. & Arai, Y. (2008) Survival of metastatic germ cell cancer patients assessed by international germ cell consensus

classification in Japan. *Jpn. J. Clin. Oncol.*, **38**, 281-287.
Simpson, A.B., Paul, J., Graham, J. & Kaye, S.B. (1998) Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours. *Br. J. Cancer.*, **78**, 1061-1066.
Trabert, B., Chen, J., Devesa, S.S., Bray, F. & McGlynn, K.A. (2015) International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. *Andrology*, **3**, 4-12.
Weir, H.K., Marrett, L.D., Kreiger, N., Darlington, G.A. & Sugar, L. (2000) Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int. J. Cancer.*, **87**, 438-443.
Ylönen, O., Jyrkkiö, S., Pukkala, E., Syvänen, K. & Boström, P.J. (2018) Time trends and occupational variation in the incidence of testicular cancer in the Nordic countries. *BJU Int.*, **122**, 384-393.
Zequi Sde, C., da Costa, W.H., Santana, T.B., Favaretto, R.L., Sacomani, C.A. & Guimaraes, G.C. (2012) Bilateral testicular germ cell tumours: a systematic review. *BJU Int.*, **110**, 1102-1109.