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ORIGINAL ARTICLE

Effect of inguinal lymph node dissection in lymph node negative patients with squamous cell carcinoma of the penis

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Abstract

Introduction The survival benefit of inguinal lymph node dissection (ILND) vs no ILND in patients with squamous cell carcinoma of the penis (SCCP) and the absence of lymph node invasion is unclear. We addressed this uncertainty within the Surveillance, Epidemiology and End Results (SEER 2000–2018) database.

Material and methods We identified lymph node negative SCCP patients who either underwent ILND (pN0) or clinical examination only (cN0). We tested for the effect of ILND vs no ILND on cancer-specific mortality (CSM) in Kaplan–Meier plots, univariable and multivariable Cox regression analyses, in a pT stage-specific fashion, before and after 1:3 propensity score matching (PSM). Sensitivity analyses were conducted according to historical and contemporary treatment periods as well as geographic regions.

Results Of 2520 SCCP patients, 369 (15%) underwent ILND (pN0) vs 2151 (85%) did not (cN0). The pN0 vs cN0 distribution according to pT stages was as follows: 80 (7%) vs 1092 (93%) in pT1b, and 289 (21%) vs 1059 (79%) in pT2-3. At 36 months, CSM-free survival in pT2-3 stage was 89% in ILND vs 74% in no ILND patients (multivariable hazard ratio: 0.42, CI 0.30–0.60, $p < 0.001$). This result was confirmed in sensitivity analyses, and after 1:3 PSM. The same analyses could not be completed in pT1b stage due to insufficient number of observations and events.

Conclusions In pT2-3 stage SCCP, a significantly lower CSM was recorded in lymph node negative patients treated with ILND than in their clinical lymph node negative counterparts who did not undergo ILND.

Keywords Inguinal lymph nodes · Lymph node dissection · Penile neoplasms

Introduction

Rates of inguinal lymph node invasion (LNI) in patients with squamous cell carcinoma of the penis (SCCP) increase with pT stage. These rates range from 11 to 18% in pT1b and are up to 20% in pT2-3 SCCP patients, or even higher [1–4]. There is no doubt about survival benefit of a therapeutic inguinal lymph node dissection (ILND) in SCCP patients when LNI is suspected or present [5]. However, despite guidelines recommend ILND even in individuals with clinically negative nodal status from pT1b stage [6, 7], this indication may often be omitted [8]. Significant morbidity of ILND most likely represents the main reason for low adherence to guidelines [8–11]. Based on the potential but unclear survival benefit of ILND, in the context of lymph node negative pT1b or higher SCCP patients [9–11], we tested for differences in cancer-specific mortality (CSM) between ILND (pN0) vs no ILND patients (cN0). We hypothesized that despite the absence of LNI, ILND patients might exhibit lower CSM rates relative to their no ILND counterparts. The rationale of such hypothesis stems from the potential survival benefit yielded by the removal of clinically negative inguinal nodes that results in more reliable pathological validation of lymph node negative status than based on clinical criteria alone. We postulated that lower CSM rates in SCCP patients treated with ILND may justify the surgical toxicity of the procedure. We addressed this uncertainty and tested for CSM differences between ILND vs no ILND

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SCCP patients, in pT stage-specific fashion (pT1b and pT2-3), within the Surveillance, Epidemiology and End Results (SEER 2000–2018) database.

Material and methods

Study population

The SEER database samples 34.6% of the US population in terms of demographic composition and cancer incidence [12]. Within the SEER database (2000–2018), we identified patients aged ≥ than 18 years, with primary histologically confirmed non-metastatic SCCP (International Classification of Disease for Oncology 2 [ICD-O-2] site codes C60.0-60.9 used to identify primary site; ICD-O-3 site codes 8070-8076 used to identify histological subtypes).

Pathological T staging was based on the eight edition of Tumor, Node, Metastasis (TNM) classification as of 2016 [13–15]. In consequence, the distinction between pT2 vs pT3 stages could not be applied, and a grouped pT2-3 stage was used. Only SCCP patients with pT1b and pT2-3 stages were considered for the analyses. ILND patients invariably harbored the absence of LNI, which was coded as pN0. Conversely the clinical absence of LNI was coded as cN0. All patients underwent primary tumor excision (local tumor excision through cautery or laser, partial penectomy, radical penectomy, and radiotherapy). Autopsy or death certificate only cases were excluded.

Statistical analyses

The endpoint of interest was CSM. All analyses between ILND vs no ILND were first performed in pT1b and subsequently repeated in pT2-3 SCCP patients. Propensity score matching (PSM) with a 1:3 ratio was applied within pT stage-specific subgroups. Matching variables consisted of age, pT stage, primary tumor treatment, marital status, and geographic region. Survival analyses relied on Kaplan–Meier plots, as well as univariable and multivariable Cox regression models. Covariates consisted of age and treatment of primary tumor. Additionally, sensitivity analyses were performed according to historical and contemporary treatment periods: 2000–2009 and 2010–2018; as well as SEER geographic regions: West and Midwest, Northeast and South. Finally, sample-power analyses [16] addressed pT1b subgroup with limited numbers of observations and events.

In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used [17]. All tests were two sided, with a level of significance set at $p < 0.05$. Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

Results

Within the SEER database, 2520 pT1b-pT3 SCCP patients with either pN0 ($n = 369$, 15%) or cN0 stage ($n = 2151$, 85%) were identified (Table 1).

Descriptive characteristics and survival analyses in pT2-3 SCCP patients

A higher proportion of SCCP patients harbored pT2-3 stage ($n = 1348$, 53%). Of these, 289 (21%) underwent ILND (pN0) vs 1059 (79%) did not (cN0).

In pT2-3 stage, ILND patients were younger relative to their no ILND counterparts (median age: 61 vs 72, $p < 0.001$). No clinically meaningful difference was recorded in terms of rates of partial or radical penectomy (93 vs 89%) vs organ sparing surgery or radiotherapy.

At 36 months of follow-up, CSM-free survival was 89% in ILND patients vs 74% in their no ILND counterparts (Fig. 1A). These rates translated into a univariable Cox hazard ratio (HR) of 0.50 (95% CI 0.36, 0.69; $p < 0.0001$). In multivariable Cox regression models (Table 2), a HR of 0.47 (CI 0.33–0.68, $p < 0.001$) was recorded.

In sensitivity analyses performed in historical (2000–2009, $n = 591$, 44%) and contemporary (2010–2018, $n = 757$, 56%) treatment periods, multivariable Cox HRs of 0.44 (95% CI 0.26, 0.75; $p = 0.003$) and 0.43 (95% CI 0.27, 0.69; $p < 0.001$) were, respectively, recorded (Table 3), favoring ILND patients vs their no ILND counterparts. In sensitivity analyses performed according to geographic regions, defined as West and Midwest ($n = 768$, 57%) and South and Northeast ($n = 580$, 43%) multivariable Cox HRs of 0.40 (95% CI 0.25, 0.64; $p < 0.001$), and 0.45 (95% CI 0.26, 0.78; $p = 0.004$) were, respectively, recorded (Table 3), favoring ILND patients vs their no ILND counterparts.

After 1:3 PSM, 271 SCCP patients remained in the ILND group vs 813 in the no ILND group (Table 1). At 36 months of follow-up, CSM-free survival was 90% in ILND patients vs 74% in their no ILND counterparts (Fig. 1B). These rates translated into a univariable Cox HR of 0.45 (95% CI 0.31, 0.64; $p = 0 < 0.0001$). In multivariable Cox regression models (Table 2), a HR of 0.48 (95% CI 0.33, 0.69; $p < 0.001$) were recorded.

Descriptive characteristics and sample power analyses in pT1b SCCP patients

Of 1172 pT1b SCCP patients, 80 (7%) underwent ILND vs 1092 (93%) did not. ILND patients were younger (median

Table 1 Descriptive characteristics of 2520 patients diagnosed with non-metastatic squamous cell carcinoma of the penis (SCCP) according to inguinal lymph node dissection (ILND) vs no ILND, before and after 1:3 propensity score matching

Characteristic	Before propensity score matching				After 1:3 propensity score matching[3]			
	Overall, $n=2520$[1]	Patients treated with ILND, $n=369$[1](15%)	Patients not treated with ILND, $n=2151$[1] (85%)	p value[2]	Overall, $n=1,396$[1]	Patients treated with ILND, $n=349$[1] (25%)	Patients not treated with ILND, $n=1047$[1] (75%)	p-value2
Age	69 (59, 79)	62 (53, 70)	70 (60, 80)	<0.001	65 (54, 74)	62 (53, 70)	66 (55, 75)	0.2
T stage				<0.001				0.1
T1b*	1172 (47%)	80 (22%) (7%)	1092 (51%) (93%)		374 (27%)	78 (22%) (21%)	296 (28%) (79%)	
T2-3*	1348 (53%)	289 (78%) (21%)	1059 (49%) (79%)		1022 (73%)	271 (78%) (27%)	751 (72%) (73%)	
Primary treatment				<0.001				0.8
Organ sparing surgery	511 (22%)	27 (7%)	484 (24%)		116 (8.3%)	27 (7.7%)	89 (8.5%)	
Partial penectomy	1380 (58%)	237 (67%)	1143 (57%)		948 (68%)	235 (67%)	713 (68%)	
Radical penectomy	410 (17%)	90 (25%)	320 (16%)		326 (23%)	85 (24%)	241 (23%)	
Radiotherapy	72 (3%)	2 (1%)	70 (4%)		6 (0.4%)	2 (0.6%)	4 (0.4%)	
Marital status				0.011				0.7
Married	1426 (57%)	214 (58%)	1212 (56%)		811 (58%)	203 (58%)	608 (58%)	
Never married	412 (16%)	77 (21%)	335 (16%)		269 (19%)	73 (21%)	196 (19%)	
Previously married	520 (21%)	59 (16%)	461 (21%)		241 (17%)	56 (16%)	185 (18%)	
Unknown	162 (6%)	19 (5%)	143 (7%)		75 (5.4%)	17 (4.9%)	58 (5.5%)	
Geographic region 0.7								0.8
West	1203 (48%)	179 (49%)	1024 (48%)		663 (47%)	173 (50%)	490 (47%)	
South	675 (27%)	101 (27%)	574 (27%)		385 (28%)	92 (26%)	293 (28%)	
Northeast	393 (16%)	50 (14%)	343 (16%)		204 (15%)	48 (14%)	156 (15%)	
Midwest	249 (9.9%)	39 (11%)	210 (9.8%)		144 (10%)	36 (10%)	108 (10%)	

[1]Median (IQR); *n* (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

[3]Matching variables: age, pT stage, primary tumor treatment, marital status, and geographic region

*First percentage relative to cN0 and pN0; second percentage relative to pT1b and pT2/3, respectively

age: 63 vs 69, $p<0.001$) and were more often treated with partial or radical penectomy than their no ILND counterparts (77 vs 55%, $p<0.001$). At 36 months of follow-up, CSM-free survival was 81% in ILND patients vs 85% in their no ILND counterparts (Fig. 1C). These rates translated into a univariable Cox HR of 0.94 (95% CI 0.53, 1.64; $p=0.82$), that did not indicate a difference between ILND vs no ILND.

Given the critically low number of observations, especially in ILND patients ($n=80$), we computed the required sample size provided a 10% CSM difference at 36 months, between ILND vs no ILND patients. In sample-power analyses based on patient rates' distribution observed in pT2-3 SCCP stage (ILND rate: 21%), given a power of 0.8 and α of 0.05, 438 ILND and 1648 no ILND SCCP patients would be required in pT1b stage. If a smaller difference in CSM was targeted (5%), based on the same considerations, as many as 1413 ILND and 5316 no ILND SCCP patients would be required.

Discussion

Despite guidelines' recommendations [6, 7], ILND is rarely performed in absence of frank clinical suspicion of LNI [8]. We tested for differences in CSM between ILND patients without pathological evidence of LNI vs no ILND patients with only clinically negative nodal examination (pN0 vs cN0). We hypothesized that despite the absence of LNI, ILND patients might exhibit lower CSM rates relative to their no ILND counterparts. We addressed the above

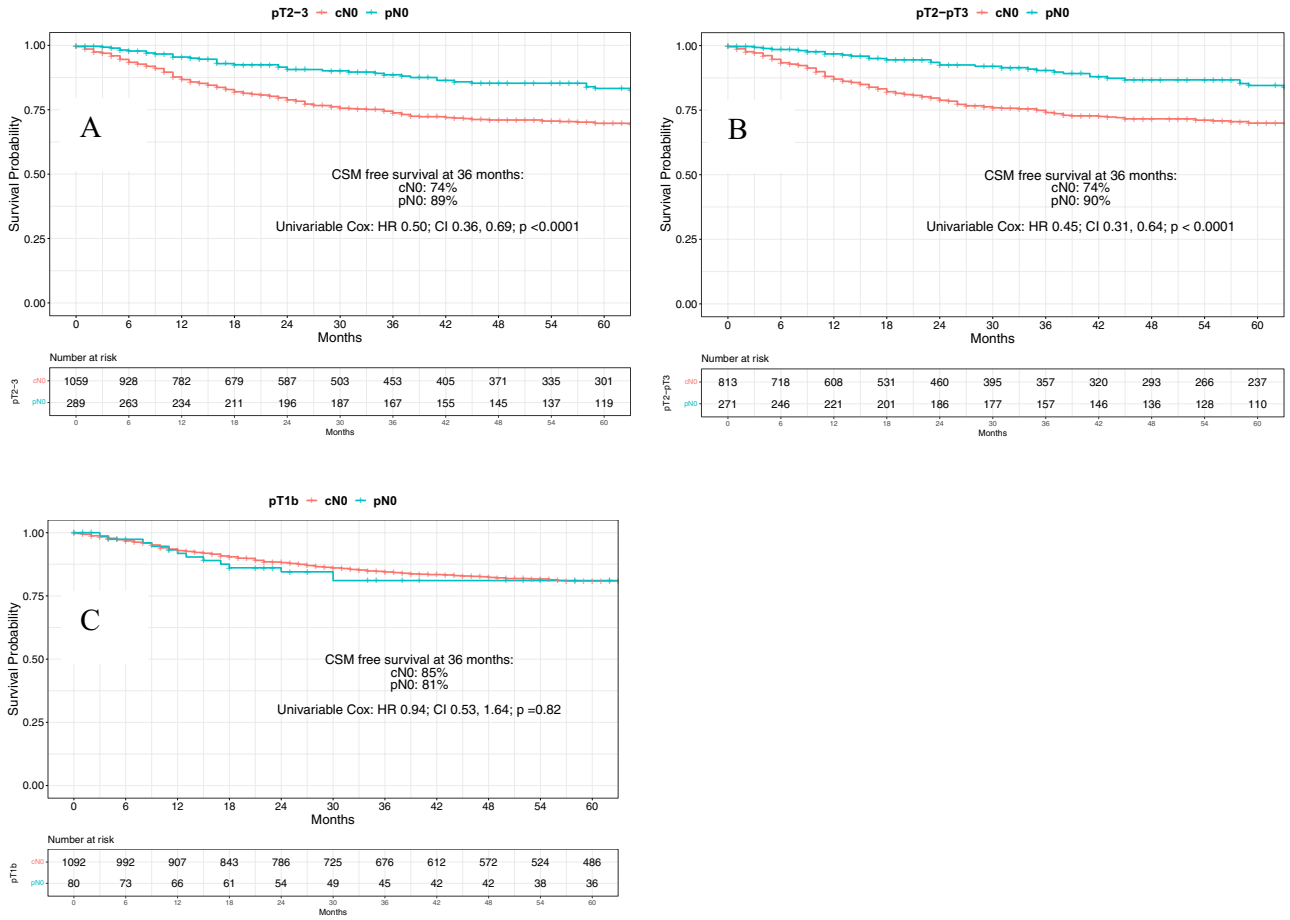

Fig. 1 Kaplan-Meyer curves of cancer-specific mortality according to inguinal lymph node dissection (ILND) vs no ILND in 2520 non-metastatic squamous cell carcinoma of the penis (SCCP), according to pT stage: **A** pT2-3 stage before 1:3 propensity score matching (PSM); **B** pT2-3 stage after 1:3 PSM; **C** pT1b (curves after PSM not reported based on sample size limitations)

Table 2 Multivariable Cox regression analyses testing the effect of inguinal lymph node dissection (ILND) on cancer-specific mortality in 2520 patients diagnosed with non-metastatic squamous cell carcinoma of the penis (SCCP), before and after 1:3 propensity score matching

ILND vs no ILND on CSM	Sensitivity analyses in pT2-3 SCCP patients		
	HR[1]	95% CI[1]	*p* value
Treatment periods			
pT2-3, 2000–2009 ($n=591$)	0.44	0.26, 0.75	**0.003**
pT2-3, 2010–2018 ($n=757$)	0.43	0.27, 0.69	**<0.001**
Geographic regions			
pT2-3, West / Midwest ($n=768$)	0.40	0.25, 0.64	**<0.001**
pT2-3, South / Northeast ($n=580$)	0.45	0.26, 0.78	**0.004**

Bold *p*values are those *p*values with a statistically significant value (≤0.05).

hypothesis within the SEER (2000–2018) database and recorded several noteworthy observations.

First, within the SEER database (2000–2018) we only identified 3563 lymph node negative SCCP patients who either underwent or did not undergo ILND. These numbers compare very unfavorably with several other urological malignancies with higher incidence and prevalence rates. For example, within a substantially shorter study span (SEER 2010–2015) Yang et al. identified 25,952 (94%) lymph node negative and 1738 (6%) lymph node positive organ-confined prostate cancer patients [18]. Similarly, Kosiba et al. (SEER 2004–2016) identified 13,615 (79%) lymph node negative and 3669 (21%) lymph node positive organ-confined bladder cancer patients. In pT1b-pT3 SCCP patients, LNI rates range or even exceed 20% as reported by reputable institutional series (from 102 to 350 patients) [1–4] as well as by even larger population-based series (from 943 to 1919 patients) [8, 19, 20]. These data confirmed the orphan status of SCCP [21, 22], and its pronounced tendency to harbor LNI [23], which is higher than prostate cancer, and comparable to bladder cancer. In consequence, studies on survival, especially those focusing on lymph node negative patients, are

Table 3 Sensitivity analyses addressing the effect of inguinal lymph node dissection (ILND) on cancer-specific mortality in non-metastatic pT2-3 squamous cell carcinoma of the penis (SCCP) according to historical and contemporary treatment periods and geographic regions

ILND vs no ILND on CSM	Before propensity score matching			After 1:3 propensity score matching		
	HR[1]	95% CI[1]	*p* value	HR[1]	95% CI[1]	*p* value
pT1b	0.94	0.55, 1.70	0.90	0.90	0.49, 1.67	0.74
pT2-3	0.47	0.33, 0.68	**< 0.001**	0.48	0.33, 0.69	**< 0.001**

Bold p-values are those p-values with a statistically significant value (≤0.05).

Adjustment variables: age, treatment of primary tumor (organ-sparing-surgery, partial penectomy, radical penectomy, radiotherapy)

HR hazard ratio, *CI* confidence interval

much more challenging in SCCP than in the majority of the other urologic malignancies.

Second, analyses of ILND in SCCP are challenging due to low rates of ILND in specific patients subgroups. This limitation particularly applied to pT1b stage, in whom only 80 (7%) out of overall 1172 pT1b patients underwent ILND. This severe sample size limitation prevented any meaningful survival analyses. We examined the ideal sample size requirements that should apply to pT1b patients to allow valid CSM comparisons. Sample size analyses based on power of 0.8 and α of 0.05, indicated that a 10% difference in CSM-free survival rates between ILND vs no ILND, would, respectively, require at least 438 ILND and 1648 no ILND pT1b SCCP patients. If a difference of 5% would have been targeted, much larger samples would be required (1413 ILND and 5316 no ILND patients). In consequence, the effect of ILND vs no ILND on CSM in pT1b stage cannot be assessed due to insufficient number of observations and events, even in large-scale epidemiological repositories as SEER.

Third, a number of observations were sufficient to warrant meaningful CSM comparisons between ILND vs no ILND in pT2-3 SCCP patients. At 36 months of follow-up, CSM-free survival was 89% vs 74% in ILND vs no ILND patients, which resulted in a multivariable HR: 0.47 ($p < 0.001$), favoring ILND. In sensitivity analyses applied to historical (2000–2009) and contemporary (20,010–2018) ILND vs no ILND pT2-3 SCCP patients, virtually the same multivariable HRs favoring ILND were recorded (historical: 0.44, $p = 0.003$; contemporary: 0.43, $p < 0.001$). Similarly, virtually the same HRs were recorded when sensitivity analyses were repeated according to geographic regions (West and Midwest: 0.40, $p < 0.001$; South and Northeast: 0.45, $p = 0.004$). Furthermore, to increase the complexity of hypothesis testing, we relied on PSM, where each ILND patient was matched with three no ILND controls. After PSM, the HR denoting lower CSM in ILND vs no ILND patients remained virtually unchanged (0.48, $p < 0.001$). Taken together all sensitivity and PSM analyses convincingly validate lower CSM in ILND relative to no ILND pT2-3 SCCP patients. In consequence pT2-3 patients treated with preventive ILND may expect 15% lower CSM despite being exposed to complications of ILND that may be multiple, long-lasting, and requiring surgical treatment [9–11]. The trade-off between lower CSM vs potential toxicity requires discussion and decision making regarding ILND, especially when the absence of LNI suspicion applies.

Fourth, similarly to the current study, Mistretta et al. [8], in part of their analyses, investigated the effect of ILND vs no ILND on CSM in nodal negative SCCP patients ($n = 96$ vs $n = 656$, respectively). In this, a non-statistically significant protective HR was recorded (multivariable HR: 0.65, CI 0.41, 1.05, $p = 0.08$). However, unlike the current study that specifically considered pT2-3 patients, Mistretta et al. included pT1b, as well as pT4 patients in their analyses [8]. In pT1b individuals the critically low number of ILND patients (approximately 40 patients), prevented meaningful analyses, as was discussed for the current study. Similarly, Mistretta et al. included pT4 patients, in whom the advanced disease stage may have obliterated the potential benefit of ILND. Taken together the reported observations of Mistretta et al. agreed with the direction of the protective HR recorded in the current study. However, their results were unintentionally diluted with observations originated in patients in whom ILND was performed excessively rarely (pT1b), and in whom ILND was possibly performed too late in the course of disease (pT4).

Several limitations apply to this study. First, despite the large scale of the SEER database, since SCCP is an orphan entity, our findings were limited by sample size.

Second, our data represent a retrospective analysis with high potential for selection biases. To maximally limit these biases, we applied multivariable adjustment analyses and propensity score matching. However, it is possible that important differences persisted according to unavailable variables. Specifically, within the SEER databases, lack of central pathology, as well as non-standardized and non-assessable rate of imaging represents weaknesses.

Third, SEER does not provide information regarding comorbidities, hospital, or surgeon information as well as patients' complications. In consequence, no assumptions relative to ILND-related morbidity could be done.

Fourth, the distinction between pT2 and pT3 SCCP patients according to eight edition TNM classification was not applicable until after 2015. In consequence, in the current study pT2 and pT3 stages patients were examined together. All the above-reported limitations reflected the retrospective and population-based nature of the SEER database.

Conclusions

In the current study, despite the absence of LNI, pT2-3 stage SCCP patients treated with ILND exhibited significantly lower CSM than their clinical lymph node negative counterparts, who did not undergo ILND. Reasonably, the pathological validation of negative inguinal lymph nodes is more reliable than the clinical inguinal nodal examination alone, and this translates in a remarkable survival benefit. In the light of this benefit in CSM, with the due caution, we can postulate that even in the absence of frank LNI suspicion, the potential surgical toxicity of ILND can be justified. Unfortunately, due to paucity of ILND cases and events, equally meaningful observations could not be made regarding pT1b stage SCCP patients.

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Data availability statement All data generated for this analysis were from the Surveillance, Epidemiology, and End Results Research Plus (SEER) database. The code for the analyses will be made available upon request.

Declarations

Conflict of interest The authors declare that there is no conflict of interests.

Ethics consent statement All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval was not required.

Patient consent statement, permission to reproduce material from other sources and clinical trial registration Not applicable.

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