REVIEW PAPER

UROLOGICAL ONCOLOGY

Late relapse of testicular germ cell tumor: An individual patient data meta-analysis of disease characteristics, treatments, and oncological outcomes

Mehdi Kardoust Parizi[1,2], Nirmish Singla[3], Siamak Daneshmand[4], Axel Heidenreich[1,5], Aditya Bagrodia[6], Vitaly Margulis[7], Akihiro Matsukawa[1,8], Ichiro Tsuboi[1,9], Shahrokh F. Shariat[1,7,10,11,12,13,14]

[1]*Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Austria*
[2]*Department of Urology, Shariati Hospital, Tehran University of Medical Sciences, Iran*
[3]*James Buchanan Brady Urological Institute, Johns Hopkins University, Baltimore, MD, United States of America*
[4]*Department of Urology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, United States of America*
[5]*Department of Urology, Uro-Oncology, Robot-Assisted and Specialized Urologic Surgery, University Hospital Cologne, Cologne, Germany*
[6]*Department of Urology, University of California San Diego, CA United States of America*
[7]*Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, United States of America*
[8]*Department of Urology, Jikei University School of Medicine, Tokyo, Japan*
[9]*Department of Urology, Shimane University Faculty of Medicine, Japan*
[10]*Departments of Urology, Weill Cornell Medical College, New York, United States of America*
[11]*Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria*
[12]*Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic*
[13]*Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan*
[14]*Research Center for Evidence Medicine, Urology Department, Tabriz University of Medical Sciences, Iran*

Citation: Parizi MK, Singla N, Daneshmand S, et al. Late relapse of testicular germ cell tumor: An individual patient data meta-analysis of disease characteristics, treatments, and oncological outcomes. Cent European J Urol. 2025; doi: 10.5173/ceju.2025.0069

Article history
Submitted: Mar. 23, 2025
Accepted: Jun. 3, 2025
Published online: Aug. 31, 2025

Corresponding author
Shahrokh F. Shariat
Department of Urology and Comprehensive Cancer Center,
Vienna General Hospital,
Medical University of Vienna,
Währinger Gürtel 18-20,
A-1090 Vienna,
Austria
sfshariat@gmail.com

Introduction Late relapse (LR) of testicular germ cell tumor (TGCT) is a relatively rare event with limited data to help refine evidence-based decision-making. This individual patient data meta-analysis aims to analyze disease characteristics, treatment modalities, and factors affecting oncological outcomes of TGCT patients suffering from LR.

Material and methods A systematic search and individual patient data gathering was performed. The primary end points were disease-free survival (DFS) and cancer-specific survival (CSS).

Results A total of 12 studies, comprising 240 patients, were selected for review. In multivariable analysis, surveillance as primary management of TGCT was associated with a higher risk of retroperitoneal LR (OR = 10.08, 95% CI: 2.34–43.31). On univariable analyses, longer time to LR, LR multiplicity, and chemotherapy (as the sole treatment of LR) were significantly associated with worse DFS and CSS, while pure teratoma at LR, teratoma element at LR, surgery (as the sole treatment of LR), and surgery-based combination treatment of LR were significantly associated with better DFS and CSS. Salvage chemotherapy for LR was associated with worse DFS and CSS compared to first-line chemotherapy in multivariable cox regression analysis (HR = 13.03, 95% CI: 1.13–150.25). Two decision-tree models are proposed to help shared decision making regarding chemotherapy-based vs surgery-only and surgery-based versus combination treatments; the accuracies of these models were 0.94 and 0.88.

Conclusions Available data suggest a benefits to surgery alone or surgery-based combination therapy compared to chemotherapy alone for LR of TGCT. We propose decision-tree models to help clinical decision-making in TGCT patients with LR.

Key Words: testicular germ cell tumor ‹› testicular cancer ‹› late relapse ‹› RPLND ‹› chemotherapy

INTRODUCTION

Late relapse (LR) of testicular germ cell tumor (TGCT) is a rare event, characterized by disease relapse occurring more than two years after completing treatment; its incidence is 1.4% for patients with seminoma and 3.2% for those with non-seminomatous germ cell tumors (NSGCT) [1]. This disease state is highly complex and heterogeneous rendering it a very challenging entity to manage adequately. There is, indeed, little high-quality evidence to help guide clinical decision-making.

Despite LR often being diagnosed when the patient exhibits symptoms, the impact of symptom presence on oncological outcomes remains unclear [2, 3]. In addition, the potential benefits of detection of recurrence at an earlier time remains uncertain [4]. Furthermore, the varied patterns of metastasis (type, location, and number), coupled with the adverse pathologic findings (i.e., histology) pose challenges in determining the optimal treatment of LR in TGCT patients.

While surgery remains a cornerstone of treatment, discussions around salvage chemotherapy protocols and high-dose chemotherapy have shown promise. The surgical resection when the tumor is resectable, as this approach can enhance survival rates. In cases where the disease is extensive and not suitable for surgery, systemic chemotherapy may be necessary. Prognosis varies significantly; studies indicate that around 68% of patients survive three years after a late recurrence, but those with vital malignant tumors generally have poorer survival rates compared to patients with teratoma or necrosis, who can achieve a 10-year cause-specific survival rate of up to 100% [4–7]. Identifying the optimal treatment strategy for each patient is particularly challenging, especially when taking into account both the effectiveness of treatment and the adverse events/safety of each treatment strategy.

Therefore, in this systematic review and individual patient data (IPD) meta-analysis, we conducted a comprehensive investigation and analysis of disease characteristics and factors influencing oncological outcomes associated with LR. Specifically, our study aimed to explore treatment approaches, striving to identify the most effective therapeutic protocols associated with improved oncological outcomes.

MATERIAL AND METHODS

Search strategy

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [8, 9]. We used the population, intervention, comparator, outcome, and study design (PICOS) to define the eligibility criteria. The studies were considered eligible if they included patients with late relapse of testicular germ cell tumor (population) who received various treatment modalities (intervention) compared to patients receiving alternative treatments or different management approaches (comparator) to evaluate disease-free survival (DFS) and cancer-specific survival (CSS) (outcomes) in individual patient data meta-analyses (study design). A full electronic literature search using PubMed, Scopus, Web of Science, and Cochrane Library was performed by two independent authors in December 2023 to find studies assessing disease characteristics, treatments and oncological outcomes of patients with LR of TGCT. After the primary screening based on study title and abstract, all full-text papers were assessed and excluded with reasons. Any discrepancies were resolved by referring to the senior author. The following terms were used in our search strategy: (testicular germ cell tumor OR testicular cancer OR testis tumor OR testis cancer) AND (late relapse OR late recurrence). The protocol of this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews database (CRD42024501175).

Inclusion and exclusion criteria

The following criteria were considered to select eligible studies: prospective or retrospective studies including full text regarding IPD on disease characteristics and treatments in LR of TGCT with oncological survival outcomes as endpoints. We excluded studies in other than English, case reports, review articles, replies, expert opinions, and comment letters. If more than one report of the same cohort of patients existed, only the largest or most recently published study was included. Oncological outcome of DFS and CSS were the primary outcomes of interest. The secondary endpoints were LR anatomical patterns and pathological findings.

Data extraction

Two authors extracted the data from all eligible studies. We used se the available IPD from each study by reviewing the main article and its supplementary materials. This includes raw patient-level data, which consists of individual clinical measurements and detailed patient information. The information contained the following characteristics: first

author's name, publication year, region, recruitment period, study design, number of patients with available clinical and survival data, chemotherapy regimen in primary and relapsed disease treatment, mean time to LR, and mean follow-up time. All available IPDs for disease characteristics, treatments, and oncological outcomes were retrieved for analysis. All discrepancies regarding data extraction were resolved by consensus among co-authors.

Statistical analyses

Analysis of clinicopathologic features

Baseline characteristics were tabulated with descriptive statistics for the population. Continuous variables were reported as mean and standard deviation (SD). Multivariable logistic regression analysis was used to assess the relationship between clinicopathologic factors and LR anatomical patterns and pathological findings in patients with LR of TGCT. The Stata logistic regression nomogram generator was employed to create a predictive model for retroperitoneal lymph node involvement at LR.

Analysis of oncological survival outcomes

Univariable and multivariable Cox regression models addressed the association of clinicopathologic factors such as age, primary clinical stage, primary treatment (post-orchiectomy), time to LR, symptomatic LR, LR site, LR multiplicity, re-relapse, tumor marker level at LR, LR pathology, and LR treatment with DFS and CSS. We used the Kaplan–Meier method and log-rank tests to compare survival outcomes between groups. Statistical analyses for analysis of oncological survival outcomes and clinicopathologic features were performed using STATA/MP 17 (Stata-Corp.). All tests were two sided, and p-values < 0.05 were considered statistically significant.

Decision-tree modelling

Decision-tree modelling of individual patient data was performed to identify patients who benefit from different LR therapeutic modalities with the target variable of DFS. Python 3.11.0 was used to generate the tests and then selects the optimal sequence of decisions based on the information taken from the individual characteristics and its relevance to the response variable. We split dataset into two subsets of training and test sets and used the random seed in the relevant functions or classes to ensure reproducibility through the machine learning algorithms including decision trees. The patient characteristics assessed in the model were primary testicular pathology, primary clinical stage (CS), primary treatment, relapse site, relapse pathology, and relapse multiplicity. Patients with unavailable data on these variables were excluded. Decision Trees' Accuracy showed the accuracy metric associated with a decision tree model. In decision trees implemented in Python, entropy measures the uncertainty or impurity in a dataset, guiding feature selection for splitting nodes. Samples are the individual data points used for training, consisting of features and target labels, with their quality influencing model performance. Value refers to specific attribute values that determine how data is split at each node, while class denotes the target variable that the decision tree aims to predict.

Risk of bias assessment

The RoB assessment of each study was performed by 2 independent authors according to the Cochrane Handbook for Systematic Reviews of Interventions for including nonrandomized studies [10, 11]. The overall RoB level was presented as "low," high, or "unclear risk." We used Review Manager Version 5.3 (RevMan Computer program, Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to design RoB assessment graph.

RESULTS

Literature search process

A total of 699 articles were identified by our initial literature search and 172 duplicates were removed. Then, 485 and 30 articles were excluded after title/abstract evaluation and full-text reading, respectively (Figure 1). This left 12 studies comprising 240 patients for this systematic review and IPD meta-analysis.

Studies and patients' characteristics

All studies had a retrospective design and were published between 1988 and 2016. The majority of reports came from Europe [2, 3, 6, 7, 12–16], with only two [17, 18] and one [19] studies coming from North America and Asia, respectively. The Mean time to LR ranging from 56 to 118 months. Furthermore, the mean follow-up time ranging 21 to 99 months (Table 1). Table 2 provides a summary of patient and tumor characteristics from studies assessing disease features and treatments

in patients with TGCT experiencing LR. The RoB assessment indicated an intermediate to high level of bias across the studies (Suppl. Figure 1).

Primary clinicopathologic features and late relapse anatomical patterns

Primary CS I was significantly associated with higher risk of retroperitoneal LR compared to other clinical stages (OR = 2.67, 95% CI: 1.39–5.15), while CS II was significantly associated with lower risk of retroperitoneal LR (OR = 0.53, 95% CI: 0.29–0.98) in univariable analysis. Primary testicular pathology of seminoma was significantly associated with higher risk of lymphatic LR compared to other pathological findings (OR = 3.64, 95% CI: 1.20–10.83) in univariable analysis. Moreover, management of primary disease with surveillance was significantly associated with higher risk of retroperitoneal LR compared to other therapeutic managements

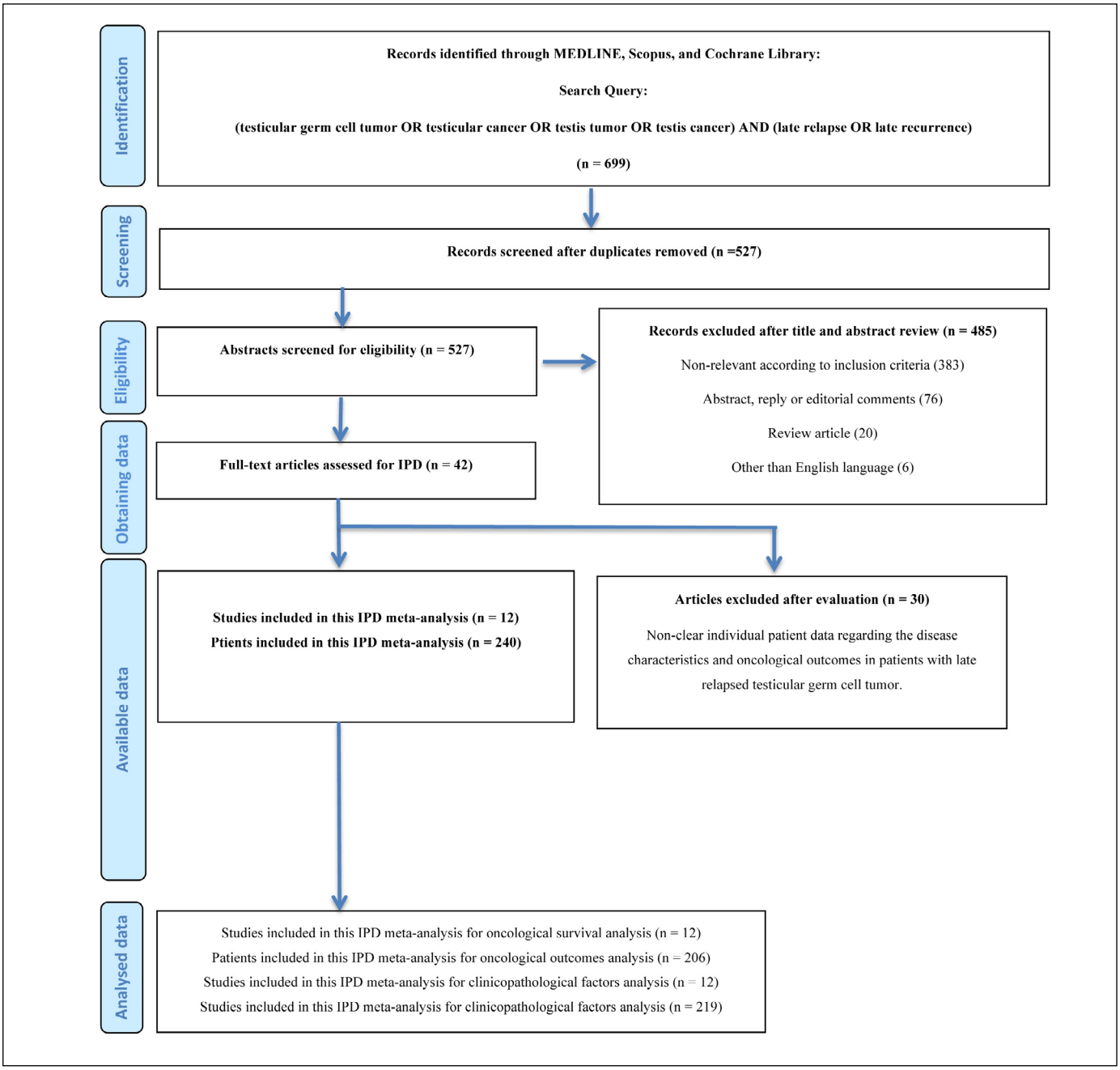


Figure 1. *PRISMA individual patient data (IPD) flow diagram for article selection process to analyze the disease characteristics and oncological outcomes of patients with late relapsed testicular germ cell tumor.*

Table 1. *Study and treatment characteristics of 12 studies assessing the disease characteristics and treatments in patients with late relapse of testicular germ cell tumor*

First author	Year	Region	Recruitment period	Design	Pts[a]	CT regimen in primary treatment	CT regimen at relapse	Mean time to LR [months]	Mean follow-up [months]
Borge [12]	1988	Europe	1972–1982	Retrospective	15	CVB, VACAM	CVB, VACAM	73	21
Ravi [6]	1997	Europe	1978–1994	Retrospective	6	BEP	MBOP, TIP, BEP, POMB/ ACE, oral Etoposide	74	21
Michael [18]	2000	North America	NA	Retrospective	91	NA	NA	85	58
Shahidi [13]	2002	Europe	1979–1993	Retrospective	14	PVB, BEP, BOP, EP, Carboplatin	NA	106	52
Kuczyk [14]	2004	Europe	1979–1995	Retrospective	14	NA	NA	56	57
Muramaki [19]	2005	Asia	1977–2001	Retrospective	6	BEP, BVA, HD-ICE, VAB-6	BEP, EP, HD-ICE, VAB-6	65	64
Ronnen [17]	2005	North America	1989–2001	Retrospective	8	VAB, BEP, EP	TIP	98	43
Geldart [15]	2006	Europe	1980–2004	Retrospective	20	BEP, VIP, PVB, BOP	TIP, VIP	108	44
Oldenburg [2]	2006	Europe	1971–1997	Retrospective	25	CVB, HOP, BEP, CEB, CAOS, EP, VIP, BOP	CVB, EP, HOP, BEP, Carboplatin, VIP, Taxol, BOP	73	99
Nolan [16]	2010	Europe	1989–2008	Retrospective	9	NA	BEP, BOP	77	50
Mayer [7]	2011	Europe	NA	Retrospective	12	BEP, PVB, VB, PD	PEI, oral Etoposide, HDCT[b]	89	50
Mortensen [3]	2016	Europe	1984–2007	Retrospective	20	NA	BEP	118	NA

[a] Patients with available data for individual patient data meta-analysis
[b] 3 × standard PEI or standard paclitaxel, ifosfamide, cisplatin followed by a single high-dose regimen with autologous blood stem cell support

BEP – bleomycin, etoposide, cisplatin; BOP – bleomycin, vincristine, cisplatin; BVA – bleomycin, vinblastine, actinomycin D; CAOS – cyclophosphamide, actinomycin-D, oncovin, sendoxan; CEB – carboplatin, etoposide, bleomycin; CVB – cisplatin, vinblastine, bleomycin; CT – chemotherapy; EP – etoposide, cisplatin; HDCT – high dose chemotherapy; HD-ICE – high-dose IFX CBDCA, NA – not available; HOP – holoxan, oncovin, cisplatin; LR – late relapse; MBOP – methotrexate, bleomycin, oncovin, cisplatin; POMB/ACE – cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide; PD – cisplatin, doxorubicine; PEI – paclitaxel, ifosfamide, cisplatin; PVB – cisplatin, vinblastine, bleomycin; TIP – paclitaxel, ifosfamide, cisplatin; VP-16; VAB-6 – vinblastine, actinomycin D, bleomycin, cyclophosphamide, cisplatin; VAB – vinblastine, dactinomycin, cyclophosphamide, bleomycin, cisplatin; VACAM – vincristine, doxorubicin, cyclophosphamide, dactinomycin, medroxyprogesterone acetate; VB – vinblastine, bleomycin; VIP – etoposide, ifosfamide, cisplatin

(OR = 7.56, 95% CI: 2.78–20.56) in univariable analysis. In multivariable analysis, surveillance as the primary management of TGCT was associated with higher risk of retroperitoneal LR (OR = 10.08, 95% CI: 2.34–43.31) (Suppl. Table 1). Figure 2 shows a logistic regression nomogram for prediction of retroperitoneal LR probability (single site or as a part of multiple relapse pattern) in patients with TGCT.

Primary clinicopathologic features and pathological finding at late relapse

Primary CS I was significantly associated with lower risk of pure teratoma at LR compared to other clinical stages (OR = 0.18, 95% CI: 0.07–0.45) in univariable analysis. Primary testicular pathology of pure teratoma was significantly associated with higher risk of pure teratoma at LR compared to other pathological findings (OR = 3.62, 95% CI: 1.50–8.72) in univariable analysis. Furthermore, teratoma element in primary testicular pathology was significantly associated with higher risk of pure teratoma at LR compared to other pathological findings (OR = 2.51, 95% CI: 1.27–4.97) in univariable analysis. Management of primary disease with surveillance was significantly associated with lower risk of pure teratoma at LR compared to other therapeutic managements (OR = 0.17, 95% CI: 0.04–0.65), while combination of surgery and chemotherapy was significantly associated with higher risk of pure teratoma at LR (OR = 6.51, 95% CI: 2.40–17.65) in univariable analysis. Surgery-based primary treatment was associated with higher risk of pure teratoma at LR compared to non-surgery-based treatments in univariable (OR = 7.42, 95% CI: 2.73–20.14) and multivariable (OR = 13.22, 95% CI: 1.36–128.27) analysis. Moreover, longer time to LR was significantly associated with lower risk of pure teratoma at LR in univariable (OR = 0.98, 95% CI: 0.98–0.99) and multivariable (OR = 0.98, 95% CI: 0.96–0.99) analysis (Suppl.

Table 2). The Kaplan–Meier curves showed that patients who underwent surveillance for primary disease were at a significantly lower risk of non-germ cell tumor at LR pathology compared to other treatments, while primary management with chemotherapy was significantly associated with higher risk of non-germ cell tumor at LR pathology compared to other treatments (Suppl. Figure 2).

Clinicopathologic features and oncological survival outcomes at late relapse

Data on oncological survival outcomes was supplied for 12 studies including 206 patients. On log-rank test and unadjusted Cox model, longer time to LR (HR = 1.004, 95% CI: 1.001–1.007), LR multiplicity (HR = 1.99, 95% CI: 1.21–3.26), mixed germ cell and non-germ cell tumor at LR pathology (HR = 2.09, 95% CI: 1.02–4.26), and chemotherapy as the sole treatment of LR (HR = 3.14, 95% CI: 1.70–5.79), were significantly associated with worse DFS. Moreover, pure teratoma at LR pathology (HR = 0.31, 95% CI: 0.17–0.58), teratoma element at LR pathology (HR = 0.38, 95% CI: 0.23–0.65), surgery as the sole treatment of LR (HR = 0.41, 95% CI: 0.22–0.73), and surgery-based LR treatment (HR = 0.87, 95% CI: 0.18–4.14) were significantly associated with better DFS (Figure 3). On log-rank test and unadjusted Cox model, longer time to LR (HR = 1.004, 95% CI: 1.000–1.008),

Table 2. *Summary of patient and tumor characteristics of 12 studies assessing the disease characteristics and treatments in patients with late relapse of testicular germ cell tumor*

Characteristic	N[a]	Result
Mean age at initial diagnosis [years] (SD)	151	33.6 (15.4)
Clinical stage at initial presentation [n (%)]		
Clinical stage I	218	60 (27.5)
Clinical stage II		74 (33.9)
Clinical stage III		84 (38.5)
Primary testicular pathology [n (%)]		
Seminoma	225	38 (16.9)
NSGCT		158 (70.2)
Pure teratoma		29 (12.9)
Teratoma element at primary testicular pathology [n (%)]		
Yes	217	112 (51.6)
No		105 (48.4)
Primary management [n (%)]		
Chemotherapy	141	39 (27.7)
Radiotherapy		17 (12.1)
Surgery[b]		3 (2.1)
Surveillance		35 (24.8)
Chemotherapy + radiotherapy		9 (6.4)
Chemotherapy + surgery		37 (26.2)
Chemotherapy + radiotherapy + surgery		1 (0.7)
Mean time to late relapse, months (SD)	240	88.2 (57.6)
Symptomatic late relapse [n (%)]		
Yes	54	36 (66.7)
No		18 (33.3)
Anatomical late relapse pattern [n (%)]		
Lymphatic relapse only[c]	219	149 (68)
Non-lymphatic relapse only[d]		35 (16)
Lymphatic and non-lymphatic relapse, both		28 (12.8)
High tumor marker only		7 (3.2)
Retroperitoneal late relapse only [n (%)]		
Yes	219	85 (38.8)
No		134 (61.2)
Late relapse site number [n (%)]		
One site	199	39 (19.6)
More than one site		160 (80.4)
Re-relapse [n (%)]		
Yes	164	61 (37.2)
No		103 (62.8)
High tumor marker at late relapse (AFP) [n (%)]		
Yes	105	41 (39)
No		64 (61)
High tumor marker at late relapse (HCG) [n (%)]		
Yes	106	25 (23.6)
No		81 (76.4)
Late relapse pathology [n (%)]		
Seminoma	176	29 (16.5)
NSGCT		59 (33.5)
Pure teratoma		61 (34.7)
Non-germ cell tumor		12 (6.8)
Mixed germ cell and non-germ cell tumor		15 (8.5)
Late relapse non-germ cell tumor pathology [n (%)]		
Adenocarcinoma	27	9 (33)
Sarcoma		8 (30)
Undifferentiated carcinoma		3 (11)
Other		7 (26)
Teratoma element at late relapse pathology [n (%)]		
Yes	173	96 (55.5)
No		77 (44.5)
Late relapse treatment [n (%)]		
Chemotherapy	140	37 (26.4)
Radiotherapy		1 (0.7)
Surgery		33 (23.6)
Chemotherapy + radiotherapy		18 (12.8)
Chemotherapy + surgery		47 (33.6)
Chemotherapy + radiotherapy + surgery		4 (2.9)
Late relapse outcomes [n (%)]		
No evidence of disease	225	133 (59.1)
Death		71 (31.6)
Mean follow-up [months] (SD)	206	56.4 (3.47)

[a] Number of patients with available data
[b] Including retroperitoneal lymph node dissection and surgery of metastatic sites according to the clinical staging
[c] Including retroperitoneal, retrocrural, mediastinal, cervical, iliac, presacral, and axillary lymph nodes
[d] Including liver, lung, bone, muscle, brain, chest wall, pancreas, spleen, and ureter
AFP – α-fetoprotein; HCG – human chorionic gonadotropin; NSGCT – non-seminomatous germ cell tumor; SD – standard deviation

LR multiplicity (HR = 2.05, 95% CI: 1.18–3.54), LR NSGCT pathology (HR = 2.13, 95% CI: 1.21–3.77), and chemotherapy as the sole treatment of LR (HR = 2.73, 95% CI: 1.34–5.57), were significantly associated with worse CSS. Furthermore, pure teratoma at LR pathology (HR = 0.20, 95% CI: 0.09–0.44), teratoma element at LR pathology (HR 0.31, 95% CI: 0.18–0.56), surgery as the sole treatment of LR (HR = 0.07, 95% CI: 0.01–0.53), and surgery-based LR treatment (HR = 0.42, 95% CI: 0.21–0.82), were significantly associated with better CSS (Figure 4). In the multivariable analyses, which accounted for the impact of clinicopathologic covariables, no statistically significant associations were observed between clinicopathologic features and DFS and CSS (Table 3). On multivariable cox regression analysis, salvage chemotherapy at LR was significantly associated with worse DFS and CSS compared to first-line chemotherapy (HR = 13.03, 95% CI: 1.13–150.25) (Suppl. Table 3).

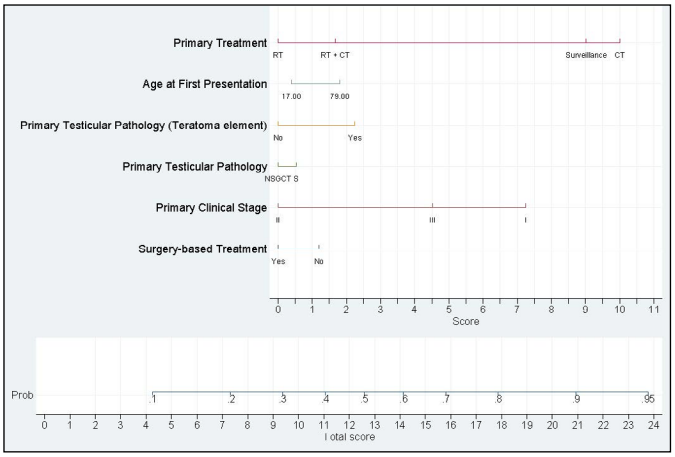
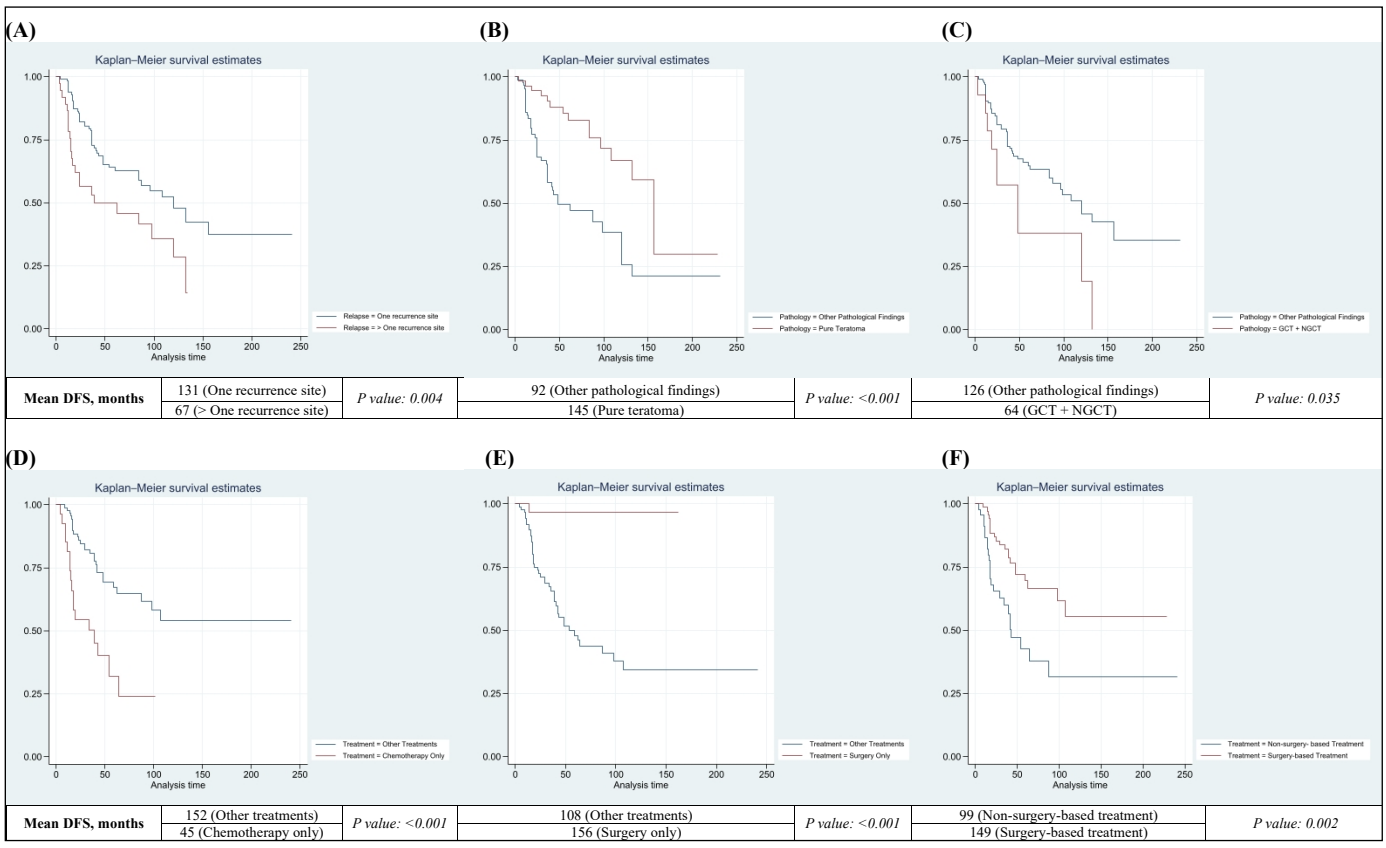


Figure 2. *Nomogram presenting retroperitoneal relapse probability (single site or as a part of multiple relapse pattern) in patients with late relapse of testicular germ cell tumor.*
CT – chemotherapy, RT – radiotherapy, S – seminoma

Decision-tree modelling

A total of 53 patients were included in decision-tree modelling with the target variable of NED. Thirty-seven and 16 patients were selected for training



Mean DFS, months	131 (One recurrence site) 67 (> One recurrence site)	*P value: 0.004*	92 (Other pathological findings) 145 (Pure teratoma)	*P value: <0.001*	126 (Other pathological findings) 64 (GCT + NGCT)	*P value: 0.035*
Mean DFS, months	152 (Other treatments) 45 (Chemotherapy only)	*P value: <0.001*	108 (Other treatments) 156 (Surgery only)	*P value: <0.001*	99 (Non-surgery-based treatment) 149 (Surgery-based treatment)	*P value: 0.002*

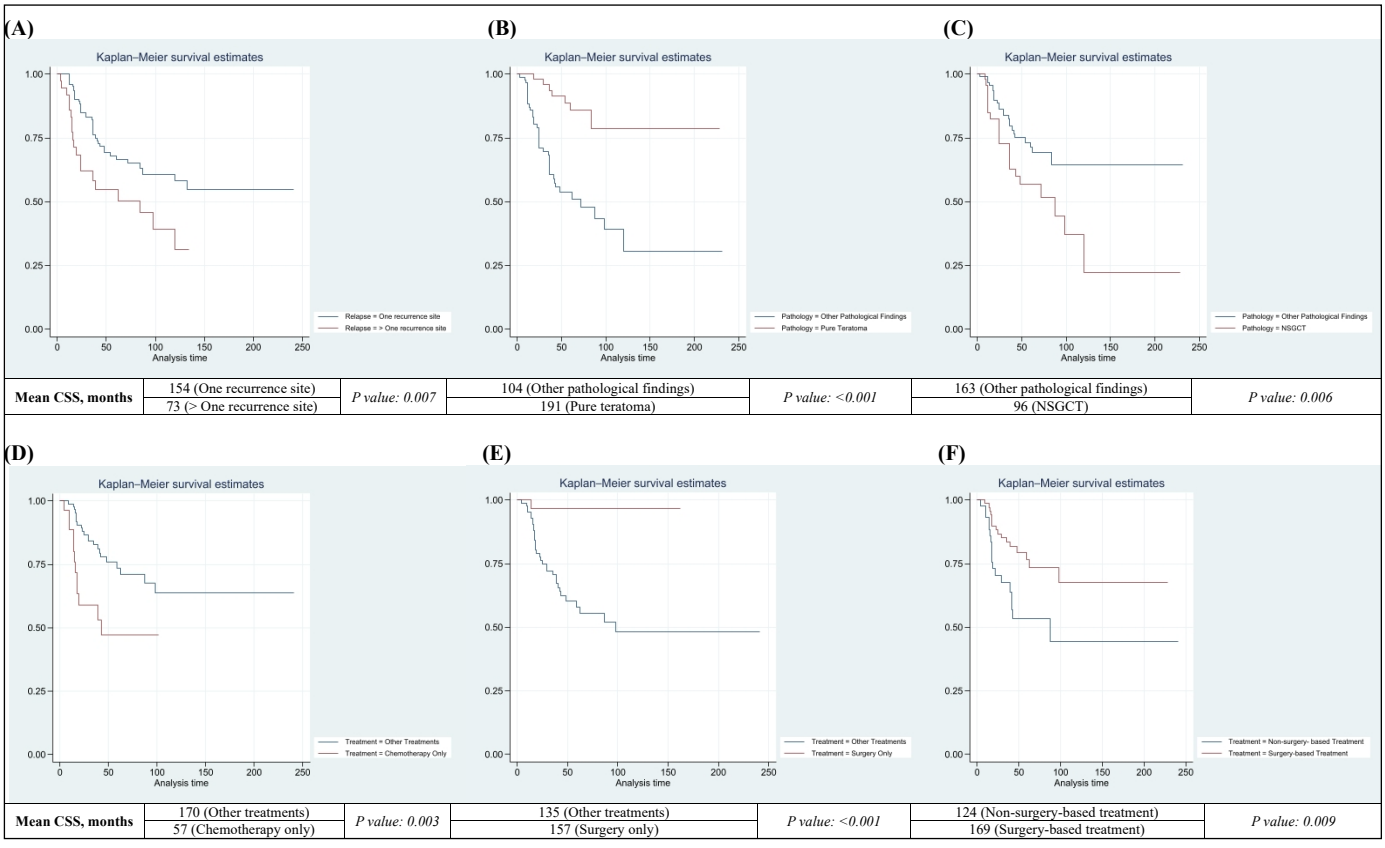
Figure 3. *Kaplan-Meier + pairwise log-rank tests for disease-free survival (DFS) according to the* **A)** *late relapse multiplicity,* **B)** *late relapse pure teratoma pathology,* **C)** *late relapse mixed germ cell and non-germ cell pathology,* **D)** *late relapse treatment with only chemotherapy,* **E)** *late relapse treatment with only surgery, and* **F)** *late relapse surgery-based treatment in patients with late relapse of testicular germ cell tumor.*

and test sets, respectively. The mean (SD) follow-up was 67 (8.8) months. Figure 5 illustrates a decision-tree model for identifying patients who benefit from chemotherapy-based treatments compared to surgery-only in the context of LR for TGCT. The model accuracy was 0.94 and effective classifiers were primary CS, primary treatment, relapse site, and relapse pathology. The second decision-tree delineates the identification of patients who derive benefits from surgery-based treatments in comparison to other treatment modalities for LR of TGCT. Surgery-based treatments included surgery-only and surgery plus chemotherapy. Non-surgery-based treatments included chemotherapy-only and chemotherapy plus radiotherapy. The model accuracy was 0.88 and effective classifiers were primary testicular pathology, relapse site, and relapse pathology (Figure 6).

DISCUSSION

In this IPD meta-analysis, we found that primary clinicopathologic features emerge as substantial predictors for both LR anatomical patterns and pathological findings. Moreover, our study demonstrated that the integration of primary clinicopathological factors with LR features, as opposed to relying on isolated factors, results in highly accurate classification models for clinical decision making. These models prove valuable in identifying therapeutic modalities associated with superior DFS.

We found that patients who underwent surveillance as the primary management for TGCT face a higher risk of retroperitoneal recurrence as the sole site of LR. While the absence of a standardized minimal follow-up recommendation after five years post-diagnosis for the primary disease suggests a need for a refined approach, our findings support the necessity of a more focused follow-up strategy. Specifically, emphasis on retroperitoneal assessment is recommended to enhance early detection of potential recurrences in patients who underwent surveillance [4]. Moreover, given the challenges associated with managing LR, this finding supports the advantageous use of surveillance as the prima-



Mean CSS, months	154 (One recurrence site) 73 (> One recurrence site)	*P value: 0.007*	104 (Other pathological findings) 191 (Pure teratoma)	*P value: <0.001*	163 (Other pathological findings) 96 (NSGCT)	*P value: 0.006*
Mean CSS, months	170 (Other treatments) 57 (Chemotherapy only)	*P value: 0.003*	135 (Other treatments) 157 (Surgery only)	*P value: <0.001*	124 (Non-surgery-based treatment) 169 (Surgery-based treatment)	*P value: 0.009*

Figure 4. *Kaplan-Meier + pairwise log-rank tests for cancer-specific survival (CSS) according to* **A)** *the late relapse multiplicity,* **B)** *late relapse pure teratoma pathology,* **C)** *late relapse non-seminomatous germ cell pathology,* **D)** *late relapse treatment with only chemotherapy,* **E)** *late relapse treatment with only surgery, and* **F)** *late relapse surgery-based treatment in patients with late relapse of testicular germ cell tumor.*

Table 3. *Univariable and multivariable cox regression analysis assessing the association of clinicopathologic features with DFS and CSS in patients with late relapse of testicular germ cell tumor*

Variable	DFS						CSS					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	N	HR (95% CI)	p-value	N	HR (95% CI)	P value	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Agea	118	1.01 (0.99–1.03)	0.09				118	1.00 (0.98–1.03)	0.484			
Primary clinical stage												
I	185	0.80 (0.45–1.44)	0.475		–	–	185	0.74 (0.37–1.46)	0.392		–	–
II		0.85 (0.53–1.36)	0.517					0.96 (0.56–1.62)	0.883			
III		1.32 (0.84–2.06)	0.217					1.25 (0.75–2.09)	0.387			
Primary testicular pathology												
Seminoma	194	0.97 (0.50–1.89)	0.941		–	–	194	1.36 (0.69–2.69)	0.364		–	–
NSGCT		1.19 (0.71–1.97)	0.499					0.96 (0.55–1.66)	0.894			
Pure Teratoma		0.77 (0.39–1.49)	0.440					0.78 (0.37–1.64)	0.515			
Primary treatment												
CT	120	1.49 (0.80–2.77)	0.200		–	–	120	1.59 (0.79–3.18)	0.188		–	–
RT		1.35 (0.62–2.92)	0.436					1.57 (0.68–3.61)	0.286			
Surgery		0.56 (0.07–4.14)	0.578					0.75 (0.10–5.57)	0.787			
Surveillance		0.45 (0.14–1.47)	0.188					0.19 (0.2–1.40)	0.105			
RT + CT		1.66 (0.59–4.65)	0.335					1.00 (0.24–4.22)	0.990			
Surgery + CT		0.63 (0.32–1.24)	0.194					0.69 (0.32–1.48)	0.348			
Surgery + RT + CT		5.38 (0.72–40.20)	0.101					6.35 (0.84–47.94)	0.073			
Time to late relapse	206	1.004 (1.001–1.007)	**0.010**	50	1.00 (0.99–1.01)	0.528	206	1.004 (1.000–1.008)	**0.018**	50	0.99 (0.98–1.01)	0.914
Symptomatic late relapse	54	1.09 (0.44–2.71)	0.839		–	–	54	1.07 (0.40–2.84)	0.890		–	–
Late relapse site												
Lymphatic	190	0.75 (0.53–1.05)	0.100		–	–	190	0.79 (0.55–1.14)	0.218		–	–
Non-lymphatic		0.94 (0.71–1.23)	0.679					0.98 (0.73–1.30)	0.890			
Both (lymphatic and non-lymphatic)		1.12 (0.90–1.38)	0.288					1.16 (0.93–1.45)	0.177			
High tumor marker only		1.00 (0.31–3.25)	0.989					1.25 (0.38–4.07)	0.707			
Retroperitoneal late relapse only	190	0.98 (0.60–1.61)	0.966				190	0.97 (0.56–1.68)	0.933		–	–
Late relapse multiplicity	171	1.99 (1.21–3.26)	**0.006**	50	0.84 (0.22–3.10)	0.841	171	2.05 (1.18–3.54)	**0.010**	50	0.80 (0.17–3.72)	0.777
Re-Relapse		–	–		–	–	150	1.44 (0.83–2.51)	0.189		–	–
High tumor marker at late relapse	85				–	–	85				–	–
AFP		1.99 (0.91–4.35)	0.083					1.34 (0.56–3.17)	0.500			
HCG		0.75 (0.28–2.00)	0.575					0.97 (0.35–2.66)	0.958			
Late relapse pathology												
Seminoma	146	1.17 (0.50–2.74)	0.710	50	–	–	146	1.48 (0.62–3.51)	0.370	50	–	–
NSGCT		1.63 (0.96–2.75)	0.066		–	–		2.13 (1.21–3.77)	**0.009**		0.57 (0.14–2.24)	0.424
Pure teratoma		0.31 (0.17–0.58)	**<0.001**		0.23 (0.01–2.98)	0.266		0.20 (0.09–0.44)	**<0.001**		0.12 (0.00–2.54)	0.177
NGCT		2.17 (0.92–5.10)	0.074		–	–		2.49 (0.97–6.32)	0.055		–	–
GCT + NGCT		2.09 (1.02–4.26)	**0.043**		–	–		1.64 (0.69–3.87)	0.258		–	–
Late relapse pathology (Teratoma element)	141	0.38 (0.23–0.65)	<0.001	50	1.65 (0.15–17.75)	0.678	141	0.31 (0.18–0.56)	**0.001**	50	2.60 (0.21–31.61)	0.452
Late relapse treatment												
CT	119	3.14 (1.70–5.79)	**<0.001**		2.46 (0.44–13.54)	0.300	119	2.73 (1.34–5.57)	**0.005**		1.55 (0.16–15.04)	0.702
Surgery		0.05 (0.00–0.40)	**0.004**		–	–		0.07 (0.01–0.53)	**0.010**		–	–
RT + CT		0.86 (0.36–2.04)	0.735		–	–		0.97 (0.37–2.51)	0.954		–	–
Surgery + CT		1.10 (0.60–2.01)	0.752		–	–		1.00 (0.49–2.03)	0.987		–	–
Surgery-based late relapse treatment	119	0.41 (0.22–0.73)	**0.003**	50	0.87 (0.18–4.14)	0.870	119	0.42 (0.21–0.82)	**0.012**		0.82 (0.17–3.78)	0.802

[a] Patient's age at the time of primary tumor diagnosis

AFP – α-fetoprotein; CI – confidence interval; CSS – cancer-specific survival; CT – chemotherapy; DFS – disease-free survival; GCT – germ cell tumor; HCG – human chorionic gonadotropin; HR – hazard ratio; NGCT – non-germ cell tumor; NSGCT – non-seminomatous germ cell tumor; RT – radiotherapy

ry strategy for TGCT. The retroperitoneum serves as a surgically manageable single site for local recurrence at the time of LR, enabling effective intervention when necessary [20–22].

Additionally, it is crucial to consider other clinicopathological features of the primary disease, particularly modifications in primary treatment, such as the introduction of modified and unilateral template retroperitoneal lymph node dissection (RPLND), single agent chemotherapy, and low-dose radiotherapy [23–27]. Furthermore, the criteria established for post-chemotherapy RPLND and the controversies involved in managing post-chemotherapy residual masses less than 1 cm are pivotal aspects in the primary management of high-stage TGCT [28, 29]. While these factors may impact the pattern of LR, the development of a nomogram could be valuable in identifying patients with a high probability of retroperitoneal LR. This tool could offer guidance on the suitable intensity of surveillance, tailoring the approach based on individual patient characteristics and optimizing the management of TGCT.

While LR with non-germ cell malignancy pathology is associated with worse survival outcomes, confirming this pathological finding is crucial to prevent misinterpretation of therapeutic morphological effects resulting from the previous treatment of TGCT [4]. Furthermore, the lower sensitivity of non-germ cell malignancy and pure teratoma to chemotherapy emphasizes surgery as the preferred treatment for both pathological findings [4, 7, 30, 31].

Chemotherapy is a potential treatment that may induce changes in tumor biology, particularly evident when different pathological findings are reported after first-line or subsequent salvage chemotherapy [32, 33]. Additionally, the underlying mechanisms of TGCT pathology may involve specific genetic mutations, which could provide further insights into non-germ cell pathologies associated with LR. Despite indications that the biological characteristics leading to LR are present at the initial presentation rather than arising as a secondary occurrence, the underlying biological mechanisms still require further clarification [7, 30].

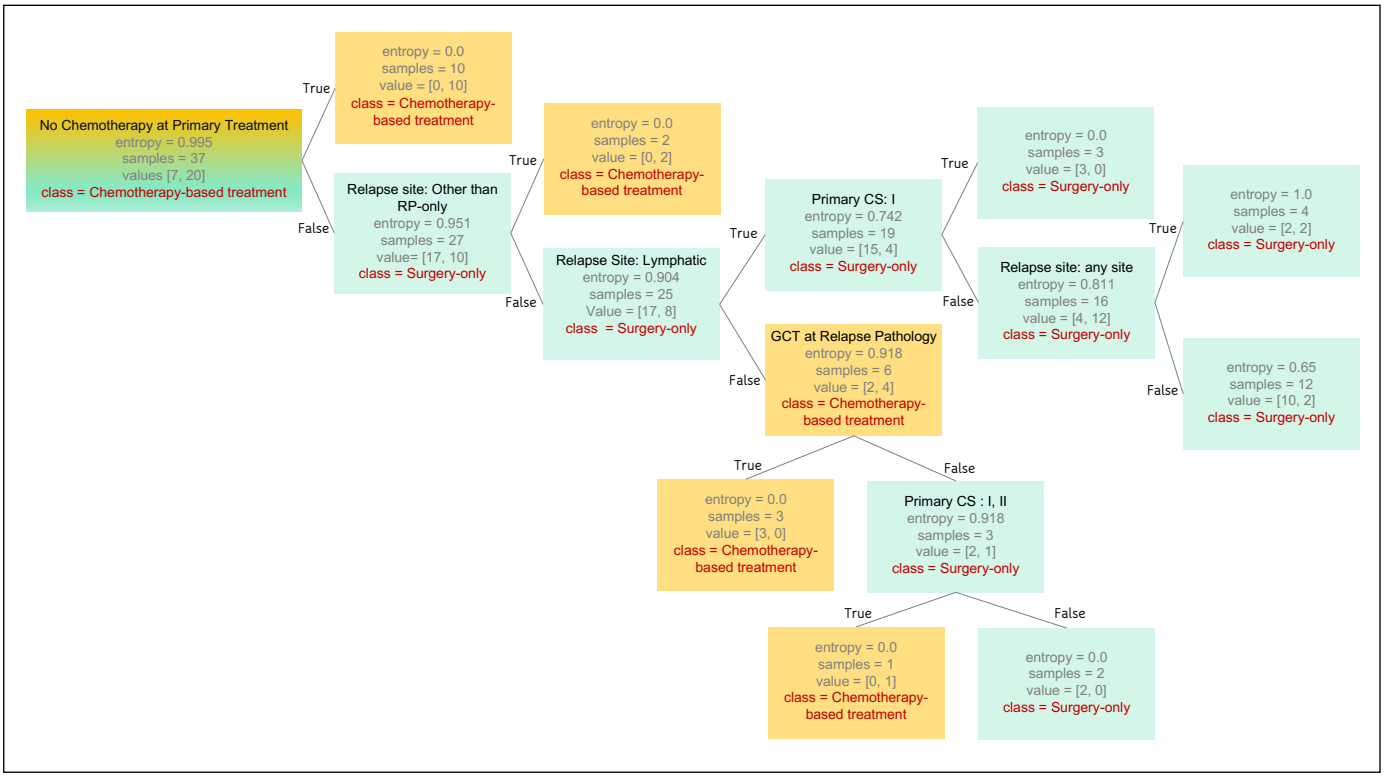


Figure 5. *Decision-tree modelling to identify patients with late relapse of testicular germ cell tumor who benefit from chemotherapy-based treatments compared to surgery-only with the target variable of NED. These patient characteristics were assessed in the model: primary testicular pathology, primary CS, primary treatment, relapse site, relapse pathology, and relapse multiplicity. primary testicular pathology and relapse multiplicity had no predictive effect and is therefore not included in this tree. chemotherapy-based treatments: chemotherapy (CT) only, CT + radiotherapy, CT + surgery. DFS: disease-free survival. Other than RP-only: out of retroperitoneal region or mixed retroperitoneal and extra retroperitoneal metastasis.*

CS – clinical stage; GCT – germ-cell tumor; NED – no evidence of disease; RP – retroperitoneum

We demonstrated that the management of the primary disease has the potential to influence LR pathological findings. Chemotherapy leads to non-germ cell malignancy in LR pathology, while surgery-based treatment is significantly associated with LR pure teratoma pathology. This suggests that addressing the shortcomings of primary surgical techniques may be crucial, especially in LR retroperitoneal pure teratoma patients who underwent RPLND for the management of the primary disease. In addition, considering comparable five-year oncological survival outcomes, surveillance could be more intentional in prompting a reevaluation of primary treatment recommendations, especially when compared to chemotherapy and RPLND [34–36].

While current guidelines advocate for the use of first-line cisplatin-based chemotherapy in LR of TGCT patients who did not receive initial chemotherapy for the primary disease [4, 37], our study brought to light significant associations between LR treatment strategies and oncological outcomes. We observed that surgery alone and surgery-based treatments correlated with improved DFS and CSS, whereas chemotherapy alone was associated with inferior oncological outcomes. While these associations were not validated in multivariable analysis, the potential of two meticulously designed classification decision trees with high accuracy exists in identifying more appropriate therapeutic strategies for LR patients. These findings emphasize the critical need for a more nuanced risk stratification of patients. Despite all the limitations we present in detail, one of the benefits of using decision trees derived from machine learning analysis is their applicability to rare diseases, such as LR of TGCT, for which conducting prospective randomized trials is challenging. Therefore, we discuss these points further in the discussion section. Furthermore, while some studies indicate the effectiveness of salvage chemotherapy regimens with conventional or high doses in managing LR patients, the quality of these studies is hampered by retrospective designs and a low number of participants [7, 15, 17, 38]. Additionally, a notable portion

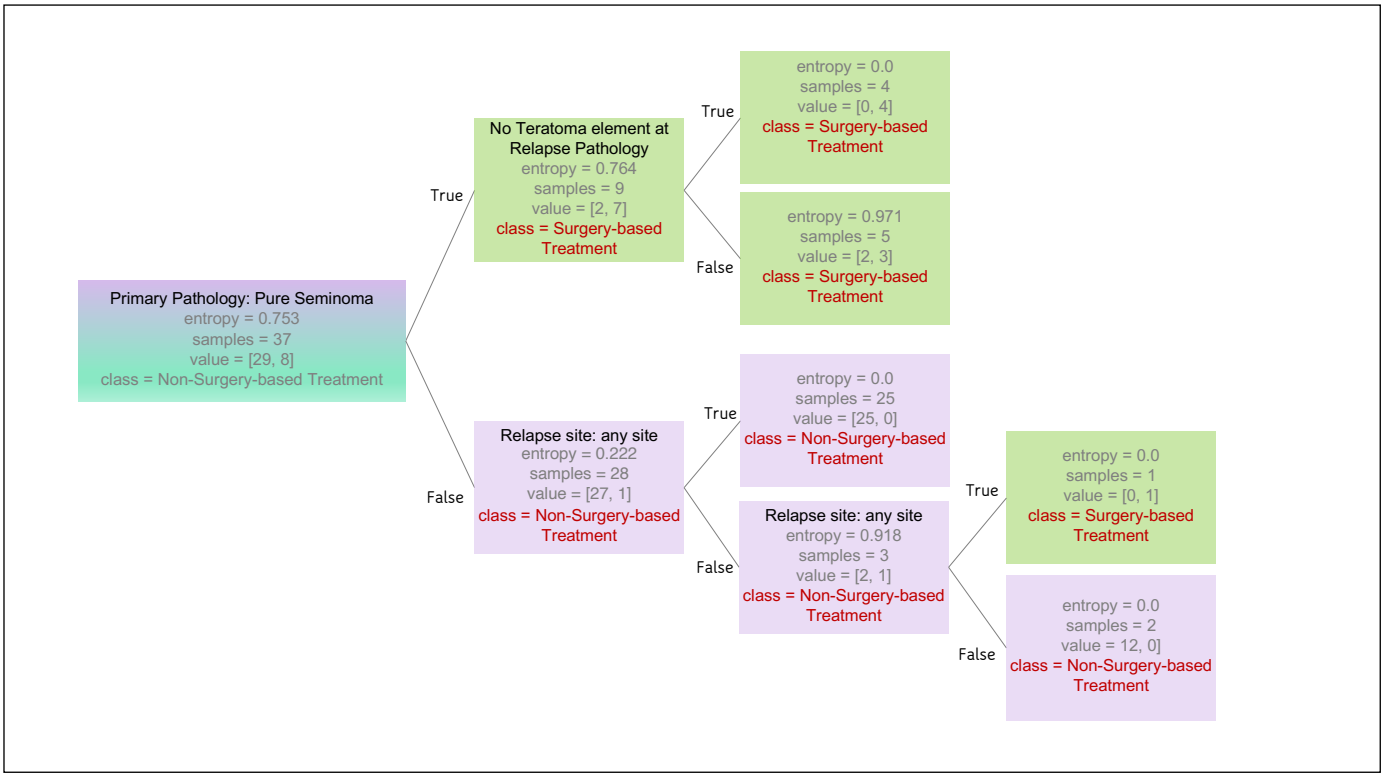


Figure 6. *Decision-tree modelling to identify patients with late relapse of testicular germ cell tumor who benefit from surgery-based treatment compared to non-surgery-based treatments with the target variable of NED. These patient characteristics were assessed in the model: primary testicular pathology, primary CS, primary treatment, relapse site, relapse pathology, and relapse multiplicity. Primary CS, primary treatment, and relapse multiplicity had no predictive effect and is therefore not included in this tree. Surgery-based treatments: surgery only, surgery + chemotherapy (CT). Non-surgery-based treatments: CT only, CT + radiotherapy.*

NED – no evidence of disease

of responders underwent surgery as a complementary treatment, enhancing the curative role of surgery in LR patients with a history of first-line chemotherapy for the primary disease [38]. In our analysis, adjusting for primary disease treatments, we demonstrated that salvage chemotherapy is associated with both worse DFS and CSS in multivariable analysis. Therefore, considering chemotherapy as the sole treatment for LR patients should be limited to inoperable patients or within the context of clinical trials [37].

To our knowledge, this is the first and only IPD meta-analysis regarding LR in patients with TGCT. Nevertheless, our study has certain limitations that deserve acknowledgment. Firstly, it is crucial to note that all the included studies were retrospective, introducing inherent limitations such as selection bias. Indeed, the rarity of the disease poses a significant challenge in designing well-controlled prospective studies. Secondly, the relatively small sample size across the included studies may potentially impact the overall robustness of the data. Thirdly, the lack of complete access to raw patient-level data, which consists of individual clinical measurements and detailed patient information from all studies limits the quality of this meta-analysis and underscores the need for further analysis with a larger dataset. The limited availability of data may also affect the quality of decision trees. Furthermore, heterogeneity was detected in the management of primary tumors, including chemotherapy and surveillance, which limits the value of these results. However, considering the type of primary management as a variable in the analysis might help improve the reliability of the findings. Future studies with expanded datasets can contribute to a more robust and reliable meta-analysis, enhancing the overall quality of evidence in the field. A notable limitation of this meta-analysis is that most of the included studies are relatively old and originate from the pre-modern era of testicular cancer management, which may affect the applicability of the findings to current clinical practice. Lastly, the insufficient data regarding the quality of surgeries, including RPLND for both primary and LR cases, as well as the lack of detailed information on chemotherapy protocols for some patients, make drawing robust conclusions challenging. The limitations in available data on these critical aspects of the treatment process may impact the overall reliability and generalizability of the study's findings. In conclusion, the management of LR in TGCT presents a challenging landscape where the optimal treatment remains controversial. While our analysis suggests that surgery may be associated with improved oncological survival outcomes, the limited available data and the rarity of the condition make drawing definitive conclusions a formidable task. The challenges are compounded by promising results from studies investigating alternative treatments, such as specific chemotherapy protocols. A comprehensive understanding of disease features, patient factors, and potential benefits and risks associated with different treatment modalities is crucial. Moreover, collaborative efforts within the multidisciplinary team, along with prospective research initiatives, are essential to accumulate more robust evidence that can inform the development of standardized approaches to managing LR. Until then, the choice of treatment should be made through a careful evaluation of available evidence and a personalized consideration of the unique aspects of each patient's situation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

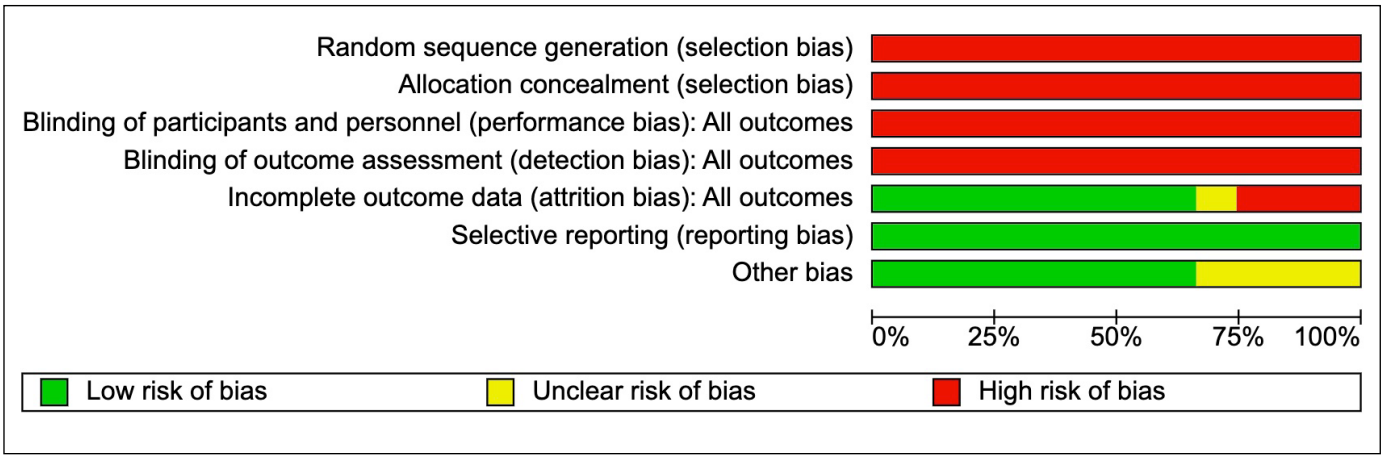
FUNDING

This research received no external funding.

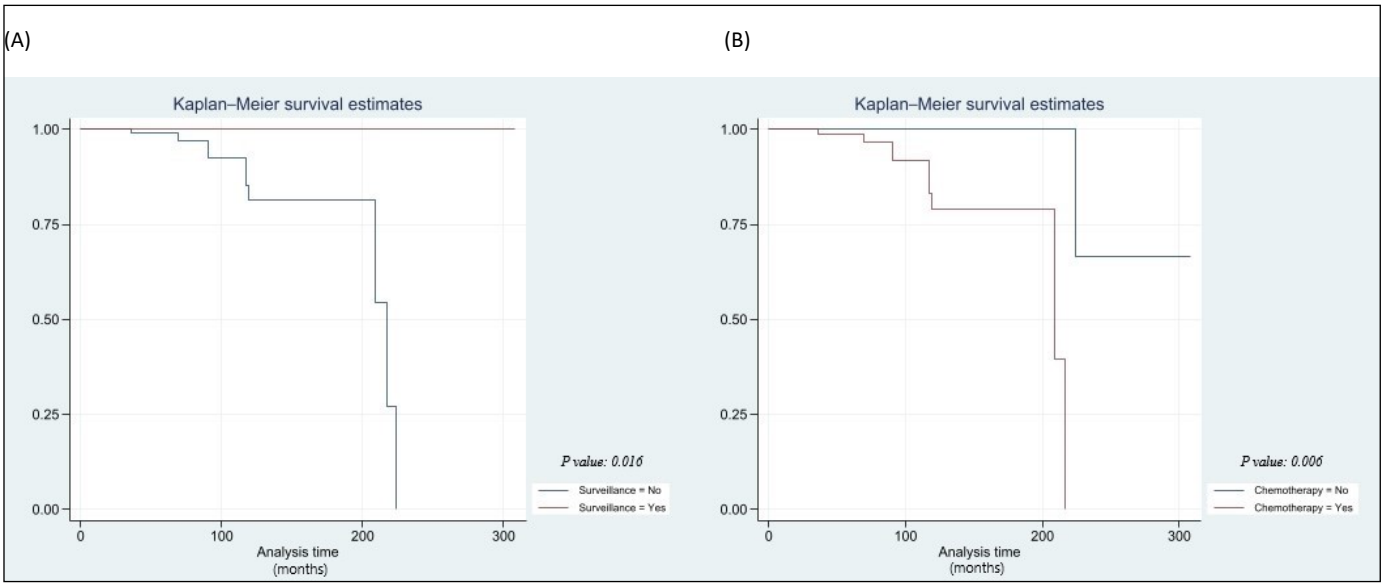
ETHICS APPROVAL STATEMENT

The ethical approval was not required.

SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *RoB table of studies included in the individual patient data (IPD) of disease characteristics and oncological outcomes of patients with late relapse of testicular germ cell tumor.*



Suppl. Figure 2. *Kaplan-Meier + pairwise log-rank tests for prediction of Non-germ cell tumor at late relapse pathology according to the primary testicular germ cell tumor treatment.* **A)** *Surveillance;* **B)** *chemotherapy. (Analysis time: time between initial diagnosis and late relapse).*

Suppl. Table 1. *Univariable and multivariable logistic regression analysis assessing the association of clinicopathologic features with late relapse anatomical patterns in patients with late relapse of testicular germ cell tumor*

Variable	Retroperitoneal late relapse only						Lymphatic late relapse only[c]					
	Univariable analysis			Multivariable analysis[b]			Univariable analysis			Multivariable analysis		
	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value
Age[a]	144	0.99 (0.97–1.02)	0.984				144	1.01 (0.98–1.03)	0.300			
Primary clinical stage												
I	199	2.67 (1.39–5.15)	**0.003**	118	0.43 (0.11–1.62)	0.214	199	1.04 (0.51–2.12)	0.907		–	–
II		0.82 (0.44–1.49)	0.520		–	–		1.44 (0.74–2.79)	0.276		–	–
III		0.53 (0.29–0.98)	**0.044**		0.39 (0.14–1.05)	0.063		0.68 (0.36–1.28)	0.241		–	–
Primary testicular pathology												
Seminoma	207	1.42 (0.68–2.95)	0.348		–	–		3.64 (1.20–10.83)	**0.020**	116	2.76 (0.80–9.45)	0.106
NSGCT		1.07 (0.58–1.96)	0.821		–	–		0.60 (0.30–1.21)	0.160		–	–
Pure teratoma		0.56 (0.23–1.33)	0.191		–	–		0.72 (0.31–1.66)	0.443		–	–
Primary treatment												
CT	123	1.60 (0.72–3.52)	0.241	118	–	–	123	0.56 (0.23–1.32)	0.190		–	–
RT		–	–		–	–		0.59 (0.20–1.76)	0.351		–	–
Surgery		–	–		–	–		–	–		–	–
Surveillance		7.56 (2.78–20.56)	**<0.001**		10.08 (2.34–43.31)	**0.002**		2.50 (0.79–7.89)	0.116		–	–
RT + CT		0.64 (0.15–2.68)	0.542		–	–		2.98 (0.35–24.87)	0.311		–	–
Surgery + CT		0.47 (0.20–1.11)	0.086		–	–		1.13 (0.45–2.86)	0.786		–	–
Surgery + RT + CT		–	–		–	–		–	–		–	–
Time to late relapse	219	1.00 (0.99–1.00)	0.079		–		219	0.99 (0.99–1.00)	0.714			

[a] Patient's age at the time of primary tumor diagnosis
[b] Multivariable analysis for statistically significant variables in univariable analysis (p-value <0.05)
[c] Including retroperitoneal, retrocrural, mediastinal, cervical, iliac, presacral, and axillary lymph nodes
OR – odds ratio; CI – confidence interval; NSGCT – non-seminomatous germ cell tumor; CT – chemotherapy; RT – radiotherapy

Suppl. Table 2. *Univariable and multivariable logistic regression analysis assessing the association of clinicopathologic features with pure teratoma pathology at late relapse in patients with late relapse of testicular germ cell tumor*

Variable	Pure teratoma at late relapse					
	Univariable analysis			Multivariable analysis		
	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value
Age[a]	127	0.98 (0.95–1.01)	0.289			
Primary clinical stage						
I	165	0.18 (0.07–0.45)	**<0.001**	81	0.55 (0.07–3.96)	0.558
II		1.75 (0.91–3.35)	0.091		–	–
III		1.91 (0.98–3.71)	0.056		–	–
Primary testicular pathology						
Seminoma	137	–	–	81	–	–
NSGCT		1.46 (0.71–2.97)	0.294		–	–
Pure teratoma		3.62 (1.50–8.72)	**0.004**		1.47 (0.32–6.72)	0.612
Primary testicular pathology (Teratoma element)	165	2.51 (1.27–4.97)	**0.008**	81	1.30 (0.26–6.40)	0.740
Primary treatment						
CT	95	1.42 (0.55–3.66)	0.458	81	–	–
RT		–	–		–	–
Surgery		–	–		–	–
Surveillance		0.17 (0.04–0.65)	**0.009**		0.84 (0.08–8.60)	0.886
RT + CT		0.50 (0.05–4.67)	0.543		–	–
Surgery + CT		6.51 (2.40–17.65)	**<0.001**		2.52 (0.58–10.89)	0.214
Surgery + RT + CT		–	–		–	–
Surgery-based primary treatment	95	7.42 (2.73–20.14)	**<0.001**	81	13.22 (1.36–128.27)	**0.026**
Time to late relapse	176	0.98 (0.98–0.99)	**0.002**	81	0.98 (0.96–0.99)	**0.028**

[a] Patient's age at the time of primary tumor diagnosis
CI – confidence interval; CT – chemotherapy; NSGCT – non-seminomatous germ cell tumor; OR – odds ratio; RT – radiotherapy

Suppl. Table 3. *Multivariable cox regression analysis assessing the association of therapeutic modalities with DFS and CSS in patients with late relapse of testicular germ cell tumor*

Variable	DFS			CSS		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Salvage chemotherapy at late relapse (Ref: BEP)	22	13.03 (1.13–150.25)	**0.039**	22	13.03 (1.13–150.25)	**0.039**
Primary treatment including CT (Ref: No CT)		0.63 (0.05–7.75)	0.723		0.63 (0.05–7.75)	0.723
Primary treatment including Surgery (Ref: No surgery)		1.88 (0.25–13.95)	0.536		1.88 (0.25–13.95)	0.536
Surgery–based late relapse treatment (Ref: No surgery)		0.39 (0.07–2.12)	0.282		0.39 (0.07–2.12)	0.282

CI – confidence interval; CSS – cancer–specific survival; CT– chemotherapy; DFS – disease–free survival; HR – hazard ratio

References

1. Oldenburg J, Martin JM, Fosså SD. Late relapses of germ cell malignancies: Incidence, management, and prognosis. J Clin Oncol. 2006; 24: 5503-5511.
2. Oldenburg J, Alfsen GC, Wæhre H, Fosså SD. Late recurrences of germ cell malignancies: A population-based experience over three decades. Br J Cancer. 2006; 94: 820-827.
3. Mortensen MS, Lauritsen J, Kier MGG, et al. Late Relapses in Stage I Testicular Cancer Patients on Surveillance. Eur Urol. 2016; 70: 365-371.
4. Patrikidou A, Cazzaniga W, Berney D, et al. European Association of Urology Guidelines on Testicular Cancer: 2023 Update. Eur Urol. 2023; 84: 289-301.
5. George DW, Foster RS, Hromas RA, et al. Update on late relapse of germ cell tumor: a clinical and molecular analysis. J Clin Oncol. 2003; 21: 113-122.
6. Ravi R, Oliver RTD, Ong J, et al. A single-centre observational study of surgery and late malignant events after chemotherapy for germ cell cancer. Br J Urol. 1997; 80: 647-652.
7. Mayer F, Wermann H, Albers P, et al. Histopathological and molecular features of late relapses in non-seminomas. BJU Int. 2011; 107: 936-943.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021; 10: 89.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1-e34.

10. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. John Wiley & Sons, Chichester 2019.

11. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003; 7: iii-173.

12. Borge N, Fosså SD, Ous S, Stenwig AE, Lien HH. Late recurrence of testicular cancer. J Clin Oncol. 1988; 6: 1248-1253.

13. Shahidi M, Norman AR, Dearnaley DP, Nicholls J, Horwich A, Huddart RA. Late recurrence in 1263 men with testicular germ cell tumors. Multivariate analysis of risk factors and implications for management. Cancer. 2002; 95: 520-530.

14. Kuczyk MA, Bokemeyer C, Kollmannsberger C, et al. Late relapse after treatment for nonseminomatous testicular germ cell tumors according to a single center-based experience. World J Urol. 2004; 22: 55-59.

15. Geldart TR, Gale J, McKendrick J, Kirby J, Mead G. Late relapse of metastatic testicular nonseminomatous germ cell cancer: surgery is needed for cure. BJU Int. 2006; 98: 353-358.

16. Nolan L, Wheater M, Kirby J, Simmonds P, Mead G. Late relapse (>2 years) on surveillance in stage I non-seminomatous germ cell tumours; predominant seminoma only histology. BJU Int. 2010; 106: 1648-1651.

17. Ronnen EA, Kondagunta G V, Bacik J, et al. Incidence of late-relapse germ cell tumor and outcome to salvage chemotherapy. J Clin Oncol. 2005; 23: 6999-7004.

18. Michael H, Lucia J, Foster RS, Ulbright TM. The pathology of late recurrence of testicular germ cell tumors. Am J Surg Pathol. 2000; 24: 257-273.

19. Muramaki M, Hara I, Miyake H, Yamada Y, Kawabata G, Kamidono S. Clinical study of six cases showing late relapse of germ cell tumors. Int J Urol. 2005; 12: 855-858.

20. Douglawi A, Calaway A, Tachibana I, et al. Long-Term Oncologic Outcomes after Primary Retroperitoneal Lymph Node Dissection: Minimizing the Need for Adjuvant Chemotherapy. J Urol. 2020; 204: 96-103.

21. Hamilton RJ, Nayan M, Anson-Cartwright L, et al. Treatment of relapse of clinical stage i nonseminomatous germ cell tumors on surveillance. J Clin Oncol. 2019; 37: 1919-1926.

22. Tachibana I, Kern SQ, Douglawi A, et al. Primary Retroperitoneal Lymph Node Dissection for Patients With Pathologic Stage II Nonseminomatous Germ Cell Tumor-N1, N2, and N3 Disease: Is Adjuvant Chemotherapy Necessary?. J Clin Oncol. 2022; 40: 3762-3769.

23. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol. 2011; 29: 957-962.

24. Cho JS, Kaimakliotis HZ, Cary C, Masterson TA, Beck S, Foster R. Modified retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. BJU Int. 2017; 120: 104-108.

25. Heidenreich A, Albers P, Hartmann M, et al. Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol. 2003; 169: 1710-1714.

26. Tandstad T, Smaaland R, Solberg A, et al. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish Norwegian testicular cancer study group. J Clin Oncol. 2011; 29: 719-725.

27. Aparicio J, García Del Muro X, Maroto P, et al. Patterns of relapse and treatment outcome after active surveillance or adjuvant carboplatin for stage I seminoma: a retrospective study of the Spanish Germ Cell Cancer Group. Clin Transl Oncol. 2021; 23: 58-64.

28. Oldenburg J, Alfsen GC, Lien HH, Aass N, Wæhre H, Fosså SD. Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. J Clin Oncol. 2003; 21: 3310-3317.

29. Nason GJ, Jewett MAS, Bostrom PJ, et al. Long-term Surveillance of Patients with Complete Response Following Chemotherapy for Metastatic Nonseminomatous Germ Cell Tumor. Eur Urol Oncol. 2021; 4: 289-296.

30. Honecker F, Wermann H, Mayer F, et al. Microsatellite instability, mismatch repair deficiency, and BRAF mutation in treatment-resistant germ cell tumors. J Clin Oncol. 2009; 27: 2129-2136.

31. Lee AHS, Mead GM, Theaker JM. The value of central histopathological review of testicular tumours before treatment. BJU Int. 1999; 84: 75-78.

32. Rick O, Bokemeyer C, Weinknecht S, et al. Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. J Clin Oncol. 2004; 22: 3713-3719.

33. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol. 2007; 25: 5603-5608.

34. Douglawi A, Calaway A, Tachibana I, et al. Long-Term Oncologic Outcomes after Primary Retroperitoneal Lymph Node Dissection: Minimizing the Need for Adjuvant Chemotherapy. J Urol. 2020; 204: 96-103.

35. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol. 1996; 14: 1106-1113.

36. Kollmannsberger C, Tandstad T, Bedard PL, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol. 2015; 33: 51-57.

37. Gilligan T, Lin DW, Aggarwal R, et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019; 17: 1529-1554.

38. Alifrangis C, Lucas O, Benafif S, et al. Management of Late Relapses After Chemotherapy in Testicular Cancer: Optimal Outcomes with Dose-intense Salvage Chemotherapy and Surgery. Eur Urol Focus. 2021; 7: 835-842.