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Platinum Priority – Testis Cancer

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Phase 2 Single-arm Trial of Primary Retroperitoneal Lymph Node Dissection in Patients with Seminomatous Testicular Germ Cell Tumors with Clinical Stage IIA/B (PRIMETEST)

Andreas Hiester[a,†], *Yue Che*[a,†], *Achim Lusch*[a,b], *Oliver Kuß*[c,d], *Günter Niegisch*[a], *Anja Lorch*[a,e], *Christian Arsov*[a,f], *Peter Albers*[a,*]

[a] *Department of Urology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany;* [b] *Urologisches Gesundheits-Zentrum, Bad Schwartau, Germany;* [c] *Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany;* [d] *Centre for Health and Society, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany;* [e] *Department of Medical Oncology and Hematology, University Hospital Zurich, Zurich, Switzerland;* [f] *Abteilung für Urologie, Städtische Kliniken Mönchengladbach, Mönchengladbach, Germany*

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Abstract

Background: Primary retroperitoneal lymph node dissection (RPLND) for clinical stage (CS) IIA/B seminoma without adjuvant treatment is an experimental treatment to avoid radiotherapy- or chemotherapy-related toxicity from standard treatment.
Objective: The PRIMETEST trial aimed to prospectively evaluate the oncological efficacy and surgical safety of primary RPLND.
Design, setting, and participants: PRIMETEST is a single-arm, single-center prospective phase 2 trial. Patients with seminoma, unilateral retroperitoneal lymph node metastases <5 cm, and human chorionic gonadotropin levels <5 mU/ml were included. Patients with CS IIA/B seminoma at initial diagnosis, and recurrence under active surveillance or following adjuvant carboplatin for CS I disease were eligible.
Outcome measurements and statistical analysis: Unilateral open or robot-assisted primary RPLND was performed. The primary endpoint of the study was progression-free survival (PFS) after 36 mo. The trial was considered positive if <30% of patients experienced a recurrence.
Results and limitations: Between 2016 and 2021, 33 patients were accrued (nine with primary CS IIA/B, 19 recurrences during active surveillance, and five recurrences following adjuvant carboplatin). Thirteen and 20 patients had CS IIA and IIB, respectively. Open and robot-assisted RPLND procedures were performed in 14 (42%) and 19 (58%) patients, respectively. After a median follow-up of 32 mo (interquartile range 23–46), ten recurrences were detected (30%, 95% confidence interval: 16–49%); thus, the primary endpoint was not met. Infield recurrences occurred in three of ten patients. The current

† These authors contributed equally.
* Corresponding author. Department of Urology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Moorenstr. 5, 40225 Duesseldorf, Germany. Tel. +49 211 811 8110; Fax: +49 211 811 8676.
E-mail address: peter.albers@med.uni-duesseldorf.de (P. Albers).

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analysis of risk factors could not identify the predictors of recurrence. Three of 33 patients (9%) presented with pN0.
Conclusions: The PRIMETEST trial did not meet its primary endpoint. Nevertheless, PFS of 70% after a median follow-up of 32 mo suggests this approach to be of interest for highly selected patients. Selection criteria, however, need to be defined and validated in a larger prospective cohort of patients. Until then, surgery alone for the treatment of patients with CS IIA/B seminoma cannot be recommended outside of a clinical trial setting.
Patient summary: In this study, we investigated primary surgery as an alternative to conventional treatment (chemotherapy or radiation therapy) in patients with metastatic seminoma. The primary objective of the study, to prevent at least 30% of patients from recurrence, was not met. However, certain patients may benefit from this approach and thereby avoid chemotherapy or radiation therapy. Predictive factors need to be analyzed to better select patients for this surgery-only approach.

1. Introduction

According to current guidelines, standard treatment of patients with clinical stage (CS) IIA and IIB seminoma is radiotherapy (30 Gy for CS IIA, and 36 Gy and extended iliac field for CS IIB); three cycles of chemotherapy with bleomycin, etoposide, and cisplatin (BEP); or four cycles of etoposide and cisplatin (EP) [1]. Radiotherapy as well as chemotherapy has several acute and long-term side effects, such as an increase in the risk of cardiovascular disease by 1.5–5.7-fold [2,3]. Furthermore, with a latency period of ≥30 yr, the rate of secondary malignancies is increased by up to 2.3-fold for solid cancers and 5.1-fold for leukemia [4–9]. One course of carboplatin followed by involved node radiotherapy or local treatment options such as primary retroperitoneal lymph node dissection (primary RPLND) with or without adjuvant treatment might be an alternative to reduce toxicity and long-term sequelae [10–13].

To our knowledge, this is the first report on primary RPLND to treat patients with seminoma CS IIA/B without adjuvant therapy.

2. Patients and methods

PRIMETEST was a single-arm phase 2 prospective trial (Fig. 1).

2.1. Patients

Patients with CS IIA/B seminoma, and unilateral and localized metastasis <5 cm in transverse diameter on computed or magnetic resonance tomography were eligible for enrollment. Patient groups with initial CS IIA/B disease as well as recurrent disease under active surveillance or after adjuvant treatment with carboplatin in CS I with serum levels of human chorionic gonadotropin (HCG) <5 mIU/ml were included.

The main exclusion criteria were abnormal alpha-fetoprotein, non-seminomatous tumors, CS III disease, retroperitoneal lymph node metastases >5 cm, previous scrotal or retroperitoneal surgery for indications other than germ cell tumor, chemotherapy other than carboplatin, or radiation therapy of the retroperitoneum. Further exclusion criteria were reduced general condition, psychiatric disorder, or insufficient knowledge of the German language (see the Supplementary material).

2.2. Trial design and intervention

Patients underwent either open or robot-assisted (RA) unilateral RPLND. Surgery was restricted to surgeons performing at least 20 RPLNDs per year. RA-RPLND was performed only by surgeons with life-time experience of >20 RA-RPLNDs. Adjuvant treatment in cases of vital seminoma was not administered.

Written informed consent was obtained prior to surgical intervention. The study was approved by the local ethics committee of the Heinrich-Heine-University (protocol number: 5123R 2015053664) and performed in accordance with the Declaration of Helsinki. The decision regarding whether to perform open RPLND or RA-RPLND was made on an individual basis depending on tumor size, location, and relationship with neighboring organs. Open RPLND was performed as described by

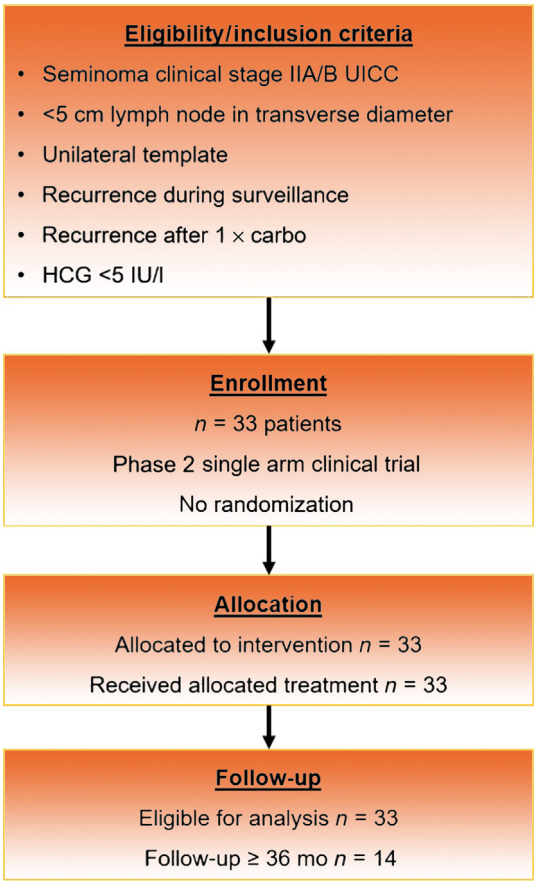

Fig. 1 – Inclusion criteria and recruitment of the PRIMETEST trial. carbo = one cycle of carboplatin; HCG = human chorionic gonadotropin; UICC = Union for International Cancer Control.

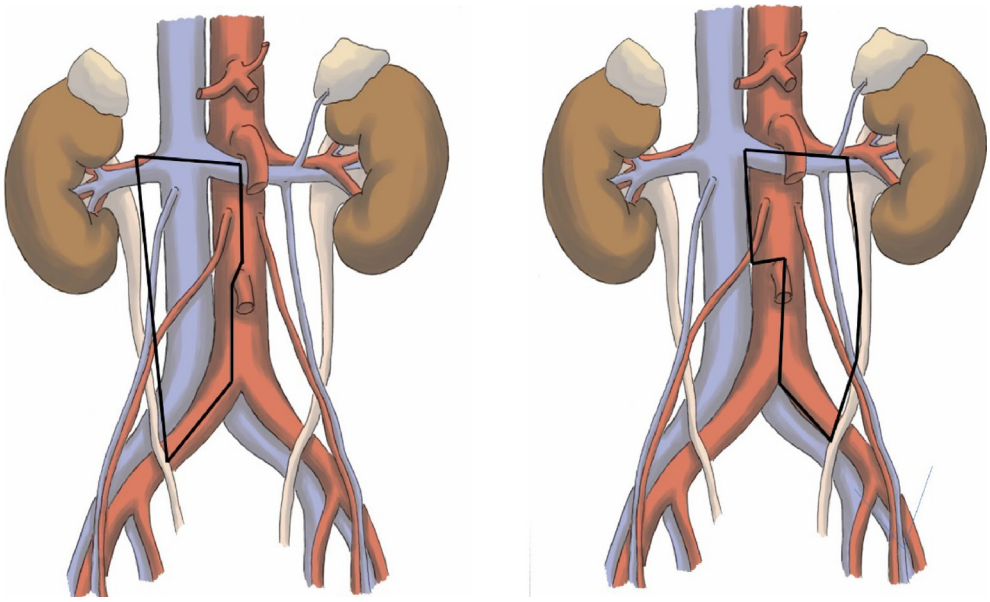

Fig. 2 – Graphical description of anatomical boundaries of right and left template RPLND. RPLND = retroperitoneal lymph node dissection. (Copyright C. Buddensieck.)

Donohue and Foster [14]. RA-RPLND was performed following the procedure previously published by our group [15]. Regardless of the surgical approach, all patients underwent unilateral modified template resection and, if feasible, ipsilateral nerve sparing (Fig. 2). The ipsilateral ureter represented the caudal and lateral boundary of resection; the renal artery was described as the cranial and the crus of the diaphragm as the posterior resection boundary.

2.3. Endpoints and assessment

The primary endpoint of this study was the proportion of patients with progression-free survival after 3 yr. The secondary endpoint was time to progression. Furthermore, intra- and perioperative complications as well as functional outcome measured by the rate of retrograde ejaculation were examined as secondary endpoints.

We performed physical examinations including determination of serum tumor markers every 3 mo for the first 2 yr and every 6 mo until year 5. Imaging was performed three times per year for 2 yr and twice in year 3. Thereafter, imaging was performed annually until year 5 (see the Supplementary material).

2.4. Statistical analysis and rationale

The aim of this study was to investigate the oncological efficacy of primary RPLND without adjuvant treatment for patients with CS IIA/B seminoma. The current standard treatment with chemotherapy or radiotherapy carries a recurrence risk of ≥10% [16]. To achieve low recurrence rates with surgery alone and avoid the known short- and long-term side effects of radiotherapy or chemotherapy would be major benefits for this young patient population.

We calculated a sample size of 30 patients based on an estimated proportion of patients with progression-free survival after 3 yr of 90%. The corresponding exact 95% confidence interval (CI) would be 73.5–97.9%, thus guaranteeing a progression-free proportion of patients of >70% at 36 mo. To be precise, we considered the trial successful if <30% of patients (upper confidence margin) recurred after 3 yr (see the Supplementary material).

Intraoperative complications were described using the Satava [17] classification. Postoperative outcomes, operative time, blood loss, length of hospital stay, as well follow-up were described using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. Postoperative complications were described using the Clavien-Dindo classification [18].

Statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient population

Between 2016 and 2021, 33 patients were accrued (Table 1). The median age at the time of primary RPLND was 37 yr (IQR 30–42). Of 33 patients, nine presented initially with CS II disease (27%) and 24 (73%) had recurrent disease after active surveillance; five of 24 had received one adjuvant cycle of carboplatin in CS I. The majority of patients presented with CS IIB (n = 20, 61%). Only open RPLND or RA-RPLND was performed, with 19 patients (58%) undergoing RA-RPLND. Eighteen patients (55%) presented with right-sided retroperitoneal metastasis. The median size of retroperitoneal tumor on preoperative computed tomography (CT) scan was 20 mm (IQR 14–25); the median number of lymph node metastasis described preoperatively was 1 (IQR 1–3).

3.2. Oncological efficacy

3.2.1. Oncological outcome

Until March 1, 2022, ten recurrences were detected (30%, 95% CI: 16–49%), five (15%) patients with CS IIA and five (15%) with CS IIB. Thus, the proportion of patients with progression-free survival after a median follow-up of 32 mo was 70% (95% CI: 51–84%), with the lower limit of the

Table 1 – Baseline characteristics of patients included in the PRIMETEST trial[a]

Age at RPLND, median (IQR)	37 (30–42)
Medical history, *n* (%)	
Initial stage II	9 (27)
Stage II during active surveillance, no carboplatin	19 (58)
Stage II after 1× carboplatin	5 (15)
Clinical stage, *n* (%)	
II B	20 (61)
Type of RPLND, *n* (%)	
Robotic	19 (58)
Side of RPLND, *n* (%)	
Right	18 (55)
Number of metastases on CT scan, median (IQR)	1 (1–3)
Size of metastasis on CT scan (mm), median (IQR)	20 (14–25)
HCG at RPLND (mU/ml), median (IQR)	0.1 (0–1)

CS = clinical stage; CT = computer tomography; HCG = human chorionic gonadotropin; IQR = interquartile range; RPLND = retroperitoneal lymph node dissection.
[a] Overall, 33 patients with CS IIA and IIB were included. All patients underwent open or robot-assisted unilateral nerve-sparing RPLND.

Table 2 – Oncological follow-up and recurrence of patients by March 1, 2022, after a median follow-up of 32 mo

Follow-up (mo)	
Median (IQR)	32 (23–46)
Patients lost to follow-up (*n*)	0/33
Recurrences	10/33
Probability of PFS	
12 mo	0.75 (95% CI 0.56–0.87)
24 mo	0.72 (95% CI 0.52–0.84)
36 mo	0.64 (95% CI 0.42–0.80)

CI = confidence interval; IQR = interquartile range; PFS = progression-free survival.

CI clearly being smaller than the expected 70% before reaching the 3-yr cut-off. Therefore, it was decided to publish these results before the follow-up of all patients of 3 yr was reached. The detailed follow-up is shown in Table 2. By the time of data lock, the median follow-up of all 33 patients was 32 mo (IQR 23–46). Five recurrences were registered in 14 patients with a follow-up of ≥3 yr (36%). The probabilities for recurrence-free survival after 12, 24, and 36 mo were 0.75 (95% CI: 0.56–0.87), 0.72 (95% CI: 0.52–0.84), and 0.64 (95% CI: 0.42–0.80), respectively. The recurrence rate was 0.13 per person-year.

Of ten patients suffering from recurrence, five and five patients underwent open RPLND and RA-RPLND, respectively. Four patients showed recurrence in the nonresected contralateral retroperitoneum and another three patients showed recurrence in the ipsilateral ureter outside of the modified template (retrocrural, inguinal, and lateral of the ureter). Three patients, however, had infield recurrences (Table 3).

One patient developed metachronous right-sided secondary testicular cancer and underwent partial orchiectomy on the right side. The same patient showed a retroperitoneal recurrence on the left side 6 mo later.

3.2.2. *Histopathological findings*

The median number of lymph nodes removed was 15 (IQR 11–19; Table 4). Three patients (9%) did not have a viable tumor on histological report. All patients with no tumor had single nodes on CT scan. Two presented with initial CS IIA (11 and 13 mm, both left sided). One patient showed an enlarging interaortocaval lymph node 6 mo after orchiectomy being treated with active surveillance for initial CS I. All three patients remained tumor free during follow-up. The remaining 30 patients had viable seminoma in RPLND specimens, of whom 19 patients had one, eight patients had two, one patient had three, and two patients showed four lymph node metastases on histological report. In two patients, preoperative CT underestimated the actual size of the retroperitoneal metastasis presenting pS IIC (size of metastasis 64 and 69 mm), whereas the preoperative CT scan suggested <50 mm.

Of 30 patients with cancer on RPLND specimen, ten patients showed extranodal extension of whom four showed a recurrence.

3.2.3. *Further treatment*

All patients with recurrence underwent chemotherapy, and are currently alive and without evidence of disease. Nine of ten patients received three cycles of BEP for recurrent disease; one patient had one cycle of BEP followed by two cycles of cisplatin, etoposide, and ifosfamide due to pulmonary comorbidity. We did not observe any complications during chemotherapy.

3.3. *Safety and surgical outcome*

3.3.1. *Surgical outcome and complications*

The median operative time was 169 min (IQR 143–205), and the median estimated blood loss was 50 ml (IQR 0–50; Table 5). The median size of lymph nodes on histological report was 28 mm (IQR 20–37). No patient needed blood transfusions. The median hospital stay was 6 d (IQR 4–8).

We saw intraoperative complications in two patients (6%, Satava I and Satava II), with bleeding from renal vein and conversion from RA-RPLND to open RPLND due to obesity. Postoperative complications of higher grade (Clavien-Dindo ≥III) occurred in four patients (12%) with one postoperative ileus requiring revision surgery, two with pulmonary embolism, and one patient with severe lymphocele requiring drainage.

3.3.2. *Functional outcome—antegrade ejaculation*

Contralateral nerve-sparing RPLND was performed in all patients. In 32 of 33 patients, data on antegrade or retrograde ejaculation were available. Thirty patients reported to have antegrade ejaculation (94%).

4. Discussion

Given the cure rates of >90% in patients with germ cell tumors independent of the initial stage, late effects and long-term consequences of treatment are becoming increasingly important in these young patients. The majority of patients live long enough to experience very-late-onset, long-term effects of chemotherapy and radiotherapy, sometimes >30 yr after initial cure [4,8,19]. Therefore, surveillance in CS I and local treatment options for low-volume metastatic disease are of interest in order to reduce the overall burden of treatment. To avoid chemotherapy

Table 3 – Detailed description of patients' recurrences

Patient	pT	CS	RPLND	Infiltration rete testis	Infield/outfield	Location	Time to recurrence (mo)
01	1	IIA	Open	Yes	Outfield	Retroperitoneal contralateral	3
03	1	IIB	Robotic	No	Outfield	Retroperitoneal lateral of the ureter	36
08	2	IIA	Robotic	Yes	Outfield	Retrocrural ipsilateral	12
09	1	IIB	Open	Yes	Outfield	Inguinal ipsilateral	6
11	2	IIA	Open	No	Outfield	Retroperitoneal contralateral	6
22	1	IIA	Robotic	No	Infield	Retroperitoneal—aortal bifurcation	15
24	2	IIB	Open	Yes	Outfield	Retroperitoneal contralateral	3
25	1	IIA	Robotic	Yes	Infield	Retroperitoneal—precaval	9
28	1	IIB	Open	No	Infield	Retroperitoneal—paracaval right	10
31	2	IIB	Robotic	No	Outfield	Retroperitoneal contralateral	4

CS = clinical stage; pT = pathological tumor stage; RPLND = retroperitoneal lymph node dissection.

Table 4 – Summary of histological findings in RPLND

Lymph node yield, median (IQR)	15 (11–19)
Number of positive lymph nodes, median (IQR)	1 (1–4)
Histology, *n* (%)	
Viable seminoma	30 (91)
No tumor	3 (9)
Lymph node positivity overall (seminoma)	30/33 (91%)
0 lymph nodes positive	3 patients
1 lymph nodes positive	19 patients
2 lymph nodes positive	8 patients
3 lymph nodes positive	1 patient
4 lymph nodes positive	2 patients
Lymph node size on CT scan (mm), median (IQR)	20 (14–25)
Lymph node size on pathological exam (mm), median (IQR)	28 (20–37)
Extranodal extension	10 patients

CT = computed tomography; IQR = interquartile range; RPLND = retroperitoneal lymph node dissection.

Table 5 – Surgical outcome and complications after primary RPLND

Operative time (min), median (IQR)		169 (143–205)
Estimated blood loss (ml), median (IQR)		50 (0–50)
Intraoperative complications, *n* (%)		
Satava I	1 (3)	Bleeding from renal vein with clamping and suturing
Satava II	1 (3)	Conversion from robotic to open surgery due to obese patient
Postoperative complications, *n* (%)		
Clavien-Dindo ≥III	4 (12)	1× ileus with small bowel resection* 2× pulmonary embolism 1× lymphocele requiring drainage**
Readmission rate		
30 d	2 (6%)	Ileus with small bowel resection* Lymphocele requiring drainage**
31–90 d	0	

IQR = interquartile range; RPLND = retroperitoneal lymph node dissection.

and radiotherapy as the main triggers for long-term toxicity and secondary malignancies, primary RPLND may therefore be considered an alternative treatment in stage II A and B disease. Owing to the rarity of the disease, properly powered randomized comparative trials may not be feasible, and single-arm prospective trials are currently performed to explore potential new treatment options [10–12,20].

The PRIMETEST trial was designed to test such a clinically relevant alternative. With ten of 33 patients recurring before 3 yr of follow-up, the trial did not reach its estimated primary endpoint but nevertheless reveals numerous important findings. First, surgical treatment of low-volume metastatic seminoma seems feasible without severe toxicity. Second, primary RPLND in CS IIA/B patients seems to provide favorable progression-free survival and may avoid further treatment, but longer follow-up is required. Currently, the number of patients within this prospective cohort is too small to reliably analyze predictive factors for recurrence in order to ideally select patients for this approach. Third, three of 33 patients (9%) presented with pN0. In these cases, surgery alone could verify pS I and prevent these patients from toxicity from chemotherapy or radiation. In further investigations, biomarkers such as miRNA371a-p might be useful to identify these patients to avoid surgery as well. For better patient selection and reducing the burden of treatment, the SEMITEP trial suggests fluorodeoxyglucose positron emission tomography monitoring of chemotherapy in low-volume seminoma patients [21]. However, this is still a systemic treatment approach and should be restricted to patients with higher tumor volume in whom local treatment is not feasible. In the PRIMETEST trial, the overall burden of chemotherapy or radiotherapy was reduced in 23 of 33 patients. Assuming the standard treatment with three cycles of BEP or four cycles of EP, a total reduction from 99 to 30 cycles of BEP or from 132 to 40 cycles of EP was achieved.

In accordance with the preliminary data of the SEMS trial, primary RPLND for metastatic seminoma to date is able to achieve progression-free survival in 70–80% of patients [12]. However, a direct comparison of both trials is difficult since the SEMS trial included patients with a maximum tumor size of 3 cm only. Results of the SAKK 01/10 study as well as standard treatment show progression-free survival of 93% [11]. However, with primary RPLND alone, a considerable number of patients may bypass chemotherapy and/or radiotherapy in CS IIA/B seminoma.

In one of the first attempts to use primary RPLND as a treatment option for metastatic seminoma, the number of recurrences was correlated with the size of metastatic disease [13]. No recurrence was described in patients with CS IIA, but recurrence rates for CS IIB and CS IIC were 67% and 40%, respectively. In our own study, neither could we detect a relationship between tumor size and recurrence rate, nor was the type of surgery (open vs robot assisted) a potential risk factor of recurrence. Furthermore, regarding the surgical approach of open RPLND versus RA-RPLND, we did not see any unusual pattern of recurrence as described in a previous study [22].

To identify predictive factors for recurrence after primary RPLND, we investigated potential clinical risk factors (CS, type of RPLND, site of RPLND, previous carboplatin, age, extranodal extension, number of positive lymph nodes, size of tumor on orchiectomy, and infiltration of rete testis, in case of active surveillance of CS I time from orchiectomy to RPLND). Owing to the small cohort, no predictive factors could be identified. Nevertheless, adjuvant treatment of pS II patients with one cycle of carboplatin remains a subject of discussion and further investigation [10]. Bilateral resection could hypothetically reduce the number of contralateral retroperitoneal recurrences. However, we noticed an inconsistent pattern of recurrences, and therefore, further data are needed before deciding on bilateral or unilateral resection.

In this study, we present the first prospective series of stage IIA/B seminoma patients undergoing primary RPLND. The strengths of this study are the homogeneous cohort, consecutive inclusion of patients, and no loss to follow-up. The limitations are certainly the small number of patients included and the additional variable of open RPLND and RA-RPLND. The results of PRIMETEST are hypothesis generating, and further research is justified. Since the probability of recurrence is higher than expected, it will be of importance to investigate predictive factors. Of note, RPLND did not preclude successful salvage treatment with chemotherapy in patients with recurrence.

5. Conclusions

In conclusion, PRIMETEST did not meet its primary endpoint. Therefore, surgery alone for the treatment of patients with low-volume metastatic disease cannot be recommended outside of further clinical investigations.

Balancing the oncological outcome of primary RPLND against long-term sequelae of systemic treatment, surgery might be discussed with the patient in the context of shared decision-making within a controlled prospective trial.

***Author contributions*:** Andreas Hiester had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Albers, Hiester, Lusch, Lorch, Niegisch.
Acquisition of data: Albers, Hiester, Lusch, Che, Arsov.
Analysis and interpretation of data: Hiester, Che, Albers, Niegisch, Lorch.
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Critical revision of the manuscript for important intellectual content: Hiester, Che, Niegisch, Lorch, Arsov, Lusch, Kuß.
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Peer Review Summary

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