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Patterns of Recurrence Following Inguinal Lymph Node Dissection for Penile Cancer: Optimizing Surveillance Strategies

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ABSTRACT

Purpose: Our primary objective is to detail the incidence, site, and timing of pSCC recurrence after ILND.

Methods: Retrospective analysis of 551 patients who underwent ILND for pSCC, from 2000 to 2017.The primary outcome was pSCC recurrence after ILND. Recurrences were identified and stratified by site. Timing of recurrence was determined. Multivariable logistic regression analysis determined associations with recurrence. Multivariable Cox regression analysis determined associations with overall survival (OS). Sub-group analysis of the distant recurrences analyzed timing, and OS by site of distant recurrence.

Results: 176 (31.9%) recurred after ILND. Median time to recurrence was 10 months for distant recurrences, 12 for inguinal, 10.5 for pelvic, and 44.5 for local. Greater than 95% of distant, inguinal, and pelvic recurrences occurred within 48 months of ILND, versus 127 months for local recurrences. Post-ILND recurrence was associated with with pN2 (OR 1.99, 95CI 1.0-4.1), and pN3 (OR 7.2, 95CI 4.0-13.7). Patients who had local recurrence had similar OS to those without (HR 1.5, 95CI 0.6-3.8), and worse OS was identified in patients with inguinal (HR 4.5, 95CI 2.8-7.1), pelvic (HR 2.6, 95CI 1.5-4.5), or distant (HR 4.0, 95CI 2.7-5.8) recurrences. Patients with lung recurrences had worse OS than other sites (HR 2.2, 95CI 1.1-4.3).

Conclusion: 31.9% of patients had post-ILND recurrence associated with high pN staging. Greater than 95% of distant, inguinal, and pelvic recurrences occurred within 48 months, suggesting surveillance beyond this is low yield. Local recurrences occurred over a longer timeline, emphasizing necessity of long-term surveillance of the primary site.

INTRODUCTION

Penile squamous cell carcinoma (pSCC) is a rare malignancy, with the highest reported incidence in developing countries.[1,2] Surgery is the mainstay of treatment for local or locoregional disease, with resection of the primary neoplasm and subsequent inguinal lymphadenectomy (ILND) if there is involvement, or a high risk of involvement, of the inguinal lymph nodes (LN).[3,4] When ILND is performed, the extent of LN metastasis is strongly correlated with cancer-specific outcomes, with ILND having the greatest curative potential when performed early versus in a delayed clinical setting.[5,6]

Despite curative intent, a subset of patients will experience recurrence after ILND, requiring prompt diagnosis and subsequent treatment.[7] For this reason, the post-ILND surveillance protocol is critical, and optimization of the surveillance schedule depends on accurate population-based information about the incidence, location, and timing of recurrence.

To date, there is very little data on post-ILND recurrences. Currently, the guideline recommendations for surveillance in this patient population are based largely on expert opinion.[3,4]

Our primary objective was to identify the incidence, site, and timing of recurrence after ILND in a large multi-institutional international cohort. Our secondary objectives were to assess the incidence, site, and timing of recurrence after ILND in a subgroup of patients who had distant recurrences, and to determine associations with recurrence site and overall survival.

METHODS

Data Source and Patient Selection

Data was reviewed from an international multi-institutional dataset from 8 centers located in 7 different countries across North America, South America, Europe, and Asia, from 2000 to 2017, as described in previous publications.[8,9] The dataset was established in May 2018, with data centralization completed at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan,

Italy. The dataset includes patients with a diagnosis of penile cancer who underwent ILND, with several having undergone concomitant PLND if indicated.

Patients were included if they underwent bilateral ILND, had SCC histology, and were not missing data on pT stage, pN stage, recurrence status, time from ILND to last follow up, or survival status.

Definitions

The TNM staging was assigned according to the 7th edition of the AJCC Staging Manual.[10] Cases prior to 2010 were reclassified according to this same edition. Available staging information was not adequate for reclassification according to the 8th edition of AJCC staging.[11]

Recurrences were identified with CT scan and/or physical examination. Post-ILND surveillance schedules were determined by each institution per their preferred guideline-based protocol. Site of recurrence was defined as the site of the first recurrence after ILND. For the main analysis, recurrence sites included: local (recurrence related to the primary tumor excision site), inguinal (recurrence in the inguinal nodal region), pelvic (recurrence in the pelvic nodal region, distal to the aortic bifurcation), and distant (all other recurrence sites). For the subgroup analysis, distant recurrence sites included: lung (pulmonary visceral metastases), retroperitoneal (metastases in the retroperitoneal lymph nodes), and other (bone metastases, non-pulmonary visceral metastases, and mediastinal and supraclavicular nodal metastases).

pT stage was reported as the pre-ILND pT stage. The pTa, pTis, and pT1 stages were merged, due to the low population of pTa and pTis patients in the cohort (N = 6 and N = 10, respectively). The pT3 and pT4 stages were merged, due to the low population of pT4 patients in the cohort (N = 13). Patients who underwent removal of the primary tumor at the time of ILND were classified as pTX. Age was defined as the age at the time of ILND. Smoking status was defined as the smoking status at the time of ILND. Recurrence free survival (RFS) was defined using time from ILND to first recurrence or censored at last follow up. Overall survival (OS) was defined using time from ILND to death or censored at last follow up.

Statistical Analysis

Baseline patient and tumor characteristics were described for the entire cohort. The cohort was then stratified by whether any recurrence occurred, and baseline characteristics were compared between each group using the Wilcoxon rank-sum test for continuous variables, chi-square test of independence for categorical variables where every cell population was ≥5, or Fisher's exact test for categorical variables where any cell population was <5.

Multivariable logistic regression analysis for the outcome of recurrence was performed using the following covariates: Age, pT stage, LVI, and pN stage. Odds ratios (OR), 95% confidence intervals (CI), and p-values were reported.

Recurrences were stratified by site of recurrence. For patients who had a recurrence, Kaplan Meier (KM) estimates for RFS were utilized to visually estimate the timeline for recurrences, by site of recurrence. For the entire cohort, for each site of recurrence, the cohort was stratified by pN status and KM estimates for RFS were used to determine site-specific recurrence risk by pN stage. Log-rank testing was used to compare survival distributions.

Several quantiles, including the 50th and 95th percentile for time to recurrence, were determined for each site. For several post-ILND timeframes, up to 60 months, the percentage of recurrences occurring within each timeframe was determined, stratified by site of recurrence.

Multivariable Cox regression was performed for the outcome of OS using the following covariates: Age, pT stage, LVI, pN stage, and site of recurrence. Hazard ratios (HR), 95% CI, and p-values were reported. KM analysis was then performed for the outcome of OS with the cohort stratified by site of recurrence. 5-year OS and 95% CI were reported for each group, and a log-rank test was performed to compare the survival distributions.

As a secondary analysis, the distant recurrence cohort was analyzed as a subgroup. Distant recurrences were stratified by site of distant recurrence. KM estimates for RFS were utilized to visually estimate the timeline for distant recurrences, by site of distant recurrence. For each distant site of recurrence, the cohort was stratified by pN status and KM estimates for RFS

were used determine distant-site-specific recurrence risk by pN stage. Several quantiles, including the 50th and 95th percentile for time to recurrence, were determined for each site. Among the subgroup of patients who had a distant recurrence, a multivariable Cox regression was performed for the outcome of OS using the following covariates: Age, pT stage, LVI, pN stage, and site of distant recurrence. Hazard ratios (HR), 95% CI, and p-values were reported. KM analysis was performed for the outcome of OS within the subgroup of patients who had a distant recurrence, stratified by site of distant recurrence. Median OS and 95% CI were reported for each group, and a log-rank test was performed to compare the survival distributions.

Statistical significance for all analyses was defined as a two-tailed alpha risk of 0.05 or less. Statistical analyses were performed using R program version 3.5.1 (The R Project for Statistical Computing; Vienna, Austria).

RESULTS

Study Population

Patients who underwent bilateral ILND were identified in the dataset (N = 965). Patients were excluded who were missing recurrence data (N = 208), had non-SCC histology (N = 43), were missing data regarding pT stage, pN stage, follow up, or survival status (N = 7), or were diagnosed prior to the year 2000 (N = 156). After application of these criteria, 551 patients were included in the final study population. Supplemental Figure 1.

Baseline Characteristics

Baseline characteristics are reported in Table 1. Median age was 60 years (IQR 50 – 68). Active smoking at the time of ILND was identified in 129 patients (18%). Positive HPV status was identified in 91 patients (13%). pT stage ≥pT2 was identified in 440 patients (62%). Positive LVI status was identified in 169 patients (24%). pN0 was identified in 171 patients (24%), and the remainder had positive LNs identified in their pathologic specimen. Median follow-up was 28 months (IQR 15 – 57).

Associations with Recurrence

Recurrence was identified in 221 patients (31%). 23 patients had a local recurrence (10% of recurrences), 61 had an inguinal recurrence (28%), 36 had a pelvic recurrence (16%), and 101 had a distant recurrence (46%). The cohort was stratified by recurrence group, and univariable analysis identified differences between groups for HPV status ($p = 0.01$), pT stage ($p < 0.01$), cN stage ($p < 0.01$), and pN stage ($p < 0.01$). Table 2. Multivariable logistic regression analysis demonstrated an association with recurrence for patients with pT3/pT4 (OR 1.6, 95% CI 1.0 – 2.5, $p = 0.045$), pN2 (OR 2.4, 95% CI 1.3 – 4.6, $p < 0.01$), and pN3 (OR 6.4, 95% CI 3.8 – 11.0, $p < 0.01$). Figure 1.

Timing of Recurrence by Site of Recurrence

Local recurrences occurred over a lengthy timeframe, with median time to recurrence of 50 months (IQR 12-89.5), and 95% of recurrences occurring within 152 months. Inguinal, pelvic, and distant recurrences occurred over a shorter timeframe (Median time to recurrence: Inguinal = 10mo. (IQR 4-20), Pelvic = 11mo. (IQR 6-20), Distant = 11mo. (IQR 6-16); 95% of recurrences: Inguinal = 38mo., Pelvic = 43mo., Distant = 36mo.). Figure 2. Supplemental Table 1. KM estimates demonstrated that patients with pN2 and pN3 were more likely to have inguinal, pelvic, and distant recurrences, than patients with pN0 or pN1. Figure 3.

Associations with Overall Survival

Multivariable Cox regression analysis demonstrated worsened OS for patients with increased age (HR 1.01/yr, 95% CI 1.00 – 1.03, $p < 0.01$), pN3 (HR 1.7, 95% CI 1.1 – 2.6, $p = 0.01$), inguinal recurrence (HR 3.5, 95% CI 2.4 – 5.1, $p < 0.01$), pelvic recurrence (HR 2.8, 95% CI 1.7 – 4.6, $p < 0.01$), and distant recurrence (HR 4.0, 95% CI 2.9 – 5.5, $p < 0.01$). Supplemental Figure 2. KM analysis and log-rank testing for OS, stratified by site of recurrence, demonstrated a statistically significant difference in survival distributions between groups (5-year OS: No

recurrence = 76%, Local = 75%, Inguinal = 16%, Pelvic = 9%, Distant = 13%; log-rank p < 0.01). Figure 4.

Subgroup Analysis of Distant Recurrences

Among patients who had a distant recurrence, lung and retroperitoneal recurrences occurred on a shorter timeframe than recurrences at other sites (Median time to recurrence: Lung = 9mo. (IQR 6-14), Retroperitoneal = 11mo. (IQR 6.75-14.5), Other = 13mo. (IQR 10-20); 95% of recurrences: Lung = 24mo., Retroperitoneal = 24mo., Other = 82mo.). Supplemental Figure 3. Supplemental Table 2. KM estimates of the subgroup of patients who had a distant recurrence revealed that patients with pN2 and pN3 were more likely to have lung, retroperitoneal, and other distant site recurrences, than patients with pN0 or pN1. Supplemental Figure 4.

Multivariable Cox regression analysis demonstrated worsened OS for patients with lung recurrences, as compared to patients who in the "Other" group of distant sites of recurrence (HR 2.2, 95% CI 1.3 – 3.9; p < 0.01). Supplemental Figure 5. KM analysis and log rank resting for OS, stratified by site of distant recurrence, demonstrated a statistically significant difference in survival distributions between groups (Median OS: Lung = 13mo., Retroperitoneum = 16.5mo., Other = 23.0mo.; p < 0.01). Supplemental Figure 6.

DISCUSSION

Here we present data on the incidence, site, and timing of recurrence in the largest reported post-ILND cohort. Of the 551 patients included in the final study population, we found that 176 (31.9%) had a recurrence following ILND. The proportion of local, nodal, and distant recurrences was significantly skewed towards distant and nodal recurrences in our patient population, as compared to prior studies that were enriched with patients who had local resection alone.[12,13]

We found that local recurrences represented 10% of recurrences, and there was a lengthy median time to local recurrence at 50 months (IQR 12-89.5). Prior investigations into

pSCC local recurrence noted the majority occurred within 12 months following resection of the primary.[14–16] These were smaller cohorts, mostly composed of patients who did not undergo ILND, and measured time to recurrence from resection of the primary and not from ILND. The NCCN guidelines recommend physical examination for the first 5 years after partial or total penectomy, and up to 10 years for less invasive excisions.[4] EAU guidelines recommend physical or self-examination of the primary site for a minimum of 5 years.[3] In our analysis, 95% of local recurrences were not captured until > 10 years after ILND, suggesting that these patients may require an even lengthier timeframe for physical examination of the primary site. Given the lengthy time to local recurrence identified in this study, an interesting consideration is that several of these "recurrences" may represent new primary tumors, and not genetic clones of the original primary. However, our data is inadequate to make this distinction, and as such we refer to these tumors as local recurrences in this manuscript.

Nodal recurrences following ILND were identified in 97 patients (61 inguinal and 36 pelvic; 44% of recurrences) with a median time to recurrence of 10 - 11 months. NCCN and EAU guidelines currently recommend physical examination including the inguinal region for a minimum of 5 years, which based on our findings would capture >95% of inguinal recurrences.[3,4] Additionally, the NCCN recommends cross-sectional imaging of the abdomen and pelvis for 2 years, which based on our data would capture ~85% of inguinal or pelvic recurrences. To capture 95% of inguinal and pelvic recurrences, our data suggests extending the surveillance timeframe for cross-sectional imaging to 48 months. The EAU guidelines consider cross-sectional imaging optional for imaging the inguinal region, and do not specifically comment on surveillance for pelvic or distant recurrences.[3]

Distant recurrence occurred in 101 patients (46% of recurrences), with a median time to recurrence of 11 months. The most common site of distant recurrence was the lung, which carried an independently worse OS than all other distant sites of metastasis. NCCN guidelines recommend chest imaging for two years, and our sub-group analysis suggested that 95% of lung recurrences would occur within that timeframe, confirming this recommendation.[4] Patients with

pN2/N3 were significantly more likely to have a distant recurrence than those who were pN0/N1, which also held true when looking specifically at lung recurrences. We suggest that pN2/N3 patients should be surveilled with chest CT, as opposed to a chest radiograph, to more thoroughly image the chest for this high-risk group.

Based on the data in this analysis, evidence-based recommendations for post-ILND surveillance timeframes are proposed in Supplemental Table 1C.

Higher pathologic primary tumor (pT3/T4) and nodal (pN2 and pN3) stages were associated with an increased likelihood of recurrence. This finding corroborates prior studies that identified associations with increasing pT and pN stages and worse oncologic outcomes.

There are several limitations to this study. The retrospective nature of the analysis introduces inherent selection bias. The multi-institutional nature of the dataset precludes a centralized pathology or radiology review. Additionally, a significant amount of our cohort, 215 patients, were excluded secondary to insufficient recurrence data, tumor characteristics or demographic information, decreasing the strength of our findings to some degree. Additionally, surveillance protocols vary by institution, potentially affecting the timing of recurrence identification. Finally, we excluded non-SCC histologic variants, potentially limiting the generalizability of the findings.

CONCLUSION

31.3% of patients had a post-ILND recurrence. Local recurrences occurred on a lengthy timeline, with 95% occurring within 152 months of ILND, stressing the necessity of very long-term follow up of the penis, perineum, and scrotum. Greater than 95% of distant, inguinal, and pelvic recurrences occurred within 48 months of ILND, suggesting that surveillance for these outcomes beyond this timeframe may be low yield. Inguinal, pelvic, and distant recurrences were confirmed to confer worse OS, and local recurrences had no effect on survival. Interestingly, patients with lung recurrences had significantly worse OS than those who recurred at other

distant sites. This data on incidence, timing, and site of post-ILND recurrence can be readily used to formulate evidence-based guideline recommendations for surveillance protocols.

REFERENCES

1. C.B. V, L. F, J. P, et al. Profile of patients with penile cancer in the region with the highest worldwide incidence. *Sci Rep*. 2020;10(1):2965. doi:10.1038/s41598-020-59831-5 LK - http://link.kib.ki.se/?sid=EMBASE&issn=20452322&id=doi:10.1038%2Fs41598-020-59831-5&atitle=Profile+of+patients+with+penile+cancer+in+the+region+with+the+highest+worldwide+incidence&stitle=Sci+Rep&title=Scientific+reports&volume=10&issue=1&spage=2965&epage=&aulast=Vieira&aufirst=Ciro+Bezerra&auinit=C.B.&aufull=Vieira+C.B.&coden=&isbn=&pages=2965-&date=2020&auinit1=C&auinitm=B.
2. Favorito LA, Nardi AC, Ronalsa M, Zequi SC, Sampio FJB, Glina S. Epidemiologic study on penile cancer in Brazil. *Int Braz J Urol*. 2008;34(5):587-591. doi:10.1590/s1677-55382008000500007.
3. Hakenberg OW, Compérat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. *Eur Urol*. 2015;67(1):142-150. doi:10.1016/j.eururo.2014.10.017.
4. Network NCC. Penile Cancer (Version 2.2019).
5. Pandey D, Mahajan V, Kannan RR. Prognostic factors in node-positive carcinoma of the penis. *J Surg Oncol*. 2006;93(2):133-138. doi:10.1002/jso.20414.
6. Veeratterapillay R, Teo L, Asterling S, Greene D. Oncologic Outcomes of Penile Cancer Treatment at a UK Supraregional Center. *Urology*. 2015;85(5):1097-1103. doi:10.1016/j.urology.2014.11.048.
7. J.L. W, K.R. Y. Challenges and Opportunities in Measuring Cancer Recurrence in the United States. *J Natl Cancer Inst*. 2015;107(8). doi:10.1093/jnci/djv134 LK - http://ucelinks.cdlib.org:8888/sfx_ucsf?sid=EMBASE&issn=14602105&id=doi:10.1093%2Fjnci%2Fdjv134&atitle=Challenges+and+Opportunities+in+Measuring+Cancer+Recurrence+in+the+United+States&stitle=J.+Natl.+Cancer+Inst.&title=Journal+of+the+National+Cancer+Institute&volume=107&issue=8&spage=&epage=&aulast=Warren&aufirst=Joan+L.&auinit=J.L.&aufull=Warren+J.L.&coden=JNCIA&isbn=&pages=-&date=2015&auinit1=J&auinitm=L.
8. Bandini M, Spiess PE, Pederzoli F, et al. A risk calculator predicting recurrence in lymph node metastatic penile cancer. *BJU Int*. 2020. doi:10.1111/bju.15177.
9. Necchi A, Lo Vullo S, Mariani L, et al. Nomogram-based prediction of overall survival after regional lymph node dissection and the role of perioperative chemotherapy in penile squamous cell carcinoma: A retrospective multicenter study. *Urol Oncol Semin Orig Investig*. 2019;37(8):531.e7-e531.e15. doi:10.1016/j.urolonc.2019.04.003.
10. Edge SB, Compton CC. The american joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471-1474. doi:10.1245/s10434-010-0985-4.
11. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol*. 2018;73(4):560-569. doi:10.1016/j.eururo.2017.12.018.
12. Rieken M, Djajadiningrat RS, Kluth LA, et al. Predictors of cancer-specific mortality after disease recurrence in patients with squamous cell carcinoma of the penis. *Eur Urol*. 2014;66(5):811-814. doi:10.1016/j.eururo.2014.05.032.
13. Leijte JAP, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence Patterns of Squamous Cell Carcinoma of the Penis: Recommendations for Follow-Up Based on a Two-Centre Analysis of 700 Patients. *Eur Urol*. 2008;54(1):161-169. doi:10.1016/j.eururo.2008.04.016.
14. Sri D, Sujenthiran A, Lam W, et al. A study into the association between local recurrence rates and surgical resection margins in organ-sparing surgery for penile squamous cell cancer. *BJU Int*. 2018;122(4):576-582. doi:10.1111/bju.14222.
15. Philippou P, Shabbir M, Malone P, et al. Conservative surgery for squamous cell carcinoma of the penis: Resection margins and long-term oncological control. *J Urol*. 2012;188(3):803-808. doi:10.1016/j.juro.2012.05.012.
16. Minhas S, Kayes O, Hegarty P, Kumar P, Freeman A, Ralph D. What surgical resection margins are required to achieve oncological control in men with primary penile cancer? *BJU Int*. 2005;96(7):1040-1043. doi:10.1111/j.1464-410X.2005.05769.x.

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	N = 551[1]
Age	61 (52, 70)
Year	2011 (2008, 2014)
Smoking	
Never smoker	111 (20%)
Current smoker	105 (19%)
Former smoker	69 (13%)
Unknown	266 (48%)
HPV	
Negative	281 (51%)
Positive	91 (17%)
Unknown	179 (32%)
pT	
pTa/Tis/T1	171 (31%)
pT2	228 (41%)
pT3/T4	152 (28%)
LVI	159 (29%)
cN	
cN0	278 (50%)
cN1	90 (16%)
cN2	103 (19%)
cN3	80 (15%)
pN	
pN0	132 (24%)
pN1	82 (15%)
pN2	104 (19%)
pN3	233 (42%)
Primary procedure	
Total penectomy	174 (32%)
Local Excision	12 (2.2%)
Partial penectomy	365 (66%)
Neoadjuvant chemo	83 (15%)
Neoadjuvant RT	9 (1.6%)
Adjuvant chemo	138 (25%)
Adjuvant RT	91 (17%)
Recurrence	
No Recurrence	375 (68%)
Local	20 (3.6%)
Inguinal	44 (8.0%)
Pelvic	32 (5.8%)
Distant	80 (15%)

[1] Statistics presented: median (IQR); n (%)

Table 2. Baseline Characteristics, by Recurrence Group

Characteristic	**No Recurrence**, N = 375[1]	**Recurrence**, N = 176[1]	**p-value**[2]
Age	61 (52, 70)	60 (53, 69)	0.7
Year	2012 (2009, 2014)	2011 (2007, 2014)	0.042
Smoking			0.12
Never smoker	85 (23%)	26 (15%)	
Current smoker	72 (19%)	33 (19%)	
Former smoker	42 (11%)	27 (15%)	
Unknown	176 (47%)	90 (51%)	
HPV			0.029
Negative	195 (52%)	86 (49%)	
Positive	70 (19%)	21 (12%)	
Unknown	110 (29%)	69 (39%)	
pT			0.008
pTa/Tis/T1	118 (31%)	53 (30%)	
pT2	168 (45%)	60 (34%)	
pT3/T4	89 (24%)	63 (36%)	
LVI	102 (27%)	57 (32%)	0.2
cN			<0.001
cN0	220 (59%)	58 (33%)	
cN1	54 (14%)	36 (20%)	
cN2	63 (17%)	40 (23%)	
cN3	38 (10%)	42 (24%)	
pN			<0.001
pN0	114 (30%)	18 (10%)	
pN1	66 (18%)	16 (9.1%)	
pN2	78 (21%)	26 (15%)	
pN3	117 (31%)	116 (66%)	
Primary procedure			0.027
Total penectomy	106 (28%)	68 (39%)	
Local Excision	7 (1.9%)	5 (2.8%)	
Partial penectomy	262 (70%)	103 (59%)	
Neoadjuvant chemo	51 (14%)	32 (18%)	0.2
Neoadjuvant RT	2 (0.5%)	7 (4.0%)	0.006
Adjuvant chemo	77 (21%)	61 (35%)	<0.001
Adjuvant RT	50 (13%)	41 (23%)	

[1] Statistics presented: median (IQR); n (%)

[2] Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test

Supplemental Table 1. A: Percentages of recurrences occurring within various time-points from ILND, stratified by site of recurrence. B: 95th percentile for time to recurrence, stratified by site of recurrence. C: Suggested evidence-based post-ILND surveillance timeframes.

A

	Time (months)									
	3	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**48**	**60**
Local	5%	5%	20%	25%	30%	40%	45%	45%	50%	65%
Nodal										
Inguinal	23%	34%	45%	57%	70%	84%	89%	93%	95%	98%
Pelvic	9%	31%	47%	62%	75%	84%	84%	91%	95%	97%
Distant										
Lung	10%	32%	51%	69%	83%	95%	98%	98%	98%	98%
Retroperitoneum	8%	33%	50%	83%	100%	100%	100%	100%	100%	100%
Other	4%	19%	26%	48%	70%	81%	85%	89%	89%	89%

B

Site of Recurrence	**95th percentile for Time to Recurrence (months)**
Local	127
Nodal	
Inguinal	38
Pelvic	47
Distant	
Lung	23
Retroperitoneum	15
Other	88

C

	Recommendation	**Minimum Timeframe (months)**
Physical Examination		
Penis, Scrotum, and Perineum	External examination	120
Inguinal Region	External examination	48
Imaging		
Abdomen/Pelvis	CT abdomen/pelvis	48
Chest		
pN0/N1	Chest radiograph	24
pN2/N3	CT chest	24

Characteristic	Institution A, N = 48[1]	Institution B, N = 84[1]	Institution C, N = 176[1]	Institution D, N = 41[1]	Institution E, N = 70[1]	Institution F, N = 27[1]	Institution G, N = 105[1]	p-value[2]
Age	67 (54, 75)	58 (47, 64)	62 (53, 70)	63 (53, 70)	62 (54, 69)	60 (48, 70)	61 (54, 70)	0.013
Year	2014.5 (2009.8, 2016.0)	2011.0 (2009.8, 2014.0)	2010.0 (2006.0, 2013.2)	2016.0 (2013.0, 2018.0)	2007.0 (2003.2, 2011.0)	2013.0 (2012.0, 2014.0)	2012.0 (2010.0, 2014.0)	<0.001
Smoking								
Never smoker	0 (0%)	56 (67%)	35 (20%)	8 (20%)	3 (4.3%)	6 (22%)	3 (2.9%)	
Current smoker	6 (12%)	28 (33%)	29 (16%)	11 (27%)	12 (17%)	15 (56%)	4 (3.8%)	
Former smoker	1 (2.1%)	0 (0%)	40 (23%)	15 (37%)	9 (13%)	0 (0%)	4 (3.8%)	
Unknown	41 (85%)	0 (0%)	72 (41%)	7 (17%)	46 (66%)	6 (22%)	94 (90%)	
HPV								
Negative	11 (23%)	28 (33%)	169 (96%)	17 (41%)	20 (29%)	23 (85%)	13 (12%)	
Positive	4 (8.3%)	27 (32%)	7 (4.0%)	24 (59%)	20 (29%)	4 (15%)	5 (4.8%)	
Unknown	33 (69%)	29 (35%)	0 (0%)	0 (0%)	30 (43%)	0 (0%)	87 (83%)	
pT								0.009
pTa/Tis/T1	26 (54%)	26 (31%)	48 (27%)	10 (24%)	22 (31%)	8 (30%)	31 (30%)	
pT2	15 (31%)	37 (44%)	83 (47%)	18 (44%)	19 (27%)	14 (52%)	42 (40%)	
pT3/T4	7 (15%)	21 (25%)	45 (26%)	13 (32%)	29 (41%)	5 (19%)	32 (30%)	
LVI	3 (6.2%)	19 (23%)	39 (22%)	22 (54%)	2 (2.9%)	7 (26%)	67 (64%)	<0.001
cN								
cN0	34 (71%)	74 (88%)	44 (25%)	7 (17%)	39 (56%)	11 (41%)	59 (56%)	
cN1	2 (4.2%)	6 (7%)	45 (26%)	13 (32%)	11 (16%)	7 (26%)	12 (11%)	

cN2	8 (17%)	4 (5%)	55 (31%)	10 (24%)	13 (19%)	9 (33%)	8 (7.6%)	
cN3	4 (8.3%)	0 (0%)	32 (18%)	11 (27%)	7 (10%)	0 (0%)	26 (25%)	
pN								<0.001
pN0	31 (65%)	50 (60%)	21 (12%)	2 (4.9%)	25 (36%)	1 (3.7%)	2 (1.9%)	
pN1	4 (8.3%)	9 (11%)	27 (15%)	10 (24%)	7 (10%)	7 (26%)	18 (17%)	
pN2	8 (17%)	15 (18%)	30 (17%)	12 (29%)	13 (19%)	9 (33%)	17 (16%)	
pN3	5 (10%)	10 (12%)	98 (56%)	17 (41%)	25 (36%)	10 (37%)	68 (65%)	
Primary_procedure								0.021
Total penectomy	16 (33%)	18 (21%)	84 (48%)	7 (17%)	16 (23%)	7 (26%)	26 (25%)	
Local Excision	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (17%)	0 (0%)	0 (0%)	
Partial penectomy	32 (67%)	66 (79%)	92 (52%)	34 (83%)	42 (60%)	20 (74%)	79 (75%)	
Inguinal LN_count	8 (4, 15)	21 (15, 26)	15 (10, 22)	15 (10, 18)	14 (9, 18)	11 (7, 13)	13 (9, 17)	<0.001
Neoadjuvant_chemo	0 (0%)	0 (0%)	47 (27%)	4 (9.8%)	9 (13%)	23 (85%)	0 (0%)	<0.001
Neoadjuvant_RT	0 (0%)	0 (0%)	2 (1.1%)	2 (4.9%)	4 (5.7%)	1 (3.7%)	0 (0%)	0.015
Adjuvant_chemo	16 (33%)	0 (0%)	46 (26%)	8 (20%)	18 (26%)	18 (67%)	32 (30%)	<0.001
Adjuvant_RT	8 (17%)	0 (0%)	9 (5.1%)	14 (34%)	20 (29%)	1 (3.7%)	39 (37%)	<0.001
Recurrence								<0.001
No Recurrence	32 (67%)	77 (92%)	113 (64%)	26 (63%)	39 (56%)	24 (89%)	64 (61%)	

Local	6 (12%)	0 (0%)	5 (2.8%)	2 (4.9%)	7 (10%)	0 (0%)	0 (0%)	
Inguinal	3 (6.2%)	6 (7.1%)	14 (8.0%)	0 (0%)	10 (14%)	1 (3.7%)	10 (9.5%)	
Pelvic	3 (6.2%)	0 (0%)	7 (4.0%)	5 (12%)	2 (2.9%)	0 (0%)	15 (14%)	
Distant	4 (8.3%)	1 (1.2%)	37 (21%)	8 (20%)	12 (17%)	2 (7.4%)	16 (15%)	
[1] Statistics presented: median (IQR); n (%)								
[2] Statistical tests performed: Kruskal-Wallis test; chi-square test of independence; Fisher's exact test								

Figure 1. Multivariable Logistic Regression Analysis for the Outcome of Recurrence

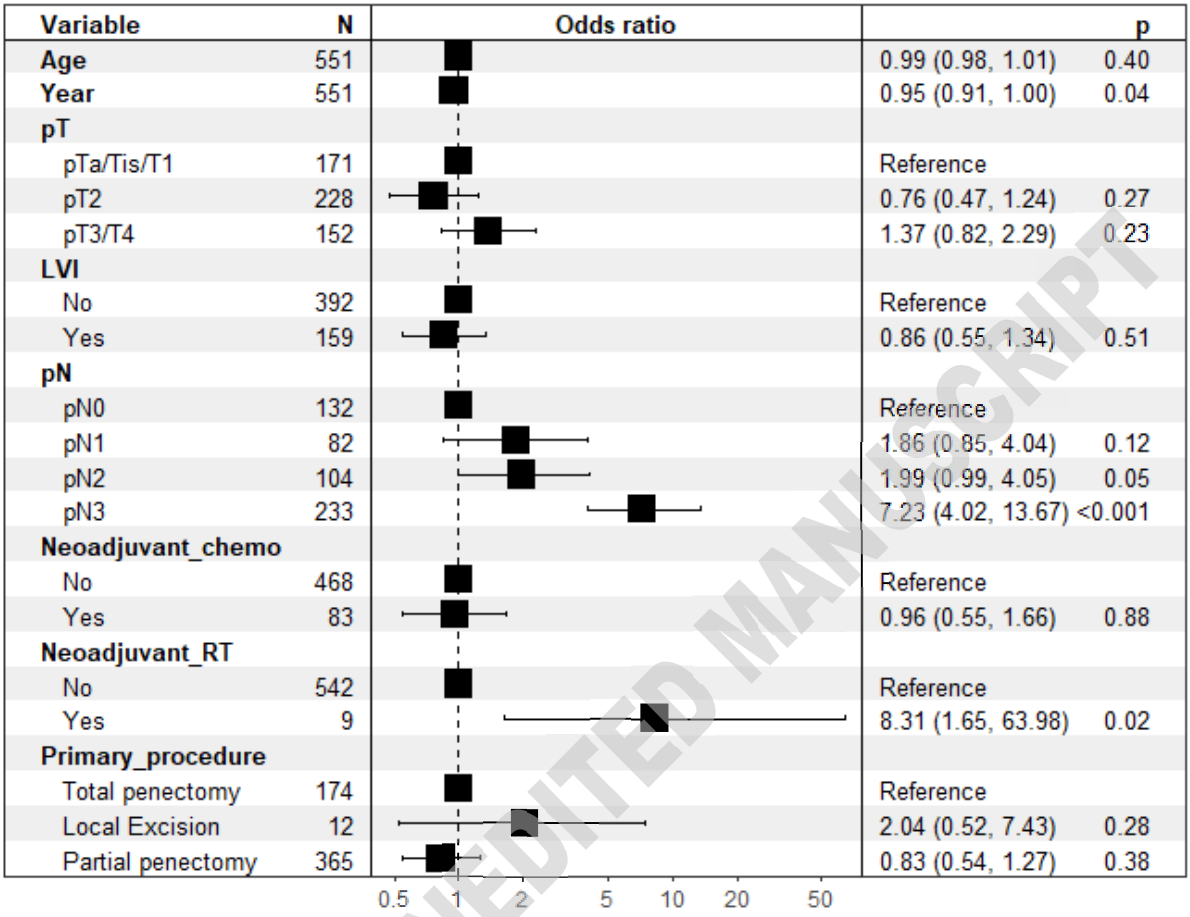
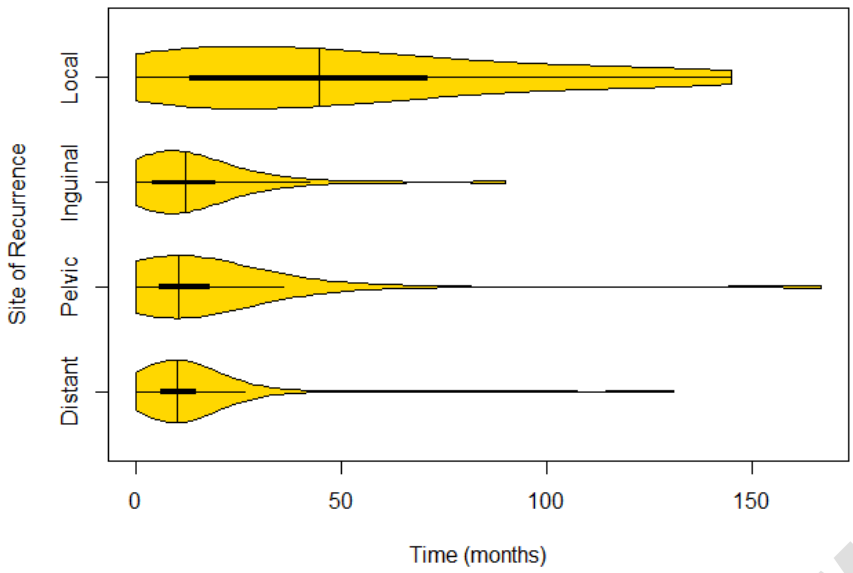
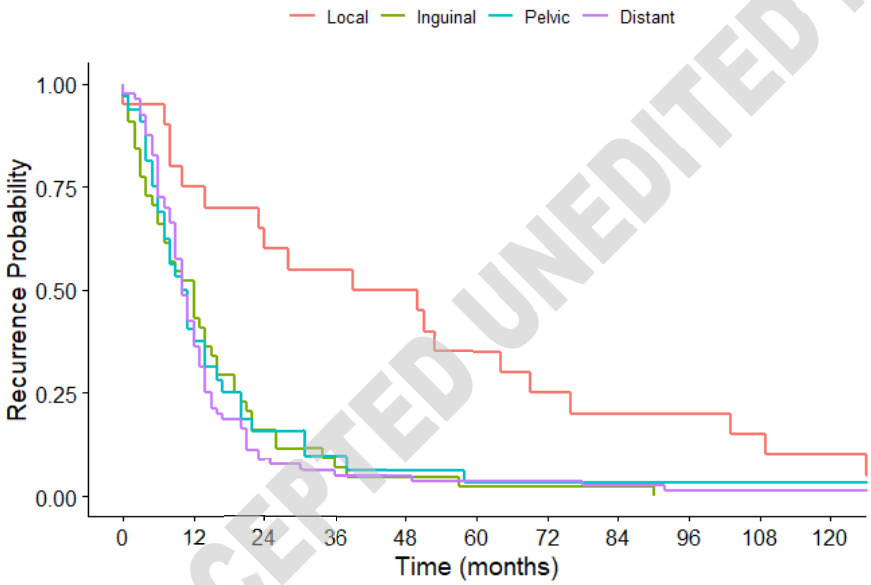


Figure 2. Cohort of all patients who recurred after ILND (N = 176). A: Violin plot for time from ILND to first recurrence, by site of recurrence. B: Kaplan Meier estimates for RFS by site of recurrence. C: Quantiles of time to recurrence, by site of recurrence.

A



B



C

		Percentage of Recurrences Captured					
		10%	**25%**	**50%**	**75%**	**95%**	**99%**
Time (months)	**Local**	8	13	44.5	71	127	141
	Inguinal	2	4	12	19	38	76
	Pelvic	4	6	10.5	18	47	133
	Distant	4	6	10	14	37	100

Figure 3. KM estimates for recurrence free survival, by site of recurrence, stratified by pN status, among all included patients (N = 551). A: Local recurrence; B: Inguinal recurrence; C: Pelvic recurrence; D: Distant recurrence

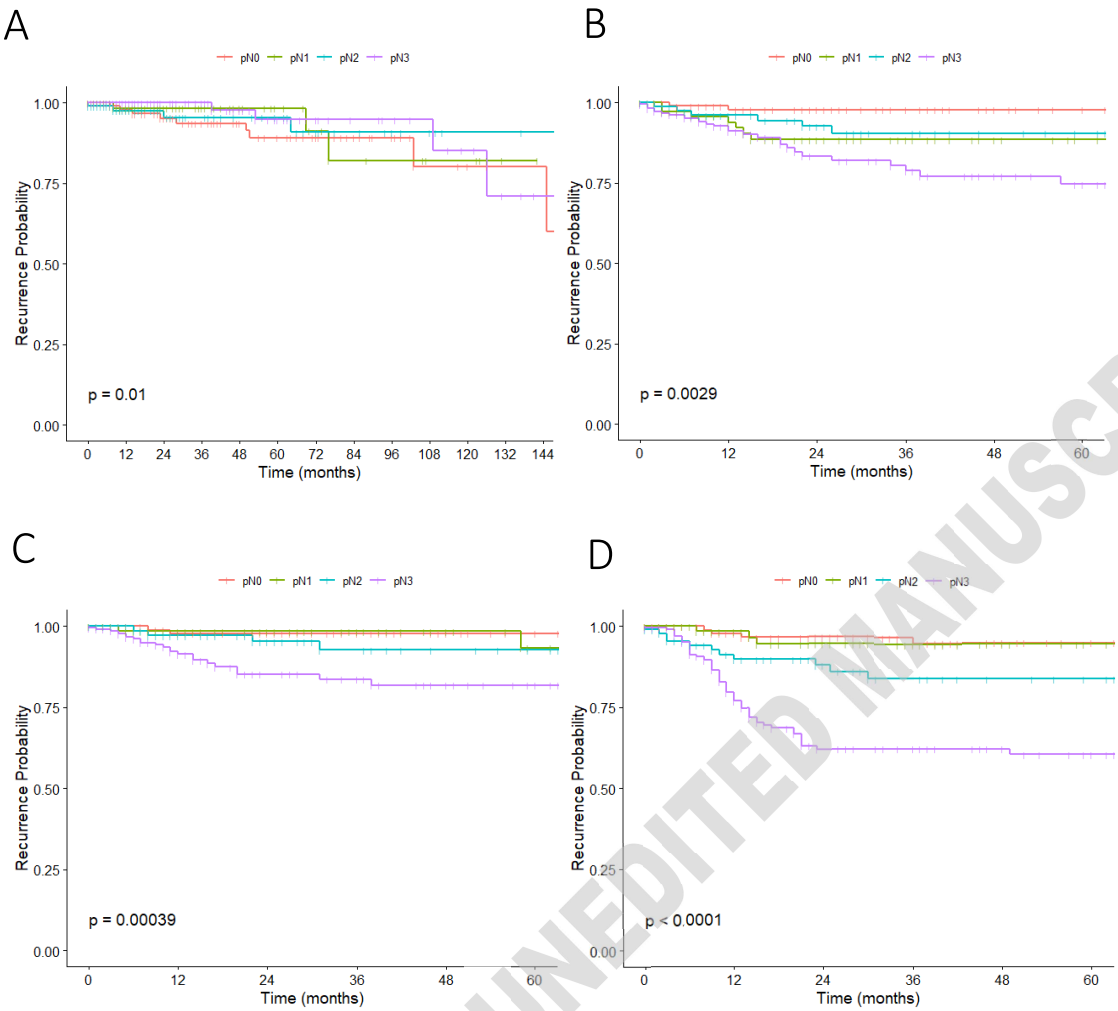
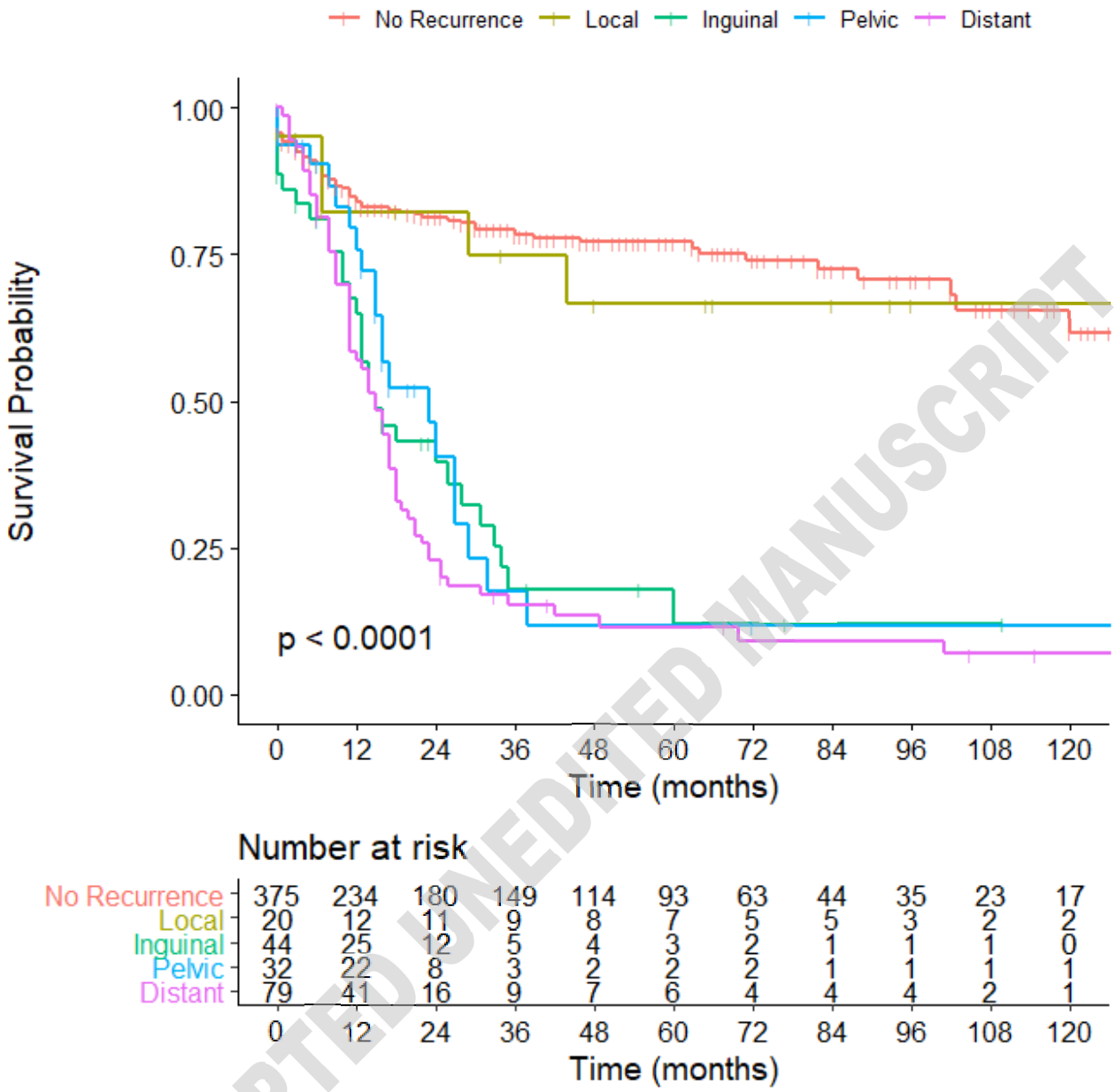
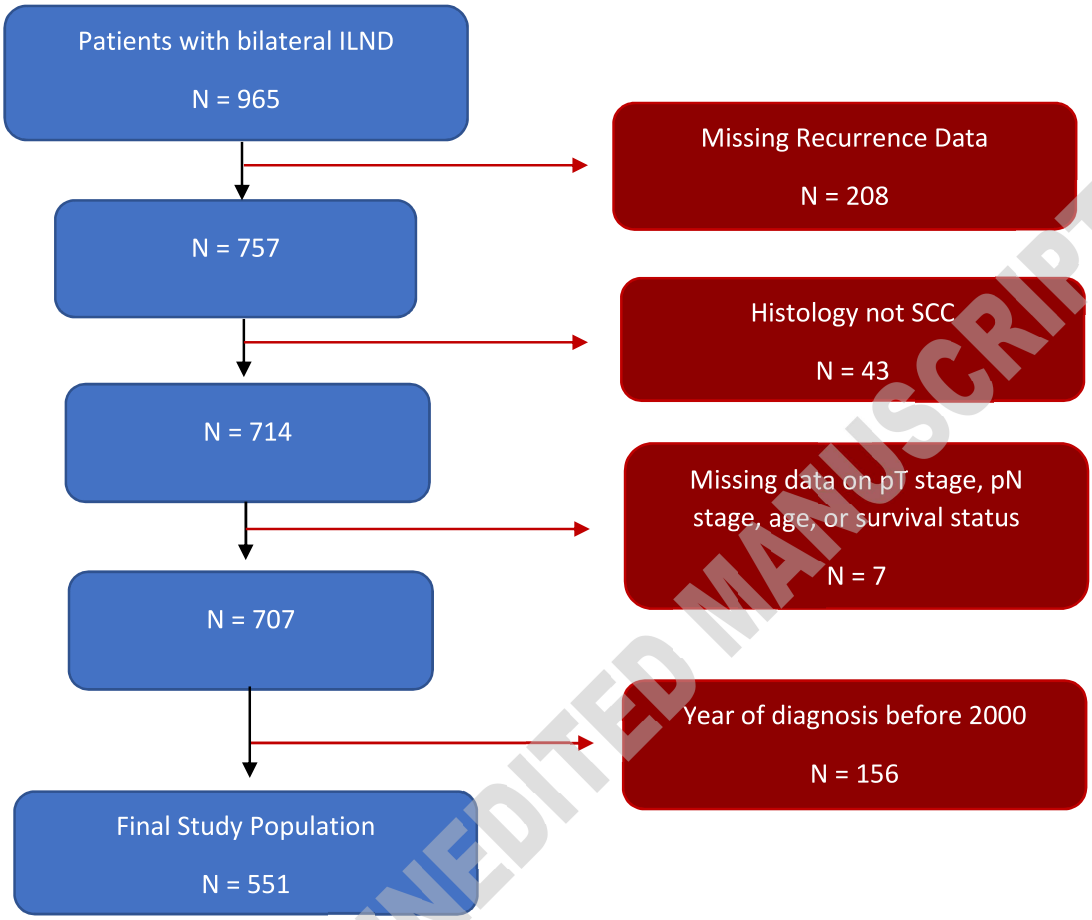


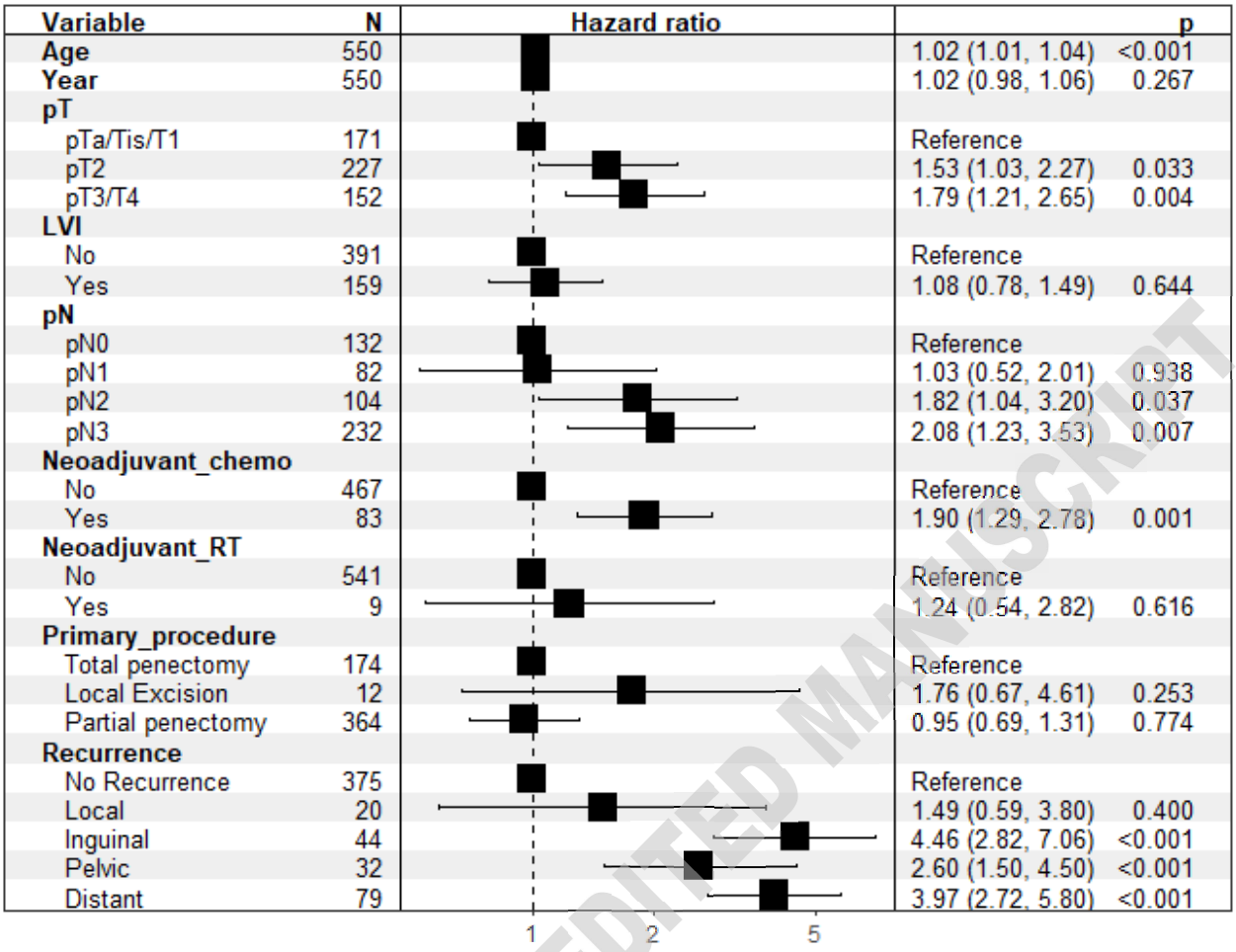
Figure 4. KM estimates for OS by site of recurrence, among all included patients (N = 551). Log-rank p-value reported.



Supplemental Figure 1. CONSORT diagram

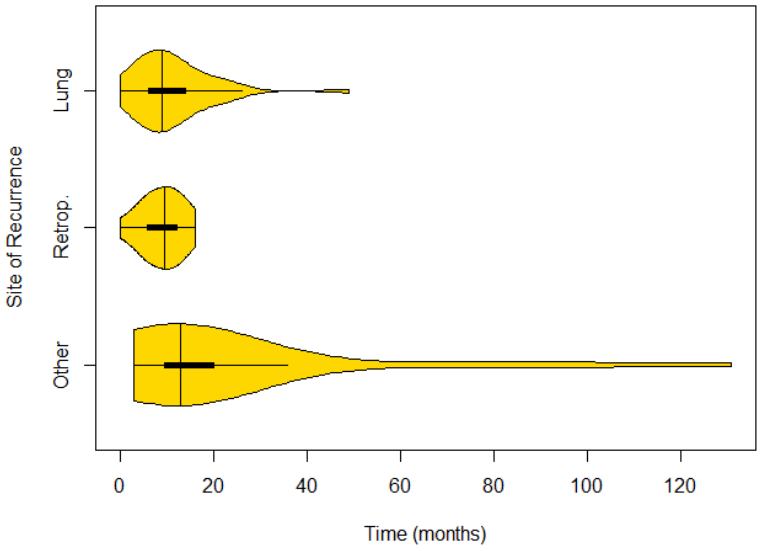


Supplemental Figure 2. Multivariable Cox regression analysis for the outcome of OS

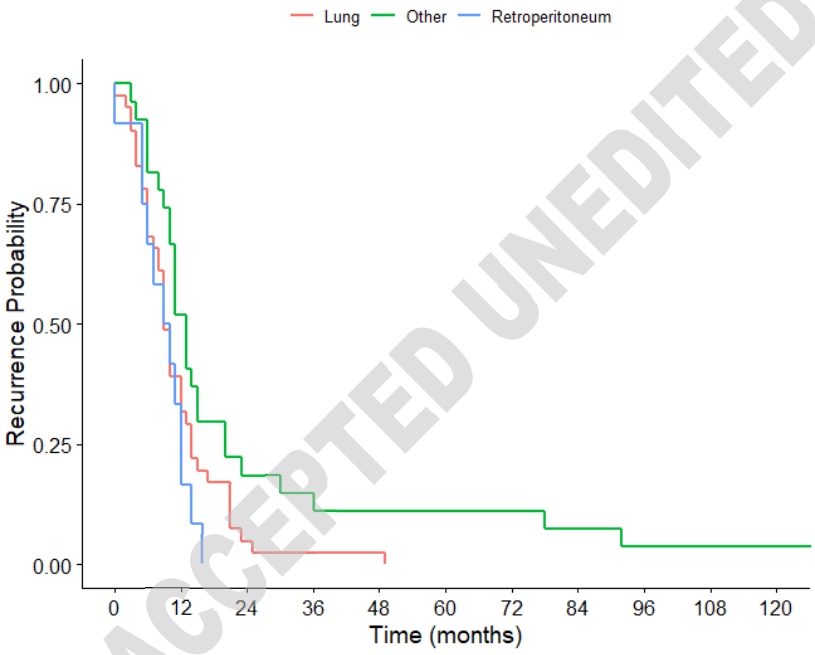


Supplemental Figure 3. Cohort of patients who had a distant recurrence (N = 80). A: Violin plot for time from ILND to first recurrence by site of recurrence. B: Kaplan Meier estimates for RFS by site of distant recurrence. C: Quantiles of time to recurrence, by site of distant recurrence.

A



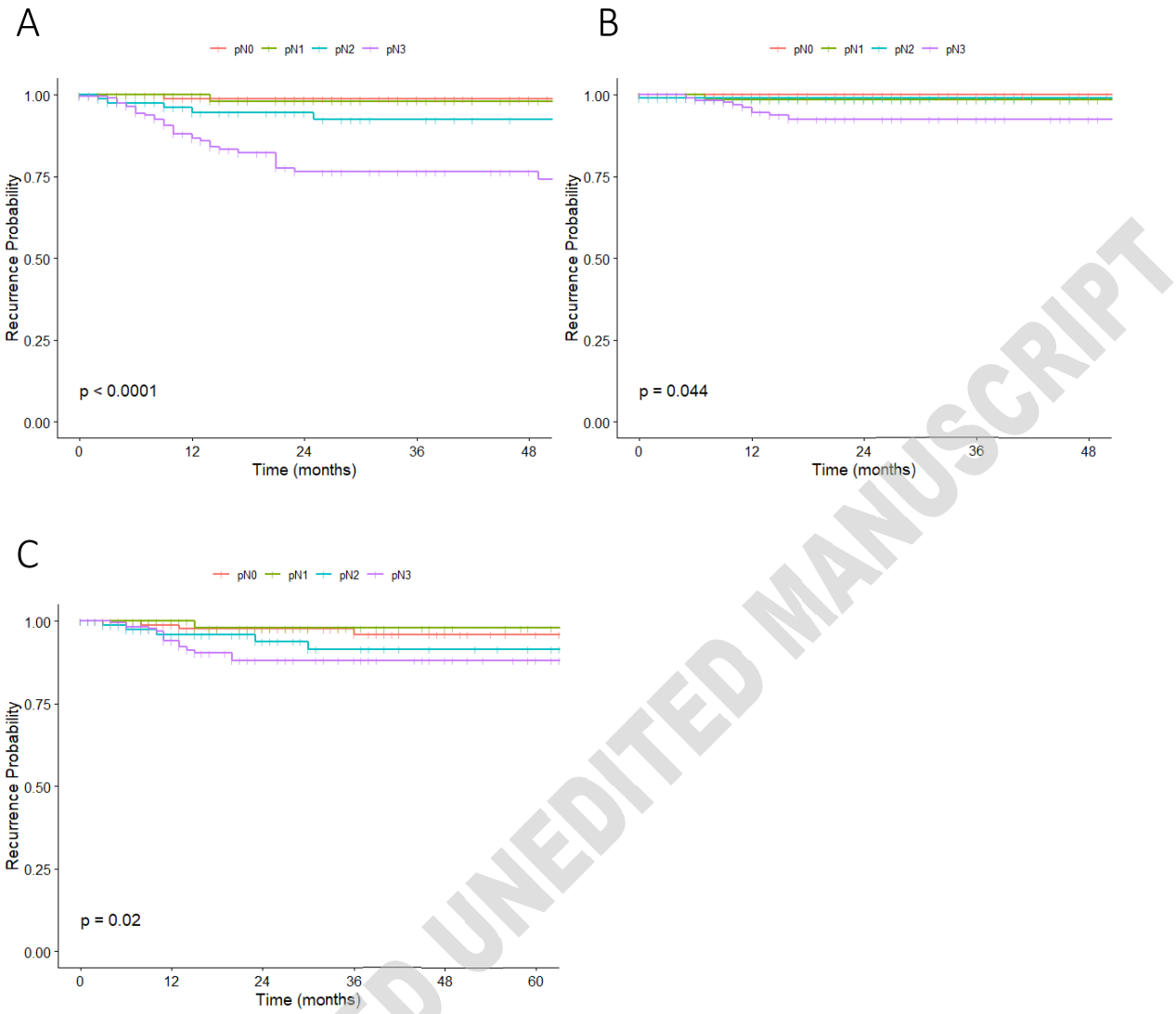
B



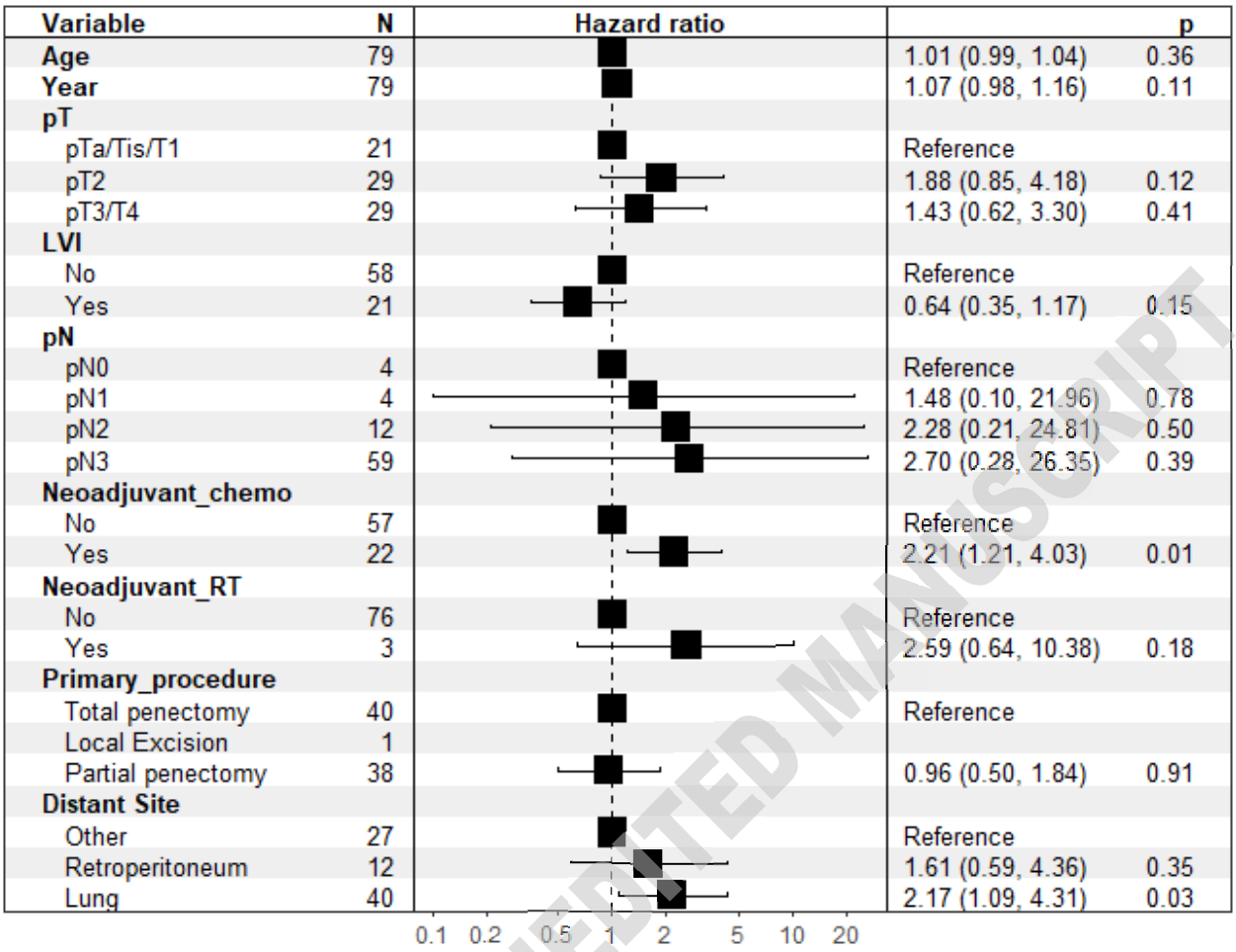
C

		Percentage of Recurrences Captured					
		10%	**25%**	**50%**	**75%**	**95%**	**99%**
Time (months)	**Lung**	4	6	9	14	23	39
	Retroperitoneum	5	6	9.5	12	15	16
	Other	6	9.5	13	20	88	121

Supplemental Figure 4. KM estimates for recurrence free survival, by site of distant recurrence, stratified by pN status, among all included patients (N = 551). A: Lung recurrence; B: Retroperitoneal recurrence; C: Other distant recurrence



Supplemental Figure 5. Multivariable Cox regression analysis for the outcome of OS for patients who had a distant recurrence.



Supplemental Figure 6. Kaplan Meier analysis for OS for patients who had a distant recurrence (N = 80), by site of recurrence. Log-rank p-value reported.