

Oncological outcomes of testicular cancer patients: 10 years of experiences resulting from a single university-based hospital

Research Article

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Abstract: **Purpose:** To explore clinical and pathological characteristics of testicular cancer and also identify factors associated with its oncological outcomes. Testicular cancer has a very good prognosis. Actually, we aim to report on 10 years of experience in the real-world practice of treating testicular cancer in a university-based hospital. **Methods:** This is a retrospective cohort study of testicular cancer patients in Songklanagarind hospital; from January 2007 and December 2016, all eligible testicular cancer patients were included. Clinical characteristics (age, physical examination findings, tumour markers, histopathology, clinical stage, and initial treatment) and clinical outcomes were collected. These patients were divided into two groups: seminoma patients (seminomas) and non-seminoma patients (non-seminomas). Clinical characteristics and outcomes of treatment were analysed, and factors associated with oncological outcomes were identified. **Results:** In 45 patients, median age 33 years, with diagnosis of testicular cancer, seminomas and non-seminomas were responsible for 23 (52.8%) and 22 (49%) of the cases, respectively. The median time of follow-up was 80.6 months (range: 1.8 to 120 months). The five-year OS was 94.7% and 57.1% in the seminoma and non-seminoma groups, respectively. For non-seminomas, five-year OS were 71.4%, 50%, and 42.9% in stage Ib–IIa, IIb, and IIc, respectively, and for seminoma they were 92.3% and 100% in stage Ib–IIa and IIb, respectively. Multivariable analysis showed that non-seminoma, higher staging, and higher IGCCG risk were associated with poorer survival, significantly ($p < 0.05$). **Conclusions:** Seminoma has a good prognosis and survival at all stages, whereas, in the non-seminoma group, higher staging and IGCCG risk were independent factors associated with a poorer prognosis.

Keywords: germ cell tumour • overall survival • testicular cancer • seminoma • non-seminoma germ cell tumour (NSGCT) • non-seminoma

1. Introduction

Testicular cancer is the most common solid tumour in young males, between the ages of 18–45 years, but it remains a rare disease^[1]. In 2020, an estimated 254 new cases were reported in Thailand, representing about 0.13% of all new cancer diagnoses in Thai men^[2]. Nowadays, treatment of testicular cancer has been improved to achieve a cure in 95% of all patients and also in metastatic disease in about 80% of patients^[3].

Comprehensive management, early diagnosis, careful staging, and a multidisciplinary approach have all promoted better outcomes from treatment. However,

there are differences in survival by staging, type of cancer, and also risk of disease. The prognosis is good for seminoma, even in the metastatic stage, with a good response to cisplatin-based regimens^[1, 4–6]. Nevertheless, non-seminomas have poorer overall survival^[OS] in the advanced stage, and recommendations may be amenable to clinical trials^[1, 4].

In particular, diverse populations and various barriers to healthcare delivery in developing countries makes the outcomes worthy of further investigation. Nevertheless, these testicular cancer patients have not been reported as to overall survival in the Thai population. This study aims to explore clinical and pathological characteristics

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Table 1: Clinical characteristics of testicular cancer testicular cancer patients.

| Variables | Seminoma (n = 23) | Non-seminoma (n = 22) | p-value |
|--|-------------------|-----------------------|---------|
| Mean age ± SD (year) | 38.1 (± 7.8) | 28.5 (± -6.9) | < 0.001 |
| Laterality of testicular mass (n (%)) | | | |
| Right | 10 (43.5) | 9 (40.9) | |
| Left | 12 (52.2) | 12 (54.5) | |
| Both | 1 (4.3) | 1 (4.5) | |
| Pre-op tumour markers (median, ng/mL) | | | |
| AFP (IQR) | 2.4 (2-3.8) | 944 (116.2-1,992.2) | < 0.001 |
| βHCG (IQR) | 12 (3.5-34.3) | 120.3 (11.2-3,588.5) | 0.005 |
| LDH (IQR) | 545 (333-1,137.5) | 500 (349.5-946.5) | 0.716 |
| Post orchietomy (median, ng/mL) | | | |
| AFP (IQR) | 2.7 (2-3.6) | 70 (3-1,609.8) | 0.012 |
| βHCG (IQR) | 2.2 (1-9.2) | 10.9 (1.1-323.6) | 0.099 |
| LDH (IQR) | 373 (323.5-734) | 438 (327.5-650.5) | 0.892 |

SD: standard deviation, ng/mL: nanogram/milliliter, IQR: interquartile range

and treatment outcomes of testicular cancer and also identify factors associated with the oncological outcomes in Songklanagarind hospital, Hat Yai, Thailand.

1.1. Patients and Methods

We conducted a retrospective analysis of 45 patients diagnosed with testicular cancer between January 2007 and December 2016, at the university-affiliated Songklanagarind hospital. The following criteria were used to determine inclusion:^[1] pathologically confirmed germ cell cancer,^[2] being over the age of 17, and^[3] treatment having started between January 2007 and December 2016. Patients with incomplete data were excluded from the study. The survival interval was determined from the date of high orchidectomy to the date of the last follow-up or death. Informal consent to participate in the study had been obtained from the research subjects before the study's commencement. The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Songklanagarind hospital and Prince of Songkla University approved this study.

1.2. Statistical analysis

The OS was calculated from the date of radical orchidectomy to the last follow-up visit or until death due to any cause. At the time of the last follow-up, patients who had not experienced an event were excluded. The Kaplan-Meier method was used to calculate the probability of survival, and the log-rank test was used

to compare subgroups of testicular cancer patients. All quantitative data were expressed as mean standard deviation (SD) or interquartile range (IQR), and comparisons between groups were made using the unpaired Mann-Whitney test or the *t*-test. The count data were represented using examples (*n*) and frequency (%). For intergroup comparisons, chi-squared or Fisher's exact tests were used. A *p*-value of 0.05 was considered statistically significant, and we used R version 4.0.1.

1.3. Follow-up

Individualised follow-up is based on the patient's stage, treatment option, and response to treatment, in addition to whether chemotherapy or radiation was used in conjunction with the treatment. Serum tumour markers, chest X-rays, abdominopelvic CT scans, and magnetic resonance imaging (MRI) are all used to monitor patients' responses to treatment^[10]. Follow-up after five years following testicular cancer treatment is generally not recommended.

2. Results

2.1. Patient characteristics

Clinical data of 45 testicular cancer patients were retrospectively reviewed. As a result, the researchers identified 23 (52%) seminomas and 22 (49%) non-seminomas in the group of patients. Table 1 shows the tumour characteristics of the two groups. The

Table 2: Tumour staging stratified by seminoma and non-seminoma.

| Variable | Seminoma, n (%) (n = 23) | Non-seminoma, n (%) (n = 22) | Total, n (%) (n-45) | p- value |
|---------------------------------------|-----------------------------|---------------------------------|------------------------|----------|
| T stage | | | | 0.484 |
| 1 | 1 (4.3) | 0 (0) | 1 (2.2) | |
| 2 | 15 (65.2) | 18 (81.8) | 33 (73.3) | |
| 3 | 6 (26.1) | 4 (18.2) | 10 (22.2) | |
| 4 | 1 (4.3) | 0 (0) | 1 (2.2) | |
| N stage | | | | 0.117 |
| 0 | 7 (30.4) | 3 (13.6) | 10 (22.2) | |
| 1 | 3 (13) | 4 (18.2) | 7 (15.6) | |
| 2 | 0 (0) | 4 (18.2) | 4 (8.9) | |
| 3 | 13 (56.5) | 11 (50) | 24 (53.3) | |
| M stage | | | | 0.024 |
| 0 | 18 (78.3) | 9 (40.9) | 27 (60) | |
| 1 | 5 (21.7) | 13 (59.1) | 18 (40) | |
| Serum marker | | | | 0.009 |
| 0 | 9 (39.1) | 1 (4.5) | 10 (22.2) | |
| 1 | 6 (26.1) | 8 (36.4) | 14 (31.1) | |
| 2 | 7 (30.4) | 6 (27.3) | 13 (28.9) | |
| 3 | 1 (4.3) | 7 (31.8) | 8 (17.8) | |
| Lymph node status | | | | 0.284 |
| No | 7 (30.4) | 3 (13.6) | 10 (22.2) | |
| Metastasis | 16 (69.6) | 19 (86.4) | 35 (77.8) | |
| Pulmonary metastasis | | | | 0.014 |
| No | 21 (91.3) | 12 (54.5) | 33 (73.3) | |
| Metastasis | 2 (8.7) | 10 (45.5) | 12 (26.7) | |
| Metastatic site | | | | 0.293 |
| No | 4 (17.4) | 3 (13.6) | 7 (15.6) | |
| Retroperitoneal LN | 14 (60.9) | 9 (40.9) | 23 (51.1) | |
| Lung | 0 (0) | 3 (13.6) | 3 (6.7) | |
| Bone | 1 (4.3) | 0 (0) | 1 (2.2) | |
| Retroperitoneal with pulmonary | 2 (8.7) | 5 (22.7) | 7 (15.6) | |
| Multiple site | 2 (8.7) | 2 (9.1) | 4 (8.9) | |

average age of the attendees was around 33.4 years. The seminoma group was found to have an average age at initial diagnosis of 38.1 years (± 7.8), while the non-seminoma group had an average age at initial diagnosis of 28.5 years (± 6.9). From this, 24 patients were afflicted with a dominant testicular tumour on the left side (53.3%). The levels of AFP and bHCG were significantly higher in the non-seminoma group of serum tumour markers ($p < 0.05$).

2.2. Clinical stage

Table 3 shows the results of all investigations and clinical staging after they were completed. Overall, the AJCC staging system is classified as stage I: 8 patients (17.8%); stage II: 10 patients (22.2%); and stage III: 27 patients (60%). According to the IGCCC risk

classification, all patients were divided into three groups: those with a good prognosis, those with an intermediate prognosis, and those with a poor prognosis, as shown in Table 3.

2.3. Treatments

All 45 testicular cancer patients were treated with radical orchidectomy and followed up with adjuvant treatment if indicated. RT was used in seminoma with retroperitoneal node metastasis in only two patients (4.4%). The majority of adjuvant treatment was chemotherapy in 37 patients (82%), including the etoposide-cisplatin regimen (EP) in 32 patients (71.1%), and the bleomycin, etoposide, and cisplatin regimen (BEP) in only five patients (11.1%). RPLND was carried out in one patient (2.2%), as shown in Table 4.

Table 3: Staging of testicular cancer patients and IGCCC risks classification stratified by seminoma and non-seminoma.

| Factors | Seminoma, n (%) (n = 23) | Non-seminoma, n (%) (n = 22) | Total, n (%) (n = 45) | p-value |
|---------------------|-----------------------------|---------------------------------|--------------------------|---------|
| Staging | | | | 0.081 |
| Ib | 4 (17.4) | 1 (4.5) | 5 (11.1) | |
| IIb | 0 (0) | 1 (4.5) | 1 (2.2) | |
| IIC | 7 (30.4) | 2 (9.1) | 9 (20) | |
| IIIa | 3 (13) | 3 (13.6) | 6 (13.3) | |
| IIIb | 7 (30.4) | 6 (27.3) | 13 (28.9) | |
| IIIc | 1 (4.3) | 7 (31.8) | 8 (17.8) | |
| Is | 1 (4.3) | 2 (9.1) | 3 (6.7) | |
| IGCCC | | | | 0.003 |
| Good | 20 (87) | 9 (40.9) | 29 (64.4) | |
| Intermediate | 2 (8.7) | 5 (22.7) | 7 (15.6) | |
| Poor | 1 (4.3) | 8 (36.4) | 9 (20) | |

Table 4: Treatment of all testicular cancer stratified by seminoma and non-seminoma.

| Treatment | Seminoma, n (%) | Non-seminoma, n (%) | Total, n (%) | p-value |
|---------------------|-----------------|---------------------|--------------|---------|
| Surveillance | 3 (13) | 2 (9.1) | 5 (11.1) | 0.451 |
| CMT | 17 (73.9) | 20 (90.9) | 37 (82.2) | |
| RT | 2 (8.7) | 0 (0) | 2 (4.4) | |
| RPLND | 1 (4.3) | 0 (0) | 1 (2.2) | |
| Chemotherapy | | | | 0.152 |
| No | 6 (26.1) | 2 (9.1) | 8 (17.8) | |
| EP | 16 (69.6) | 16 (72.7) | 32 (71.1) | |
| BEP | 1 (4.3) | 4 (18.2) | 5 (11.1) | |
| Cycle | | | | 0.234 |
| median(IQR) | 3 (1,4) | 4 (3,4) | 3 (2,4) | |

CMT: chemotherapy, RT: radiotherapy, RPLND: retroperitoneal lymph node dissection, EP: cisplatin-etoposide, BEP: cisplatin-etoposide

2.4. Survival

From 45 patients, the five-year OS of our study was 75.4%, as shown in Figure 1A, and comparisons between the two groups were 94.7% and 57.1% in the seminoma and non-seminoma groups, respectively, as shown in figure 1B. AJCC staging was classified as Ib-IIIa, IIIb, or IIIc, and the comparison OS found poorer survival, as shown in Figure 1C ($p = 0.022$). For non-seminoma, five-year OS was 71.4%, 50%, and 42.9% in stage Ib-IIIa, IIIb, and IIIc, respectively, and for seminoma, it was 92.3% and 100% in stage Ib-IIIa and IIIb, respectively. The seminoma and non-seminoma groups are compared (AJCC Staging; Ib-IIIa as shown in Figure 1D, IIIb as shown in Figure 1E, and IIIc as shown in Figure 1f).

For IGCCC risk classification, we have reported the two-year OS of patients with good, intermediate, and poor prognosis as being 96.2%, 71.4%, and 50%, and the five-year OS was 92.0%, 53.6%, and 37.5%, respectively. There was a significant difference in the OS between patients with good, intermediate, and poor prognoses, as shown in Figure 2 ($p = 0.01$).

This study has focused on patients with large retroperitoneal metastasis who were treated with chemotherapy and who were evaluated for a response to treatment. In our cohort, the majority of cases showed an improvement (tumour size decreased by more than 50%) with adjuvant treatment found at about 80%, and all tumour responses after treatment are shown as a waterfall plot in Figure 3. Testicular tumour size, which decreased more than 75% after adjuvant treatment as measured by the RECEIST criteria, has better survival compared with that of a group that has a tumour response of less than 75%, which was statistically significant, as shown in Figure 4 ($p = 0.01$).

2.5. Univariable analysis and multivariable analysis

Non-seminoma, higher AJCC staging, and poor IGCCC risk classification were identified to be independent mediators of higher mortality rates when using the Cox proportional hazards model. Patients with non-seminoma had a significantly higher mortality rate

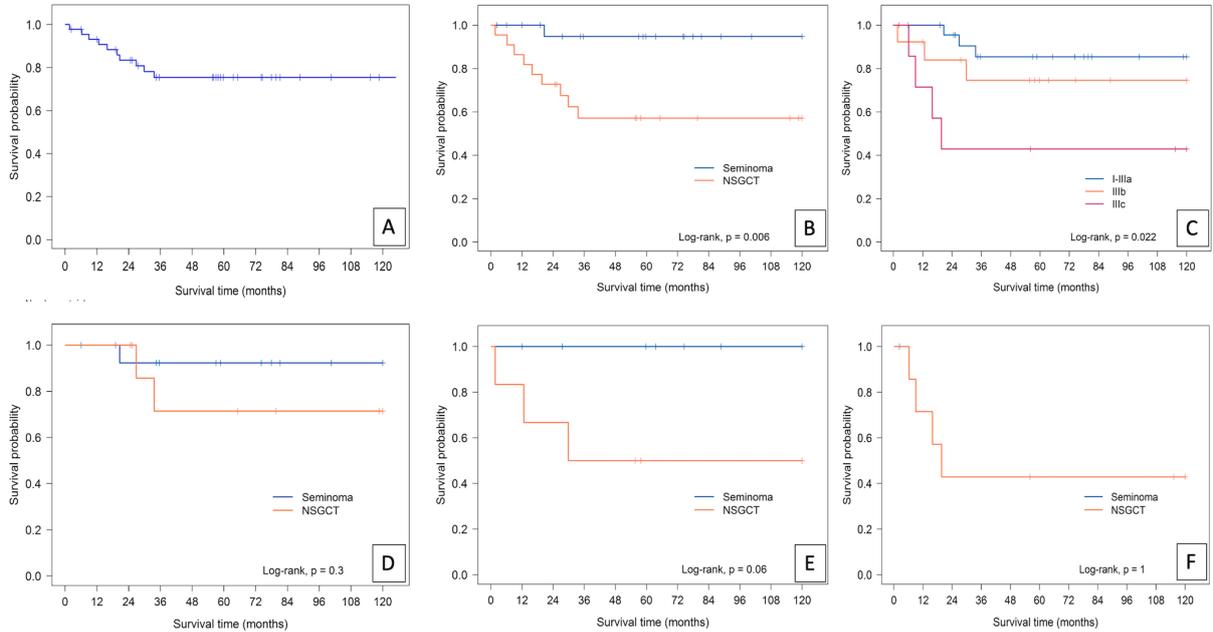


Figure 1: Kaplan-Meier survival curve of: (1A) all 45 patients in our cohort; (1B) patients stratified by seminoma of non-seminoma, stratified by stratum; (1C) AJCC staging; (1D) stage Ib-IIIa; (1E) stage IIIb; and (1F) stage IIIc.

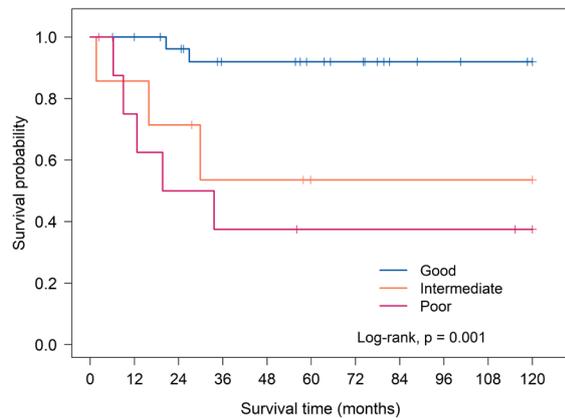


Figure 2: Kaplan-Meier survival curve of IGCCC classification.

compared with seminoma patients (HR = 10.4; 95% CI: 1.32–82.21, $p = 0.003$), and multivariable analysis showed that non-seminoma, higher staging, and higher IGCCC risk were significantly associated with poorer survival ($p < 0.005$), as shown in Table 5.

3. Discussion

This is the first study of the characteristics, treatment outcomes, and survival of testicular cancer patients

in Southern Thailand based on a single institute: Songklanagarind Hospital. Testicular cancer care in clinical practice is treated according to the recommended guidelines from the EAU or National Comprehensive Cancer Network, which are currently up to date^[4, 11]. Our cohort demonstrates that the average age at the time of diagnosis of testicular cancer is about 33.4 years, which is similar to a report in the USA that gave this age as 33 years^[12]. From the 45 patients, seminoma and non-seminoma patients numbered 23 (52.8%) and 22 (49%), respectively. The low incidence of this disease in the Asian population is reflected in the limited number of patients in this cohort. Another Asian study that lasted 20 years found that each of the 20 participating hospitals had an average of roughly 24 testicular germ cell tumours.^[13] It is well known that Caucasian men have a higher incidence of testicular cancer than Asian or African men^[14–17]. Among the Asian countries, the incidence of testicular cancer in Thailand was in the middle ranking^[18].

Our cohort had a significantly higher proportion of distant cancer at diagnosis when compared with the Western population. This trend contributed to the high metastatic rate. This tendency may be due to the abundance of alternative medicine available in the region, which can be found in both rural and urban regions. Patients who had to choose between losing a testis surgically or through non-surgical conventional

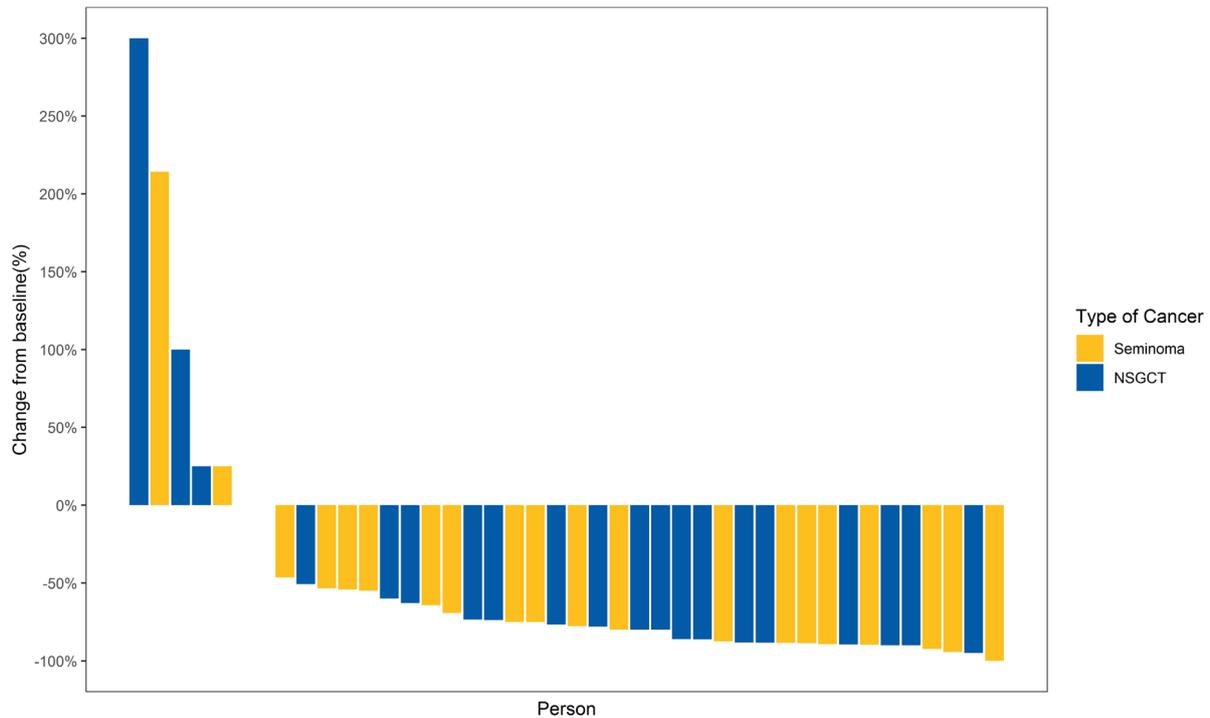


Figure 3: Tumour response after treatment at a response rate cut-off of 75%.

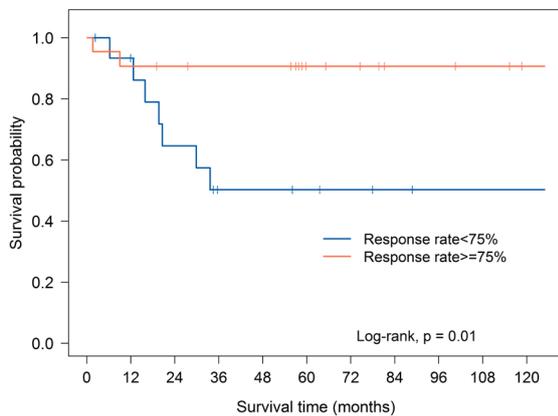


Figure 4: Kaplan-Meier survival curve of tumour response at a cut-off of 75%.

procedures might be swayed by such an approach. Another explanation could be ignorance of the condition. Public education and testicular self-examination are the keys to early detection and diagnosis. As testicular cancer generally has a favourable prognosis, the low mortality overall may have made it difficult to identify a statistically significant difference in deaths between groups, owing to the low size of the population. The management of testicular cancer is conducted by a multidisciplinary team that consists of a urologist,

medical oncologist, radio-oncologist, radiologist, and a pathologist. As treatment for the primary lesion, all patients underwent orchidectomy, with the goal of surgical resection as well as a confirmed histological diagnosis. Histopathological findings showed an equal prevalence of pure seminoma, accounting for approximately 50% of the non-seminoma group. The metastatic sites were usually found in the retroperitoneal lymph node and lung, in this present study, compared with previous studies. The average duration of follow-up was 80.6 months (range: 1.8 to 120 months). There are two obvious major findings from our study. First, overall, the median OS rate of 57.8 months for the five-year-OS was 94.7% and 57.1% in the seminoma and non-seminoma groups, respectively. Non-seminomas have significantly lower survival rates than seminomas, according to the data. For non-seminomas by staging, five-year OS was 71.4%, 50%, and 42.9% in stage Ib-IIIa, IIIb, and IIIc, respectively, and for seminomas, it was 92.3% and 100% in stage I-IIIa and IIIb, respectively. Even in patients with metastases, the utility of chemotherapy has a promising outcome for testicular cancer treatment, offering a cure rate of at least 80%.^[19]

The combination rate of BEP chemotherapy has become the standard treatment of metastatic testicular cancers^[20]. Cycles of the BEP regimen are

Table 5.: Univariable and multivariable Cox regression analyses predicting overall survival (OS) in 45 patients with diagnosed testicular cancer between 2007 and 2016.

| Variables | Univariable analysis | | Multivariable analysis | |
|------------------------------------|----------------------|---------|------------------------|---------|
| | HR(95%CI) | P value | HR(95%CI) | P value |
| Classification: | | | | |
| seminoma | ref | | | |
| non-seminoma | 10.4 (1.32-82.21) | 0.003 | 10.2 (1.34-80.12) | 0.002 |
| T stage: | | | | |
| T3-T4 vs T1-T2 | 0.67 (0.14-3.14) | 0.607 | | |
| N stage : | | | | |
| N=0 | ref | | | |
| N1-N2 | 0.77 (0.05-12.31) | 0.113 | | |
| N3 | 3.76 (0.47-30.1) | | | |
| Serum marker | | | | |
| 1 | 1.27 (0.11-14.02) | | | |
| 2 | 2.15 (0.22-20.72) | 0.141 | | |
| 3 | 7.23 (0.8-64.88) | | | |
| Metastasis | | | | |
| no | ref | | | |
| Retroperitoneal LN | 1.82 (0.21-15.63) | | | |
| Lung | 0 (0- inf) | 0.625 | | |
| Bone | 0 (0- inf) | | | |
| Retroperitoneal LN and lung | 3.33 (0.35-32.03) | | | |
| Multiple | 2.45(0.15-39.18) | | | |
| Staging | | | | |
| Ib-IIIa | ref | | ref | |
| IIIb | 2.06 (0.42-10.23) | 0.006 | 2.05 (0.40-10.20) | 0.005 |
| IIIc | 6.45 (1.43-29.13) | | 6.43 (1.41-29.11) | |
| IGCCC risk classification | | | | |
| good | ref | | ref | |
| Intermediate | 7.48 (1.25-44.87) | 0.003 | 7.42 (1.21-44.82) | 0.002 |
| Poor | 12.05 (2.33-62.45) | | 12.01 (2.31-62.41) | |

recommended, depending on the risk groups, for usually three or four cycles^[21]. Four cycles of EP and three courses of BEP chemotherapy are equally recommended for patients with good prognosis^[22]. EP and BEP chemotherapy were widely used for both seminoma and non-seminoma patients, with more than 90% of patients in this cohort receiving this treatment. However, our series had a lower overall survival rate than previous reports, particularly in non-seminoma patients, and it may not require second- or third-line chemotherapy for survival extension. Moreover, as testicular cancer generally has a favourable prognosis, the low overall mortality may have made it difficult to identify a statistically significant difference in deaths between groups, owing to limited data. Nonetheless, the higher proportion of distant staged cancers at diagnosis in our study's population as compared with a Western population may indicate a delay in diagnosis. Our cohort had several barriers to care, including low insurance coverage, a physician shortage, and a rural population. Perhaps the most obvious barrier to care are from all statements in our cohort when it is compared with the United States. However, the more advanced staging at presentation did not appear to imply a higher five-year mortality

rate. Second, we observed a significant difference in the OS between each IGCCCG prognostic patient. For the results of the IGCCC risk classification, the two-year overall survival of our patients with good, intermediate, and poor prognoses was 96.2%, 71.4%, and 50%, and the 5-year overall survival (OS) was 92.0%, 53.6%, and 37.5%, respectively. Our findings are consistent with those in the literature. A large study reported an international consortium with contributed data on 9,530 advanced non-seminoma GCC patients treated with cisplatin/etoposide-based first line chemotherapy between 1990 and 2013. As originally reported, the five-year survival rates in IGCCC in the good, intermediate, and poor prognosis groups were at 91%, 79%, and 48%, respectively^[24]. Additional data from 2,302 advanced seminoma patients showed the five-year OS as being 96%, 89%, and 67% for patients in the good-, intermediate-, and poor-risk groups, respectively^[24]. For IGCCC classification, five-year OS rates were reported to be 95% and 87% for good- and intermediate-risk patients, respectively^[10]. There is a dearth of information on the prognosis of Asian men with testicular cancer, and only a limited percentage of the data on Asian patients comes from Western studies that include naturalised citizens from Asia. Asian-

American men with testicular GCT had an overall five-year survival rate of 88%, according to an American study^[25]. Asians had a survival rate of between 92% and 99% in a study of the American population that included all types of testicular cancer histology^[17]. Overall, patients in our study had a lower survival rate than those in the previous study, although no significant difference in overall survival was detected between good- and intermediate-risk individuals. Poor prognosis and intermediate groups had worse survival than the good prognosis group, according to a multivariable analysis, HR: 12.05, 95% CI: 2.33–62.45 and 7.48, 95 % CI: 1.25–44.87, respectively. Additionally, it was found that non-seminoma, greater staging, and higher IGCCC risk were all linked with considerably lower survival ($p < 0.05$).

This current study had some limitations, including the fact that it was a single-centre study with limited sample size and was conducted from a retrospective approach. Important real-world data on patient clinical outcomes, on the other hand, may be handled differently from data in a clinical trial context. To acquire more accurate results in the future, we plan to design a multi-centre, completely prospective and randomised control study with a high sample size, combined with cancer-specific mortality analysis. Our patients, who are TC survivors (TCS), are a valuable resource that will become a valuable cohort for adult-onset cancer survivorship research, because of their prolonged survival. Commensurately, long-term treatment-related complications have emerged as important survivorship issues. Finally, this is the first regional research into testicular cancer patients' characteristics, treatment, and survival in a single university-referral hospital in Southern Thailand.

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4. Conclusion

Our cohort demonstrated worse outcomes in terms of five-year survival compared to previous literature, and a higher proportion of regional and distant cancers at diagnosis. Seminoma patients have a fair prognosis at all stages and have a greater survival rate than non-seminoma patients. However, higher staging and IGCCC risk were independent factors linked to a worse prognosis. These patients' survival has increased as a result of correct diagnoses, using available tumour markers and sophisticated imaging modalities, successful multimodal treatment, improved surgical methods, and efficient chemotherapy. Patients with metastatic testicular cancer who had adjuvant chemotherapy and radiotherapy had better results. Seminoma patients have a superior five-year overall survival rate than non-seminoma patients in real-world experience.

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Conflict of interest

No conflicts of interest to report.

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