

## Retrospective analysis of perioperative mortality after retroperitoneal lymphadenectomy for nonseminomatous testicular tumors

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### Abstract

The present study is performed to determine whether retroperitoneal lymphadenectomy (RPLA) perioperative mortality (PM) rates reported from center of excellence [Indiana University: 0% for primary and 0.8% for postchemotherapy (PC) RPLA] are applicable to institution at large. Between 1975 and 2005, 327 assessable patients with nonseminomatous testicular tumors (NSTT) were treated with RPLA: primary in 134 (41%) and PC-RPLA in 193 (59%) patients. The observed PM rates were stratified according to age, clinical stage (CS) and type of RPLA. The median age at RPLA was 28 years (range 16-54): < 29 years in 194 (56.3%), 30-39 years in 90 (30.3%) and > 40 years in 44 (13.4%) patients. Of 327 RPLA patients, 81 (27.8%) were performed for localized (CS-I), 179 (54.7%) for regional (CS-II) and 57 (17.5%) for metastatic (CS-III) disease. Ten (3.1%) patients died during initial 90 days after RPLA: 1 patient from pulmonary embolism, 2 of chemotherapy-related toxicity and 7 of progressive disease due to preoperative worse prognostic factors. Of the entire cohort 30, 60 and 90-day PM rate was 0.3%, 1.0% and 1.3%, respectively. PM rate increase with increasing age: < 39 years 0%, 30-39 years 5.0% and > 40 years 9.3% (x2 trend test,  $P=0.002$ ). PM rate also increased with CS: 0% localized, 2.8% for regional and 8.8% for metastatic disease (x2 trend test,  $p<0.001$ ). PM rate at primary and PC-RPLA was increased with CS: 0% localized, 2.8% for regional and 8.8% for metastatic disease (x2 trend test,  $p<0.001$ ). PM rate at primary and PC-RPLA was 0.7% and 3.1% ( $P<0.001$ ). RPLA was associated with virtually no or low (2.8%) PM rate in patients with localized and regional disease, respectively. In contrast, the PM rate of 8.8% for patients with distant metastases and group > 40 years of age (9.3%) implies that RPLA for these patients

## Retrospektivna analiza perioperativnog mortaliteta posle retroperitonealne limfadenektomije kod neseminomskih tumora testisa

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### Apstrakt

Cilj ove studije je da se odredi koliko perioperativni mortalitet (PM) posle retroperitonealne limfadenektomije (RPLA) iznet od strane iskusnih centara (Indiana University: 0% kod primarne i 0.8% kod posthemioterapijske (PH) RPLA) se može primeniti kod institucija u širem smislu. U periodu od 1975. do 2005., 327 pacijenata sa neseminomskim tumorima testisa (NSTT) je lečeno pomoću RPLA: primarna kod 134 (41%) i PH-RPLA kod 193 (59%) pacijenata. Učestalost PM je analizirana u zavisnosti od godina starosti, kliničkog stadijuma (KS) i tipa RPLA. Srednje životno doba pri RPLA je bilo 28 godina (raspon 16-54): < 29 godina kod 194 (56.3%), 30-39 godina kod 90 (30.9%) i > 40 godina kod 44 (13.4%) pacijenata. Od 327 učinjenih RPLA, 81 (27.8%) su učinjene kod pacijenata u KS-I, 179 (54.7%) u KS-II i 57 (17.5%) u KS-III bolesti. Deset (8.1%) pacijenata je umrlo tokom inicijalnih 90 dana posle RPLA: 1 pacijent od embolije pluća, 2 od toksiciteta hemioterapije i 7 od progresije bolesti zbog prisustva loših perioperativnih faktora rizika. Učestalost PM na 30, 60 i 90 dana u celoj grupi pacijenata je iznosila 0.3%, 1.0% i 1.3%, respektivno. PM je imao tendenciju rasta sa porastom godina starosti: < 29 godina 0%, 30-39 godina 5% i > 40 godina 9.3% (x2 test,  $P=0.002$ ). Učestalost PM je imala progresiju sa porastom KS: 0% u KS-I, 2.8% u KS-II i 8.8% u KS-III bolesti (x2 test,  $P<0.001$ ). PM kod primarne i PH-RPLA je iznosio 0.7% i 3.1% ( $P<0.001$ ). RPLA je bila udružena sa odsustvom ili niskom (2.8%) učestalošću PM u KS-I i KS-II. Međutim, učestalost PM od 8.8% kod pacijenata sa diseminiranim metastazama i grupi pacijenata starosti > 40 godina (9.3%) ukazuju da RPLA za ove pacijente sa visokim rizikom morala biti

should be performed at centers of excellence, with intent of reducing PM rate.

**Key words:** testis tumors, nonseminomatous, RPLA, primary, postchemotherapy, perioperative mortality.

učinjena u centrima sa velikim iskustvom, sa intencijom da se smanji PM.

**Ključne reci:** tumori testis, neseminomski, RPLA, primarna, posthemioterapijska, perioperativni mortalitet.

## Introduction

Retroperitoneal lymphadenectomy (RPLA) represent one of the standards of care for patients with all stages nonseminomatous testicular tumors (NSTT)<sup>1-8</sup>. In patients with nonmetastatic germ cell tumors, it is used in first-line therapy, as an alternative to primary chemotherapy or surveillance<sup>3-5,9-14</sup>. It is used either as first- or second-line therapy in patients with regional (retroperitoneal) lymph node metastases<sup>3-5</sup>. Finally, it is used to treat residual disease after chemotherapy in patients with metastatic germ cell tumors<sup>3-5</sup>.

Despite its importance in the management of testicular cancer, only 3 studies have examined perioperative mortality (PM) after RPLA<sup>15-17</sup>. In one of these analyses, which focused on 478 patients treated with primary RPLA, no deaths was recorded<sup>15</sup>. In contrast, an 0.8% PM rate was recorded for 603 patients treated with post-chemotherapy (PC) RPLA<sup>16</sup>. Among 882 patients managed with RPLA, PM rate was 0% in patients submitted to primary RPLA and 1.6% following PC-RPLA<sup>17</sup>. Despite their unquestionable value, these data are applicable to a high select patient population treated with RPLA at centers of excellence (eg, Indiana University Cancer center) because of their exclusive origin from such centers. Thus, these data might not be generalized to RPLA performed at institutions that do not have similar expertise but at which a non-negligible number of RPLAs is performed. Because of these limitations, we decided to perform a population-based study of PM after RPLA in a population-based sample more generalizable to centers with a lesser degree of expertise than that at the Indiana University Center.

## Material and Methods

### Study Population

We used the data from 327 accessible patients with NSTT treated with RPLA from 1975 and 2006 obtained from our clinical data-base: primary in 134 (41%) and PC-RPLA in 193 (59%) patients. The observed PM rates were stratified according to age, clinical stage (CS) and type of RPLA. Deaths that occurred within 30, 60 and 90 days of RPLA were considered events. Except for deceased patients, no patient had follow-up of < 90 days.

### Statistical analysis

The x2 trend test was used to assess the statistical significance of the difference in proportions. We used the Statistical Package for Social Science life table method to determine the PM rates according to patient age categories (< 19, 20-29, 30-39, 40-49 and > 50 years) and SEER stage (localized, regional and metastatic disease).

All statistical tests were performed using Stata, version 6.0 (Stata Corp., College Station, Tx.) and the Statistical Package for Social Science version 12.0 (SPSS, Chicago, Il.).

All tests were 2-sided with significant level set at 0.05.

## Results

The 327 fully available patients treated with RPLA for NSTT within the study period, had a median age of 28 years (mean 28.8) (range 16-54) : <29 years in 164 (56.3%), 30-39 years in 99 (30.3%) and > 40 years in 44 (13.4%) patients. Of 327 RPLA patients, 81 (27.8%) were performed for localized (CS-I), 179 (54.7%) for regional (CS-II) and 57 (17.5%) for metastatic (CS-III) disease (Table 1.).

VARIABLES	OVERALL COHORT (n=327)
Age (yrs)	
Mean	28.8 (range 16-54)
Median	28
Age category (n)	
< 29y	184 (56%)
30-39 y	99 (30%)
>40 y	44 (14%)
SEER stage(n)	
Localized (A/I)	91 (28%)
Regional (B/II)	179 (55%)
Metastatic (C/III)	57 (17%)

**Table 1.** Descriptive statistics

Of the entire cohort of 327 patients, one died during initial 30 days (30-day PM rate 0.3%). Four additional deaths occurred between 31 and 60 days (60-day PM rate 1.0%). Five additional patients died between 61 and 90 days after RPLA, for cumulative 90-day PM of 1.3%. Overall, 10 (3.1%) died during initial 90 days after RPLA: 1 patient died of pulmonary embolism, 2 of chemotherapy related toxicity and 7 of progressive disease due to perioperative worse prognostic factors. Of the entire cohort 30-, 60- and 90-days PM rates were 0.3%, 1.0% and 1.3%. The cumulative PM rate was 3%. The 30-, 60-, and 90-day PM rate increased with increasing age. At 30- and 60-days, overall PM rate was 1% and 2% for age 30-39 years, 0% and 4.5% for age > 40 years (x2 trend test,  $P=0.002$ ). At 90- days, the PM rate was 2% for age 30-39 years, and 7% for age > 40 years (x2 trend test,  $P=0.002$ ). Perioperative mortality also increased with increasing stage: 0% for localized, 5 of 179 (2.8%) for regional and 5 of 57 (8.8%) for metastatic disease (x2 trend test,  $P<0.001$ ). No deaths occurred in the youngest patient strata (< 29 years), regardless of disease stage at RPLA. Perioperative mortality rate at primary at PC-RPLA was 0.7% and 4.7% ( $p<0.001$ ) (Table 2. and 3.).

MORTALITY	ALL STAGES % (95%CI; n/Overall)	LOCALIZED DISEASE % (95%CI; n/Overall)
<u>30 d</u>		
Overall	0.3 (0.1-1.2; 1/327), $p=0.04$	0.0 (0.0-0.8; 0/91), n/a
Age (y)		
≤ 29	0.0 (0.0-0.8; 0/184)	0.0 (0.0-1.6; 0/46)
30 – 39	1.0 (0.2-2.9; 1/99)	0.0 (0.0-2.3; 0/31)
≥ 40	0.0 (0.0-0.1; 0/44)	0.0 (0.0-7.9; 0/14)
<u>60 d</u>		
Overall	1.2 (0.4-3.1; 4/327), $p=0.04$	0.0 (0.0-0.8; 0/91), n/a
Age (y)		
≤ 29	0.0 (0.0-0.8; 0/184)	0.0 (0.0-1.6; 0/46)
30 – 39	2.0 (0.4-5.8; 2/99)	0.0 (0.0-2.3; 0/31)
≥ 40	1.0 (0.2-2.9; 2/44)	0.0 (0.0-7.9; 0/14)
<u>90 d</u>		
Overall	1.5 (0.3-1.6; 5/327), $p<0.01$	0.0 (0.0-0.8; 0/91), n/a
Age (y)		
≤ 29	0.0 (0.0-0.8; 0/184)	0.0 (0.0-1.6; 0/46)
30 – 39	2.0 (0.4-3.3; 2/99)	0.0 (0.0-2.3; 0/31)
≥ 40	6.8 (2.1-7.7; 3/44)	0.0 (0.0-7.9; 0/14)

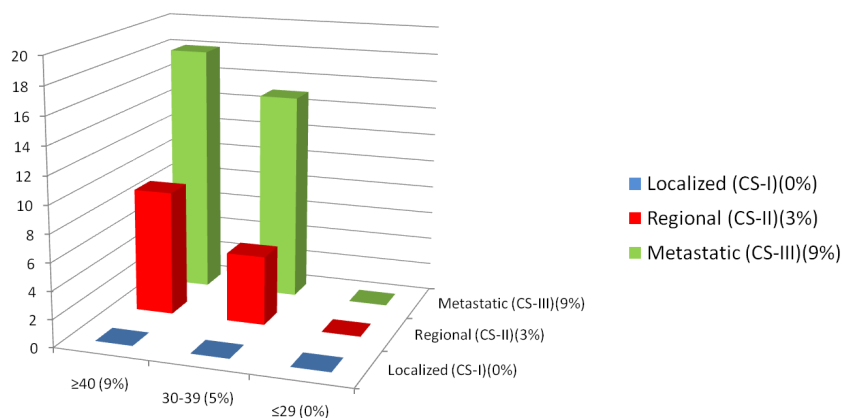
**Table 2.** Mortality rates at 30, 60 and 90 days after RPLA

MORTALITY	REGIONAL DISEASE % (95%CI; n/Overall)	METASTATIC DISEASE % (95%CI; n/Overall)
<u>30 d</u>		
Overall	0.3 (0.0-1.5; 1/179), p=0.6	0.0 (0.0-6.0; 0/57), p=0.2
Age (y)		
≤ 29	0.0 (0.0-1.8; 0/101)	0.0 (0.0-5.1; 0/27)
30 – 39	0.8 (0.0-4.6; 1/55)	0.0 (0.0-1.1; 0/13)
≥ 40	0.0 (0.0-6.6; 0/23)	0.0 (0.0-1.3; 0/17)
<u>60 d</u>		
Overall	1.1 (0.0-4.5; 2/179), p=0.6	3.5 (0.9-12.5; 2/57), p=0.3
Age (y)		
≤ 29	0.0 (0.0-1.8; 0/101)	0.0 (0.0-5.1; 0/27)
30 – 39	3.6 (0.0-6.9; 2/55)	8.3 (2.5-30.2; 0/13)
≥ 40	0.0 (0.0-6.6; 0/23)	5.9 (0.0-11.9; 1/17)
<u>90 d</u>		
Overall	1.1 (0.0-4.5; 2/179), p=0.8	5.3 (1.7-14.6; 3/57), p=0.05
Age (y)		
≤ 29	0.0 (0.0-1.8; 0/101)	0.0 (0.0-11.9; 0/27)
30 – 39	0.0 (0.0-9.9; 0/55)	11.5 (2.5-30.2; 1/13)
≥ 40	8.7 (8.1-24.2; 2/23)	16.7 (2.1-48.4; 2/17)

**Table 3.** Mortality rates at 30, 60 and 90 days after RPLA

Data stratification according to disease stage at RPLA revealed that at 30-, 60-, and 90- days, no deaths occurred in patients with pathologically confirmed localized NSTT. In patients with regional disease, 5 (3.8%) deaths of 179 patients occurred (95% CI, 1.2%-10.5%). Finally, in patients with metastatic disease, 5 of 57 patients died, for a 8.8% 90-day PM rate (95% CI, 2.1%-14.6%).

Our findings can be summarized in the following fashion. RPLA carries virtually no risk of PM in patients with localized disease, regardless of stage. However, patients with regional and metastatic disease should be informed about moderate (2.8%) and significantly greater (8.8%) PM rate, respectively. When no pathologically confirmed lymph node metastases were recorded at RPLA, No PM deaths occurred. Similarly, no deaths were recorded when the RPLAs were performed in younger men (< 30 years), regardless of stage of disease. However, a low, yet detectable, PM rate was recorded for patients with regional (retroperitoneal) lymph node metastases whose age was > 30 years. In those patients at 30-, 60-, and 90-days the PM rate was 0.6%, 0.6% and 1.7%, respectively. Significantly greater PM rates were recorded in patients with metastatic NSTT treated with RPLA. In those patients, at 30-, 60- and 90-days, the PM rate was 4.5%, 4.5% and 6.0%, respectively (Figure 1.).



**Figure 1.** 90-day mortality rates after RPLA for 327 pts stratified according to age and stage

## Discussion

RPLA represents a therapeutic and/or staging modality for patients with virtually all stage NSTT. RPLA, performed by expert surgeons, is believed to represent a safe surgical intervention with minimal morbidity and virtually no mortality<sup>18,19</sup>. Despite its central role in the management of testicular cancer, only 2 studies from the same institution have addressed PM after RPLA<sup>15,16</sup>. In these reports, 478 patients treated with primary RPLA<sup>15</sup> and 603 patients treated with PC-RPLA<sup>16</sup> were studied. No mortality was recorded in the setting of primary RPLA<sup>15</sup>. However, a 0.8% mortality rate at < 47 days after surgery was reported for patients who had undergone PC-RPLA<sup>16</sup>.

These studies have demonstrated that patients treated at a tertiary care referral center can expect outstandingly safe surgical outcomes. However, many RPLAs will be performed at institutions with substantially less expertise than that at Indiana University or Memorial Sloan-Kettering Cancer center, examples of RPLA centers of excellence. At centers with lesser clinical and surgical expertise, patient selection and perioperative patient care might differ from those at centers of excellence. This could have a significant effect on postoperative complications and, possibly, on PM. Thus, PM data from a center of excellence, such as Indiana University, are applicable to another center of excellence but not to institutions at which RPLAs are performed in much lower numbers. Therefore, we examined the PM rate after RPLA for NSTT using data from the SEER data base, which does not include Indiana University or the Memorial Sloan-Kettering Cancer Center. Our objective was to determine the population-based RPLA PM rates providing from our center.

The SEER data demonstrated that, in general, PM rate is low for patients treated with RPLA for NSTT<sup>15, 16, 20, 21</sup>.

Several points deserve mention. First, our PM data regarding localized disease were comparable to those from Indiana University. Thus, patients with localized disease treated with RPLA have virtually no risk of PM at tertiary care centers, as well as at other centers with lesser degrees of expertise.

Second, data from Capitanio and colleagues<sup>17</sup> on PM rate in patients with regional-stage NSTT treated with RPLA were also comparable to those reported from Indiana University (0.8% vs. 0.8%). However, PM rate in CS-II disease reported in our study is substantially higher in comparison to previously reported results (4.7% vs. 2.6% vs. 0.8%). Thus, in patients treated with RPLA for regional disease PM outcomes equally favorable to those from centers of excellence can also be expected.

Third, the present report is the second published till now on PM rate exclusively in men with metastatic NSTT. Our findings indicate that RPLA in this setting is associated with a non-negligible PM rate (8.8%) across all age categories, similar to those reported by Capitanio and colleagues (7%)<sup>17</sup>. This finding needs to be addressed during the informed consent process with the patient. Moreover, RPLA should be performed at centers of excellence, with the intent of reducing the PM rate.

Although we only focused on PM, several other indicators of quality of care also deserve attention; for example, the completeness of the RPLA. The recurrence and cause-specific mortality rates represent others. Our study was not designed to address these end points. Nonetheless, our results should be interpreted in light of those considerations. Additionally, we could not assess the effect of comorbid conditions at baseline. Some comorbidities, for example pulmonary toxicity, might predispose patients to a greater risk of PM. Information about the specific non-cancer causes of death could help in identifying the most frequent risk factors for PM after RPLA, such as bleeding, pulmonary embolism, or myocardial infarction. Finally, our database contains the length of stay or discharge information. These data could allow more detailed analyses, which could potentially be completed with other databases. Despite these limitations, our results have provided valuable information that warrants additional corroboration.

## Conclusions

Our results have shown that RPLA is associated with virtually no PM in patients with localized disease. Our finding virtually perfectly replicated the PM rate reported at Indiana University with CS-I. An intermediate





PM rate (2.8%) can be expected in men with regional disease. Finally, elevated PM (8.8%) might be expected in men with metastatic NSTT.

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