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ARTICLE

External validation of the heidenreich criteria for patients with post-chemotherapy residual masses of non-seminomatous germ cell tumor

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Objectives: Residual Disease after adjuvant chemotherapy for non-seminomatous germ cell tumor (NSGCT) poses a significant clinical challenge and difficulties in tailored management. This study aimed to externally validate the Heidenreich criteria among patients eligible for unilateral post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for residual masses of NSGCT.

Methods: For validation, these criteria were retrospectively applied in 23 patients undergoing PC-RPLND for residual masses of NSGCTs. In patients qualified for unilateral-modified PC-RPLND according to the Heidenreich criteria but treated with fully bilateral dissection, pathological reports were evaluated to identify teratoma or active cancer cells inside the contralateral field. Patients treated with unilateral-modified PC-RPLND were followed to identify relapse within the contralateral field.

Results: Of those 23 patients included, 6 (26.1%) and 17 (73.9%) patients could have been treated with unilateral-modified or fully bilateral template dissection, according to the Heidenreich algorithm, respectively. Within a median follow-up of 85.4 months (IQR, 49.0–165.4), 4 (17.4%) and 2 (8.7%) retroperitoneal and distant recurrences occurred, respectively. Among these, 2 patients (40.0%) were treated with fully bilateral template resection. One patient (4.3%) experienced both distant and retroperitoneal recurrence. Of the 6 patients with an indication for a unilateral-modified PC-RPLND, one patient (16.7%) presented an in-field retroperitoneal recurrence. No recurrences were observed in the contralateral field when the unilateral-modified template dissection would have been performed according to the Heidenreich criteria.

Conclusions: The retrospective application of the Heidenreich criteria in our cohort correctly classified our patients, facilitating a tailored selection for sparing a surgical procedure without interfering with oncological outcomes and potentially minimizing early and late complications.

Key Words: Chemotherapy, germ cell tumor, lymph node dissection, radiation therapy, relapse, testis cancer

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Introduction

Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) represents a crucial step in the multidisciplinary management of metastatic non-seminomatous germ cell tumor (NSGCT). Currently, the European Association of Urology (EAU) guidelines recommend PC-RPLND for residual masses greater than 1 cm for NSGCT in men with normalized or plateauing serum tumor markers within six weeks of completion of chemotherapy.¹ The rationale behind PC-RPLND is to remove all persistent retroperitoneal lymph nodes that may harbor mature teratoma and active cancer cells in approximately 50% and 6–10% of these patients, respectively.^{2,3}

The site, technique performed, and anatomical extent of PC-RPLND in NSGCT have been a matter of debate in recent years. The role of bilateral open PC-RPLND has been well established as the standard of care by both EAU and National Comprehensive Cancer Network (NCCN) guidelines,^{1,4} but nowadays the minimally invasive approaches are evolving parallel to the widespread acceptance of modified templates in well-selected patients without impairing oncological safety.^{5–7} Unilateral or modified template dissections have been reported with similar oncological results to fully bilateral approaches by several working groups.^{8–10} In this regard, necrotic-fibrotic tissue is found in more than 50% of all patients at final pathological evaluation, and frequently, active cancer and/or teratoma are mainly reported in the primary landing zone of the affected testis.^{9,11} Modification of dissection templates has led to both increasing the rate of antegrade ejaculation preservation and decreasing perioperative morbidity, whose impact even in specialized centers is not negligible.^{8,12}

Currently, no diagnostic, clinical biomarkers, or risk calculators can accurately predict the histology of the residual masses. Neither novel promising predictive markers¹³ nor new combined models are currently and constantly employed. Although no standardized consensus for unilateral or bilateral PC-RPLND is indicated across Guidelines, the 2020 Swedish & Norwegian Testicular Cancer group (SWENOTECA) suggested a unilateral template up to 49 mm residual mass, a bilateral template for those who exceed this threshold, and excluding lumpectomy as a safe and reliable alternative.¹⁴ Here, in 2009, Heidenreich et al. identified a group of criteria that could spare the application of the fully bilateral template resection in well-selected patients without interfering with oncologic outcomes and decreasing

treatment-associated morbidity. Considering a retrospective series of 152 cases, they proposed to offer unilateral-modified template dissection to a 5 cm residual mass on the primary landing zone, excluding the interaortocaval location.⁸

To the best of our knowledge, this algorithm was externally validated in 2014 by a single experience reported by Vallier et al.⁶ Thus, the present study aims to perform a second external validation of the Heidenreich criteria.

Materials and Methods

Study population

The present study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained for all the patients included. Ethics approval for this study was exempted by our internal Committee due to the observational retrospective nature of our investigation. We performed a retrospective analysis of data capturing individuals who had undergone either open or minimally invasive RPLND after cisplatin-based chemotherapy for residual retroperitoneal masses of NSGCT. All procedures were carried out between January 1st, 1998, and January 1st, 2018, by two surgeons beyond their learning curve at the Department of Urology of the Institut Valencià de Oncologia Fundació. In this analysis, only primary PC-RPLNDs were selected for validation. Secondary PC-RPLNDs, salvage RPLNDs, PC-RPLND of residual masses of seminomatous GCTs (SGCTs), or RPLNDs for late relapse were excluded. Before chemotherapy, all patients underwent a standardized staging with thoraco-abdominal computed tomography scan and evaluation of serum tumor markers. These included Human Chorionic Gonadotrophin beta-subunit (β -hCG), Alpha-Fetoprotein (AFP), and Lactate Dehydrogenase (LDH). In all patients, bleomycin, etoposide, and cisplatin (BEP) or etoposide, cisplatin (EP) chemotherapy scheme was administered. Within six weeks after termination of chemotherapy, all patients were restaged with the same modalities. All patients included in the analysis had either normalized or plateauing tumor serum markers.

Patients' demographics, such as age at initial diagnosis, Body Mass Index (BMI), Charlson Comorbidity Index (CCI), Testicular Dysgenesis Syndrome (TDS), which encompasses cryptorchidism, hypospadias, and decreased spermatogenesis, primary tumor location, histological data about orchidectomy specimen, serum tumor markers at initial diagnosis

as well as before PC-RPLND, chemotherapy regimen, risk stratification according to the International Germ Cell Cancer Collaborative Group (IGCCCG),¹⁵ site of the residual masses, surgical technique, extent of template dissection, perioperative morbidity according to the Clavien-Dindo classification,¹⁶ pathological outcomes and length of hospital stay were recorded. Central pathological review was performed for patients that has undergone orchidectomy in an outside Institution. With regard to oncologic outcomes, recurrence rates, and location according to the template dissection, cancer-specific survival, and overall survival were further evaluated. Follow-up was performed according to EAU guidelines¹ and was defined as the time interval between PC-RPLND and the date of last imaging or last visit, or documented recurrence/progression, or death.

Anatomical boundaries for PC-RPLND

A modified right-sided template dissection included precaval, caval, paracaval, retrocaval, and interaortocaval areas. The region lateral to the right common iliac vessels with the ureteral crossing served as the distal margin. The right renal vein represented the cranial border unless suprahepatic and retrocrural masses were encountered. In these cases, the crura of the diaphragm represented the cranial border of resection. A modified left-sided template dissection included the pre-aortic up to the inferior mesenteric artery, retro-aortic, and para-aortic areas. Lateral and caudal boundaries were represented by the ureteral crossing. The left renal artery represented the cranial boundary. Radical or fully bilateral template resection comprised the removal of lymph nodes on both sides as described above.⁸

External validation of the Heidenreich criteria

According to the Heidenreich algorithm, a fully bilateral template resection is recommended in patients with contralateral spread to the tumor-bearing testicle, interaortocaval location, or the presence of a residual mass with a diameter greater than 5 cm. In all other cases, a modified unilateral template dissection could be safely proposed.

This second external validation was intended to assess whether, in patients potentially eligible for unilateral-modified PC-RPLND based on the Heidenreich algorithm, histopathology did not reveal teratoma or viable cancer cells outside of the unilateral dissection template, but inside of the full bilateral template. Because of the long period reviewed, in certain cases unilateral-modified RPLND was performed, in others a fully bilateral dissection was carried out. Likewise, both open and laparoscopic

techniques were used. The decision whether to perform a unilateral template or a fully bilateral resection was taken based on both the size and location of the initial and residual tumor at the multidisciplinary internal consensus meeting. Usually, unilateral small-volume or small-diameter diseases were approached with unilateral resections. Historically, a cut-off of 5 cm was set since it has been demonstrated that the increasing size of the mass increased the risk of contralateral teratoma.^{9,17,18} Although nerve-sparing PC-RPLND was not done systematically, especially in unilateral approaches, an attempt was made to improve the rate of antegrade ejaculation. For validation, the Heidenreich criteria were retrospectively applied to our study cohort. In patients qualified for unilateral-modified PC-RPLND according to the Heidenreich criteria but treated with fully bilateral dissection, pathological reports were evaluated to identify teratoma or active cancer cells inside the contralateral field. Patients treated with unilateral-modified PC-RPLND were followed to identify relapse within the contralateral field.

Statistical analysis

Descriptive analysis included frequencies and proportions for categorical variables. Medians and interquartile range (IQR) or means and standard deviation (SD) were reported for continuous coded variables. The Kruskal-Wallis and Mann-Whitney U test were used for comparison of the continuous data, and the Chi-squared test or Fisher's exact test for categorical data. All tests were two-sided with a level of significance set at $p < 0.05$. Statistical analyses were performed using RStudio v.1.2.1335 (Integrated Development for RStudio).

Results

Between January 1st, 1998, and January 1st, 2018, 56 RPLNDs for germ-cell tumors were performed at our single tertiary referral center. A total of 23 patients met the inclusion criteria and were included in our external validation. A total of 6 (26.1%) and 17 (73.9%) patients could have been treated with unilateral-modified or fully bilateral template dissection, respectively, according to the Heidenreich algorithm (Figure 1).

Of those patients qualified for a unilateral template dissection according to the Heidenreich criteria, 5 (83.3%) underwent a unilateral dissection; the remaining patient was treated with a fully bilateral template dissection. Clinicopathological characteristics of the entire study cohort were reported

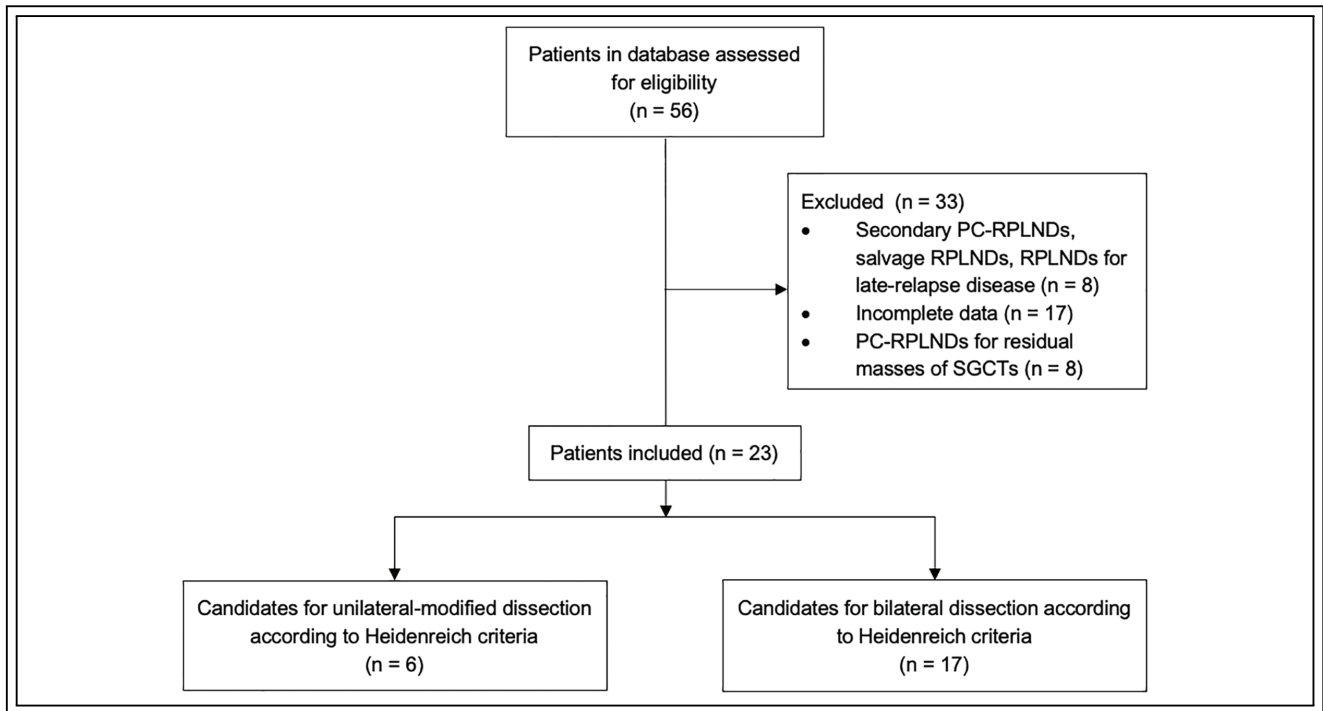


FIGURE 1. CONSORT flow diagram. Of the 56 patients in our database, 33 were excluded due to missing data ($n = 17$), or secondary PC-RPLNDs, salvage RPLNDs, RPLNDs for late-relapse disease ($n = 8$), or PC-RPLNDs for residual masses of SGCTs ($n = 8$) were performed. This resulted in a total of 23 patients eligible for the current validation purpose, 6 of whom were candidates for unilateral-modified dissection, while the other 17 were candidates for fully bilateral template dissection according to the Heidenreich criteria

in [Table 1](#). Overall, 10 (43.5%) and 13 (56.5%) patients underwent unilateral template and bilateral resection, respectively.

Median percentage of embryonal carcinoma at orchidectomy specimen was significantly higher among the candidates for unilateral-modified template dissection. The majority of patients (69.6%) were classified as “good prognosis”, 13% as “intermediate prognosis”, and 17.4% as “poor prognosis” according to IGCCCG classification. The most frequently administered chemotherapy scheme was BEP (21 patients, 91.3%). The median size of residual mass was 14.5 mm (IQR, 13.3–21.8) in patients who could have been scheduled for unilateral resection and 49.0 mm (IQR, 30.0–80.0) in those who could have been scheduled for bilateral template resection. The need for adjacent organs’ removal was required in only 1 (4.3%) patient in the full bilateral template group. Involvement of additional resection of major vessels was not further intraoperatively needed. The final pathological report of patients undergoing PC-RPLND showed fibrotic-necrotic tissue in 5 patients (21.7%), mature teratoma in 17 patients (73.9%), and the combination of vital

tumor-teratoma in 1 case (4.3%). There was no significant difference in histopathological findings between unilateral and bilateral template candidacy according to the Heidenreich criteria. The overall rate of high-grade postoperative complications (Clavien-Dindo ≥ 3) was 26.1%. Median length of hospital stay was 7 days (IQR, 5–8.5).

Within an overall median follow-up of 7.1 years (IQR, 4.1–13.8), 4 (17.4%) and 2 (8.7%) retroperitoneal and distant recurrences occurred, respectively ([Table 2](#)). Among these, 2 patients (40.0%) were treated with fully bilateral template resection. One patient (4.3%) experienced both distant and retroperitoneal recurrence. Of the 6 patients with an indication for a unilateral-modified PC-RPLND, one patient who received bilateral template resection (16.7%) presented an in-field retroperitoneal recurrence. No relapses were observed in the contralateral field when a unilateral-modified template dissection would have been performed according to the Heidenreich criteria. [Table 3](#) shows data on retroperitoneal recurrence status stratified by whether the treatment received PC-RPLND was in accordance with the Heidenreich criteria. No any-cause or cancer-related deaths were

TABLE 1. Demographical and clinicopathological characteristics among the overall cohort and after stratification according to template dissection candidacy

Variable	Overall cohort	Candidates for unilateral-modified template dissection	Candidates for fully bilateral template dissection	<i>p</i>
Patients, n (%)	23 (100.0)	6 (26.1)	17 (73.9)	
Age (years), median (IQR)	28.0 (26.0–30.5)	27.1 (26.4–28.8)	28.1 (25.9–31.6)	0.94
BMI (kg/m²), median (IQR)	24.9 (23.9–26.7)	25.6 (25.4–27.1)	24.3 (23.9–26.0)	0.51
CCI, n (%)				0.12
0	18 (78.3)	5 (83.3)	13 (76.5)	
1	4 (17.4)	0 (0.0)	4 (23.5)	
≥2	1 (4.3)	1 (16.7)	0 (0.0)	
Risk factors, n (%)				0.09
Family history of GCTs	1 (4.3)	1 (16.7)	0 (0.0)	
TDS	3 (13.0)	2 (33.3)	1 (5.9)	
Location of primary lesion, n (%)				0.07
Right testis	13 (56.5)	1 (16.7)	12 (70.6)	
Left testis	10 (43.5)	5 (83.3)	5 (29.4)	
Preorchidectomy AFP (ng/mL), median (IQR)	44.0 (6.1–160.5)	11.9 (4.8–22.9)	93.5 (27.5–302.3)	0.07
Preorchidectomy β-hCG (mIU/mL), median (IQR)	195.0 (10.2–1098.2)	3.3 (2.2–246.2)	308.0 (63.5–2415.8)	0.04
Preorchidectomy LDH (IU/L), median (IQR)	296.0 (198.0–563.0)	214.5 (183.3–227.8)	464.0 (297.0–795.0)	0.01
Primary pathological T stage, n (%)				0.75
pT0/burned-out tumor	1 (4.3)	0 (0.0)	1 (5.9)	
pT1	5 (21.7)	2 (33.3)	3 (17.7)	
pT2	16 (69.6)	4 (66.7)	12 (70.6)	
pT3	1 (4.3)	0 (0.0)	1 (5.9)	
Presence of GCNIS, n (%)	4 (17.4)	1 (16.7)	3 (17.7)	1
Presence of LVI, n (%)	15 (65.2)	6 (100.0)	9 (52.9)	0.11
Histology (%), mean (SD)				
Seminoma	6.4 (14.9)	5.8 (12.0)	6.6 (16.1)	0.92
Embryonal Carcinoma	65.8 (35.9)	90.0 (12.6)	57.8 (37.7)	0.05
Yolk sac tumor	3.1 (10.8)	0.0 (0.0)	4.2 (12.4)	0.43
Post-pubertal Teratoma	5.5 (13.7)	1.7 (2.6)	6.8 (15.7)	0.44
Teratoma with somatic-type malignancies	7.7 (22.6)	2.5 (6.1)	9.4 (25.8)	0.52
Trophoblastic tumor	11.5 (27.5)	0.0 (0.0)	15.3 (31.0)	0.25
Regimen chemotherapy, n (%)				0.38
PEB	21 (91.3)	6 (100.0)	15 (88.2)	
PE	2 (8.7)	0 (0.0)	2 (11.8)	
Size of PC residual mass (mm), median (IQR)	32.0 (21.0–62.5)	14.5 (13.3–21.8)	49.0 (30.0–80.0)	0.01
AFP before PC-RPLND (ng/mL), median (IQR)	2.9 (1.9–4.1)	2.5 (1.9–3.4)	3.2 (2.0–5.5)	0.4
β-hCG before PC-RPLND (mIU/mL), median (IQR)	0.5 (0.5–1.2)	0.5 (0.5–0.5)	0.7 (0.5–1.9)	0.16
LDH before PC-RPLND (IU/L), median (IQR)	166.0 (152.0–197.0)	169.0 (165.3–188.5)	164.0 (143.0–200.0)	0.52
IGCCCG Classification, n (%)				0.17
Good prognosis	16 (69.6)	6 (100.0)	10 (58.8)	
Intermediate prognosis	3 (13.0)	0 (0.0)	3 (17.7)	
Poor prognosis	4 (17.4)	0 (0.0)	4 (23.5)	
Surgical technique, n (%)				0.01
Open	16 (69.6)	1 (16.7)	15 (88.2)	
Laparoscopic	7 (30.4)	5 (83.3)	2 (11.8)	
Pathology at PC-RPLND, n (%)				0.63
Fibrotic-necrotic tissue	5 (21.7)	2 (33.3)	3 (17.6)	
Mature teratoma	17 (73.9)	4 (66.7)	13 (76.5)	
Vital tumor and mature teratoma	1 (4.3)	0 (0.0)	1 (5.9)	
Complication Grade ≥ 3, n (%)	6 (26.1)	1 (16.7)	5 (29.4)	0.54
Length of hospital stay (days), median (IQR)	7.0 (5.0–8.5)	5.5 (4.3–6.0)	8.0 (5.0–10.0)	0.04

Note. IQR, interquartile range; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; GCTs, Germ-Cell tumors; TDS, Testicular Dysgenesis Syndrome; AFP, Alpha-Fetoprotein; β-hCG, Human Chorionic Gonadotrophin beta-subunit; LDH, Lactate Dehydrogenase; GCNIS, Germ Cell Neoplasia *in situ*; LVI, invasion of the primary tumor into blood or lymphatic vessels; PC, post-chemotherapy; PEB, cisplatin, etoposide, bleomycin; PE, cisplatin, etoposide; PC-RPLND, post-chemotherapy retroperitoneal lymph node dissection; IGCCCG, International Germ Cell Cancer Collaborative Group.

TABLE 2. Descriptive statistics of oncological outcomes on the overall population and after stratification according to template dissection candidacy

Variable	Overall cohort	Candidates for unilateral-modified template dissection	Candidates for fully bilateral template dissection
Patients, n (%)	23 (100.0)	6 (26.1)	17 (73.9)
Follow-up (years), median (IQR)	7.1 (4.1–13.8)	6.2 (4.4–12.0)	9.4 (4.2–13.9)
Retroperitoneal recurrences, n (%)			
In field recurrences	4 (17.4)	1 (16.7)	3 (17.6)
Contralateral field recurrences	0 (0.0)	0 (0.0)	NA
Distant recurrences, n (%)	2 (8.7)	0 (0.0)	2 (11.8)
Adjuvant surgical procedures, n (%)	5 (21.7)	1 (16.7)	4 (23.5)
Further chemotherapy lines, n (%)	3 (13.0)	0 (0.0)	3 (17.7)
Status at last follow-up, n (%)			
Alive without disease	22 (95.7)	6 (100.0)	16 (94.1)
Alive with disease	1 (4.3)	0 (0.0)	1 (5.9)

Note. IQR, interquartile range; NA, not applicable.

TABLE 3. Template resection received according to the Heidenreich algorithm stratified by retroperitoneal recurrence status

Variable	Overall	No retroperitoneal recurrence	Retroperitoneal recurrence
Treated according to the Heidenreich criteria, n (%)			
Yes	12 (52.2)	11 (91.7)	1 (8.3)
No	11 (47.8)	8 (72.7)	3 (27.3)
Patients, n (%)	23 (100.0)	19 (82.6)	4 (17.4)

reported. All patients were alive at the last follow-up visit, with only one (4.3%) alive with disease.

Discussion

In this retrospective 20-year single tertiary referral center experience, we externally validated the retrospective application of the Heidenreich criteria in a cohort of patients undergoing PC-RPLND for

retroperitoneal residual masses of NSGCT. Our findings suggested that the Heidenreich algorithm did not misclassify a single patient in our cohort.

As the nature of teratoma and active cancer cells found at the pathological report of PC-RPLND are considered chemo- and radio-resistant, surgical excision of residual masses is a curative-intent strategy.⁸ Historically, large series experiences coming from the 1980s were mainly based on patients with high-volume residual diseases.^{19,20} Starting from these, the adoption of fully bilateral template dissection has become the standard practice. Contemporary series

demonstrated that presentation patterns of metastatic testicular cancer have changed,^{6,10,21} and altogether, the management of these patients might be reshaped.

In a systematic review, Haarsma et al. stated that the adoption of modified template dissection is oncologically safe, and assumed that patients' accurate selection is a crucial step, combined with the centralization of procedures, as cornerstones of PC NSGCT residual masses management.²² In this context, the Heidenreich criteria are widely adopted in current routine daily practice.^{21,22} One of the main pitfalls of the assumption of unilateral-modified PC-RPLND is represented by the cross-spreading risk of active tumor or teratoma that might occur in up to 8–20% of patients.^{23,24} Whereas all low-volume left-sided primary tumors followed a predictable pattern of spread, crossover was mainly reported in high-volume disease and from the primary right-sided landing zone, underlining how the interaortocaval station can be a crucial hub for the definition of the diffusion pattern.^{8,9,19,20}

A large population-based prospective observational mapping study among 213 patients undergoing PC-RPLND for metastatic NSGCT found that individuals with residual disease of 10–49 mm and radiological evidence of unilateral metastases had a low risk of contralateral disease and should be considered for a unilateral template resection.¹⁴

Moreover, the widespread use of minimally invasive approaches combined with the increasing patients' demand for either laparoscopic or robot-assisted techniques requires mention. In a recent systematic review, the minimally invasive approach has demonstrated substantial advantages, such as reduction of both perioperative morbidity and length of hospital stay, and showed an average rate of ante-grade ejaculation of 95.5%.^{25,26} Furthermore, lowering the rate of major complications among a potentially fragile population who have just completed a full course of chemotherapy represents a negligible aspect. Moreover, a sparing and tailored approach may improve the quality of life of these young patients by reducing the rates of late complications such as anejaculation or retrograde ejaculation. Notwithstanding, a robot-assisted bilateral template dissection was described as feasible with only a single docking⁵ most studies described the minimally invasive approach within a unilateral template, and in this regard, the application of the Heidenreich criteria could serve as a starting algorithm that should be interrogated.

The indication to perform PC-RPLND should be based on the individual and risk-adapted strategy, considering the pathological features of the tumor

that may harbor adverse characteristics, the experience of the surgeon, the potential impact on quality of life, the expectancy, and age of these chiefly young patients by balancing the oncological and functional outcomes. If the criteria and boundaries defined by Heidenreich had been applied to our cohort, no patients would have had an inappropriate template resection. Therefore, this underlined no oncological safety impairment since no recurrences were noted in the contralateral field of dissection.

Such criteria could readily be complemented by additional variables, already established as prognostic determinants in NSGCT patients, which have not been examined in previous modified template resection models. The percentage of embryonal carcinoma within the orchidectomy specimen outperforms the predictive value of LVI.²⁷ It's not a coincidence that the very patient who would have been treated with a modified-unilateral template dissection and experienced an in-field recurrence harbored both LVI and pure embryonal carcinoma features in the primary testis tumor.

Furthermore, from a future perspective, these criteria may represent a first step of a tailored counseling for an individual risk-adapted strategy that could be even further implemented by novel tools. Promising data in predicting the presence of malignant histopathology at the time of PC-RPLND has indeed been demonstrated by both novel predictive models²⁸ and a computed tomography radiomics-based machine learning classifier.²⁹ Moreover, circulating microRNAs (miRs) have emerged as additional tumor serum markers that can complement the management of such a cohort of surgical candidates.³⁰ Particularly, miR-371a-3p levels have been evaluated in different scenarios, including inconclusive small testicular mass definition, response monitoring during chemotherapy,¹³ PC residual masses,³¹ and follow-up after treatment with curative intent.³² Results were very promising, as it has been established that increased levels of this miR can potentially identify recurrences earlier than standard follow-up strategies.³²

The wider adoption of a tailored strategy in clinical daily practice is confirmed by recent reports. Here, 69 patients who underwent RPLND between 2010 and 2022 at referral European Centers were recently evaluated by Klemm et al. A particular focus was given to PC setting, accounting for 93% of the included cohort.³³ Unilateral template removal was performed in 55 patients (80%). Moreover, Heidenreich and colleagues presented the final results of the COTRIMS (Cologne trial of retroperitoneal lymphadenectomy in metastatic seminoma) trial at

the 2025 American Society of Clinical Oncology (ASCO) Genitourinary (GU) Annual Symposium. The COTRIMS trial is a prospective, single-arm, single-center clinical study designed to evaluate the efficacy and safety of unilateral, nerve-sparing retroperitoneal lymph node dissection (RPLND) using a modified surgical template in patients with clinical stage IIA/B seminoma.³⁴ Circulating miR-371a testing was performed to predict retroperitoneal specimen histology. Of the 34 patients included, 31 (91%) received an open approach, with 3 (9%) undergoing a robot-assisted RPLND. Histological analysis identified metastatic testicular GCTs in 22 of 24 patients (92%), of whom 20 (91%) demonstrated positive miR-371a expression. Additionally, false-negative miR-371a findings were observed in one patient with pure teratoma and another with a microscopic seminomatous lymph node metastasis. The miR-371a assay demonstrated a sensitivity of 91% and a specificity of 50%, with a positive predictive value of 100% and a negative predictive value of 75%. Although the COTRIMS trial considered a different case scenario, it confirmed that the need for a patient-tailored approach is increasingly recognized, aiming to achieve an appropriate balance between oncological radicality and functional outcomes in young TC patients.

Hence, this second external validation of the Heidenreich criteria is additive to the results reported by Vallier et al. Even though the bilateral approach remains the standard of reference, a paradigm shift in the PC residual masses is suggested by the clinical daily practice.²² Our data provide further confirmation that a sparing approach could be easily and safely proposed in well-selected patients without interfering with oncological outcomes and decreasing treatment-associated morbidity and related side effects.

Our study is not devoid of limitations that must be acknowledged. First, this study was limited by the fact that it was retrospective in nature and thus is subject to the shortcomings inherent to this type of analysis, requiring further confirmation by large multicenter series. Second, data about quality of life, such as retrograde ejaculation, fertility rate, and erectile dysfunction, were not always available. Third, the rate of major complications was slightly higher compared to the literature, and this could be associated with the large time span of our analysis, in which different temporal practice patterns may have existed. Nevertheless, this study has some important strengths. Firstly, a multidisciplinary internal consensus meeting was preoperatively mandatory at our Institution. Second, compared to the first external

validation, our series benefited from a large follow-up, including late relapses of teratoma that might occur even after 5 years of follow-up. Furthermore, a central review and more detailed pathological data about the orchidectomy specimen, which includes the percentage of the different NSGCTs, were provided.

Conclusions

We herein report the second external validation of the Heidenreich algorithm, identifying patients who could be candidates for unilateral-modified template dissection at the time of PC-RPLND for NSGCT residual masses. The retrospective application of these criteria did not result in any patient misclassification, thereby enabling a tailored selection of sparing procedures that maintained oncological safety while also minimizing at both early and late stages associated with potential overtreatment. Furthermore, the reproducibility and ease of application could serve as the first step in preoperative counseling, which can be further combined with established novel clinical biomarkers.

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Author Contributions

Francesco Claps, Miguel Ramírez-Backhaus: Conceptualization, Methodology, Writing—Review & Editing, Supervision, Project Administration. Álvaro Gómez-Ferrer: Methodology, Writing—Review & Editing, Supervision. Juan Manuel Mascarós: Methodology, Formal Analysis. Argimiro Collado Serra: Writing—Review & Editing. Augusto Wong: Writing—Review & Editing. Ana Calatrava Fons: Methodology, Writing—Review & Editing, Supervision. Miguel Ángel Climent: Methodology, Writing—Original Draft. Antonio Amodeo, Angelo Porreca: Writing—Review & Editing. Jose Rubio-Briones: Conceptualization, Methodology,

Writing—Review & Editing, Supervision, Project Administration. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials

The fully anonymized data is available upon request.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki. Local Institutional Review Board (IRB) approval was waived because of the retrospective observational nature of the study as the research conducted posed low risk, relied on available and non-identifiable data. General written informed consent was obtained for all the patients included.

Conflicts of Interest

The authors declare no conflicts of interest to report regarding the present study.

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